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Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations (Review)

Macfadyen CA, Acuin JM, Gamble CL

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[Intervention Review]

Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations

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ABSTRACT

Background

Chronic suppurative otitis media (CSOM) causes ear discharge and impairs hearing.

Objectives

Assess topical antibiotics (excluding steroids) for treating chronically discharging ears with underlying eardrum perforations (CSOM).

Search methods

The Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 1, 2005), MEDLINE (January 1951 to March 2005), EMBASE (January 1974 to March 2005), LILACS (January 1982 to March 2005), AMED (1985 to March 2005), CINAHL (January 1982 to March 2005), OLDMEDLINE (January 1958 to December 1965), PREMEDLINE, *metaRegister* of Controlled Trials (*mRCT*), and article references.

Selection criteria

Randomised controlled trials; any topical antibiotic without steroids, versus no drug treatment, aural toilet, topical antiseptics, or other topical antibiotics excluding steroids; participants with CSOM.

Data collection and analysis

One author assessed eligibility and quality, extracted data, entered data onto RevMan; two authors inputted where there was ambiguity. We contacted investigators for clarifications.

Main results

Fourteen trials (1,724 analysed participants or ears). CSOM definitions and severity varied; some included otitis externa, mastoid cavity infections and other diagnoses. Methodological quality varied; generally poorly reported, follow-up usually short, handling of bilateral disease inconsistent. Topical quinolone antibiotics were better than no drug treatment at clearing discharge at one week: relative risk (RR) was 0.45 (95% confidence interval (CI) 0.34 to 0.59) (two trials, N = 197). No statistically significant difference was found between quinolone and non-quinolone antibiotics (without steroids) at weeks one or three: pooled RR were 0.89 (95% CI 0.59 to

1.32) (three trials, N = 402), and 0.97 (0.54 to 1.72) (two trials, N = 77), respectively. A positive trend in favour of quinolones seen at two weeks was largely due to one trial and not significant after accounting for heterogeneity: pooled RR 0.65 (0.46 to 0.92) (four trials, N = 276) using the fixed-effect model, and 0.64 (95% CI 0.35 to 1.17) accounting for heterogeneity with the random-effects model. Topical quinolones were significantly better at curing CSOM than antiseptics: RR 0.52 (95% CI 0.41 to 0.67) at one week (three trials, N = 263), and 0.58 (0.47 to 0.72) at two to four weeks (four trials, N = 519). Meanwhile, non-quinolone antibiotics (without steroids) compared to antiseptics were more mixed, changing over time (four trials, N = 254). Evidence regarding safety was generally weak.

Authors' conclusions

Topical quinolone antibiotics can clear aural discharge better than no drug treatment or topical antiseptics; non-quinolone antibiotic effects (without steroids) versus no drug or antiseptics are less clear. Studies were also inconclusive regarding any differences between quinolone and non-quinolone antibiotics, although indirect comparisons suggest a benefit of topical quinolones cannot be ruled out. Further trials should clarify non-quinolone antibiotic effects, assess longer-term outcomes (for resolution, healing, hearing, or complications) and include further safety assessments, particularly to clarify the risks of ototoxicity and whether quinolones may result in fewer adverse events than other topical treatments.

PLAIN LANGUAGE SUMMARY

A Cochrane systematic review assessing topical antibiotics without steroids for treating chronically discharging ears with underlying eardrum perforations, in participants of any age

Chronic suppurative otitis media (CSOM) is an infection of the middle ear with pus and a persistent perforation in the eardrum. It is a common cause of preventable hearing impairment, particularly in low and middle-income countries. This review assesses topical antibiotics (without steroids), to clarify whether they are better than no treatment or aural toilet (cleaning of the ear discharge), or treatment with topical antiseptics and to identify which antibiotic is best. Fourteen randomised controlled trials were included (1,724 analysed participants or ears); most were poorly reported, and some included a range of diagnoses.

Quinolone antibiotic drops (considered to be the 'gold standard' topical antibiotics) are better than no drug treatment or antiseptics at drying the ear. The effects of non-quinolone antibiotics (without steroids) when compared to antiseptics are less clear. Studies were also inconclusive regarding any differences between quinolone and non-quinolone antibiotics, although indirect evidence suggests a benefit of quinolones cannot be ruled out. Less is known about longer-term outcomes (producing a dry ear in the long term, preventing complications, healing the eardrum, and improving hearing), or about treating complicated CSOM. The evidence in these trials about safety is also weak. More research is needed to assess whether there may be fewer adverse events with topical quinolones than with alternative topical treatments.

BACKGROUND

Chronically discharging ears associated with underlying persistent eardrum perforations (chronic suppurative otitis media, CSOM) are a common cause of preventable hearing impairment in low and middle-income countries (McPherson 1997; WHO 1998). CSOM usually occurs in the first five years of life (although it often persists into adulthood), and is related to poor socio-economic conditions. Therefore, while this review aims to address the global perspective of CSOM, much of the information discussed here relates to low-income settings and may differ in developed countries (e.g. age distribution).

What is CSOM?

CSOM is one of several types of otitis media (infection of the middle ear). The World Health Organization (WHO) defines CSOM as "a stage of ear disease in which there is chronic infection of the middle ear cleft, a non-intact tympanic membrane (i.e. perforated eardrum) and discharge (otorrhoea), for at least the preceding two weeks" (WHO 1998), although this could more strictly be considered a childhood definition. Perforations and infection can be in one ear (unilateral) or both (bilateral). A variety of underlying pathologies can cause CSOM including: an acute episode of acute

otitis media that has burst the ear drum and not settled within two weeks; a recurrent episode of acute otitis media in an ear with a perforation from a previous episode of acute otitis media; or an ear with a persistent perforation with active chronic otitis media with metaplastic changes to the mucosa of the middle ear and mastoid air cell system (Browning 2003, personal correspondence). In adults, the majority of patients are likely to have CSOM with a perforation that will not spontaneously heal.

What are the effects of CSOM?

Hearing impairment, aside from the disability from recurrent ear discharge, is the most frequent effect of CSOM. A school survey in Kenya found 63% of ears with CSOM had more than 30 decibels (dB) hearing loss, compared to only 3.4% of ears without outer or middle ear pathology (Hatcher 1995). Hearing impairment due to otorrhoea and a perforated eardrum will usually improve as the disease resolves. However, untreated CSOM may result in permanent hearing loss due to damage to the ossicles which transmit sound vibrations from the eardrum to the cochlea. Because otitis media occurs mostly in children during preschool years, the years in which the most dynamic phase of speech and language development occurs, there is concern that the associated hearing deficits may result in speech and language delays or permanent learning disabilities, as well as disturbances in behaviour (Klein 2000).

In addition to hearing impairment (with its associated consequences), complications of otitis media can often result in death or severe disability, especially in low-income countries (WHO 2000), where immunity, housing conditions, and access to medical services are often poorer than in high income settings. The infection may extend and spread to the head and neck structures and to the brain. Intracranial infections include meningitis, abscesses, hydrocephalus, or thrombosis of the lateral venous sinus (from suppuration within the mastoid causing clots occluding the lumen of the vessel) (Ludman 1997). Alternatively complications may be extracranial, such as subperiosteal abscess (superficial accumulations of pus that have broken the bony mastoid cortex), facial paralysis, cholesteatoma (a destructive formation of layers of keratinising epithelium, accumulating in the middle ear and mastoid (Bluestone 1996), also described as 'active squamous (epithelial) chronic otitis media (Browning 1997)), labyrinthitis (extension to the labyrinth through the round window), or acute mastoiditis (spread of the infection to the mastoid air cells), which may spread further due to necrosis of the bony wall of the cells resulting in further life-threatening complications (Dhillon 1999; Ludman 1997).

How much of a burden is CSOM?

Around 91% of the burden of otitis media (all types) and nearly all related deaths occur in low and middle-income countries (World Bank 1993; WHO 2002). Reliable data on prevalence of CSOM

are uncommon. One study estimated it at 1.1% in Kenyan school children (Hatcher 1995) and a review of school and community-based studies reported a prevalence between 0.4% and 6.1% in low and middle-income countries (Berman 1995). Data from the World Health Organization and World Bank suggest the global burden of otitis media has dropped dramatically since 1990, to approximately 6000 deaths (0.01% of all deaths) and 1,474,000 disability adjusted life years (DALYs) lost (0.1% of all DALYs) worldwide in 2001 (WHO 2002). Most of these deaths are likely to be due to chronic otitis media and its complications, because acute otitis media is usually a self-limiting infection (Acuin 2004). Although most of the background literature cited in this review relates to children, reliable and generalisable data for the global burden in children are not readily available; the WHO estimates therefore quoted here are for both adults and children.

What are the causes of CSOM?

The causes and risk factors associated with CSOM are unclear, and few studies have examined these for CSOM. Instead authors have extrapolated results of studies for acute otitis media and otitis media with effusion to CSOM. However these studies often have conflicting findings, and there is no proven correlation between the various host and environmental factors associated with CSOM and the factors associated with acute otitis media and otitis media with effusion. Despite this, some important factors that may be associated with CSOM include: environmental factors such as inadequate treatment (of CSOM and acute otitis media), poor access to medical care, poor socioeconomic conditions, season, exposure to tobacco smoke, overcrowding, attendance at day care centres, lack of breastfeeding, or poor nutrition or hygiene; and host factors such as altered immunity and underlying diseases (e.g. HIV/AIDS (Barnett 1992; Singh 2003), frequent upper respiratory tract infections), early onset of otitis media in the first months of life, and family history of otitis media. Some populations are at increased risk of developing CSOM, and have high rates reported, including certain ethnic groups (such as Native American tribes of Apache and Navajo, Australian Aborigines, and Inuits of Canada, Greenland and Alaska), and individuals with anatomical defects (e.g. cleft palate or submucous cleft), altered physiological defences (Eustachian tube dysfunction) or Down's syndrome (Bluestone 1998).

What management approaches are there?

The aims of treatment are to stop the discharge (and to eradicate infection), to heal the tympanic membrane, improve hearing, prevent the common problems of recurrent or new infections, and to prevent potentially life-threatening complications. Treatment options for uncomplicated CSOM include dry mopping, ear wicking, gentle syringing, or suctioning, to clean the ear discharge (au-

ral toilet); systemic antibiotics (e.g. oral antibiotic preparations, or intravenous antibiotics); and topical treatment with either antiseptics or antibiotics, sometimes with steroids. If complications develop, surgery is usually required to remove the infected tissue from the middle ear and mastoid air cells, and possibly repair the damaged eardrum and ossicles. Each of these treatments will be considered in the following Cochrane reviews:

- *aural toilet*: aural toilet versus no treatment or various methods of aural toilet
- *systemic antibiotic treatment*: systemic antibiotics versus no treatment or aural toilet, or various methods of systemic antibiotics
- *topical antiseptics*: topical antiseptic versus no treatment or aural toilet, or various topical antiseptics
- *topical antibiotics without steroids (THIS REVIEW)*: topical antibiotic, versus no treatment or aural toilet, topical antiseptics or various topical antibiotics, excluding steroids
- *systemic versus topical treatments*: any systemic treatment against any topical treatment excluding steroids
- *systemic or topical steroids*: steroids, as monotherapy or combination therapy, versus no treatment or aural toilet, topical antiseptics, topical antibiotics, or systemic antibiotics
- *surgical treatment*: surgery versus no treatment or any other treatment

A report of a WHO/Ciba Foundation workshop held in 1996, recommends administration of topical (and/or systemic) antibiotics as well as dry mopping/wicking, since wicking alone is suggested to be ineffective (as found by [Smith 1996](#)) ([WHO 1998](#)). However, the WHO guidelines still currently recommend treating CSOM by using wicking to dry the ear alone (and a five-day follow-up).

Topical treatment with antibiotics

A number of topical antibiotics have been used in the treatment of CSOM. However, concern exists regarding their ability to penetrate the middle ear and mastoid cavities as well as their activity against the causative bacteria (usually gram-negative). There also remains controversy and uncertainty about the possible ototoxic effect, in particular of topical aminoglycoside antibiotics (by damaging the hair cells in the basal turn of the cochlea), particularly where the eardrum is not intact. The newer 4-quinolone antibiotics (e.g. ciprofloxacin) are widely considered to be the 'gold standard' topical antibiotics, but are expensive and not generally available as otological preparations in many countries. Topical antibiotics may be superior to topical antiseptics, although this needs investigating, particularly as topical antiseptics are cheap and easily available, and are thus widely used in many low and middle-income countries.

OBJECTIVES

To assess the effects of topical antibiotics (excluding steroids) for chronically discharging ears with underlying eardrum perforations (CSOM) in participants of any age.

METHODS

Criteria for considering studies for this review

Types of studies

Individual randomised controlled trials.
Cluster randomised controlled trials.

Types of participants

People of any age with a diagnosis of CSOM as defined by the trial authors.

Types of interventions

Intervention: topical (aural) antibiotics without steroids.
Comparator: no intervention; aural toilet; placebo; other topical antibiotics without steroids; antiseptics.
(Treatments containing steroids will not be included here, but will be considered in a separate Cochrane review, as indicated above).

Types of outcome measures

Primary outcomes

Resolution of CSOM at two to four weeks, and after four weeks, according to the investigators' criteria

Secondary outcomes

- Healing of perforation at two to four weeks, and after four weeks
- Time to resolution of CSOM as defined by the investigators
- Improvement in hearing threshold, as measured by audiometry at two to four weeks, and after four weeks
- Time to re-appearance of discharge and perforation after its previous resolution
- Adverse events that
 - a) are fatal, life-threatening, require inpatient hospitalisation or prolongation of existing hospitalisation, or result in persistent or significant disability/incapacity, such as permanent hearing loss, tinnitus or vertigo ([Karbwan 1999](#); [UMC 2003](#))

- b) result in withdrawal or discontinuation of treatment
- c) any other adverse events, such as ear pain, ear canal reactions and transient dizziness

Where outcomes (resolution of discharge, healing of the tympanic membrane, and hearing threshold) are reported at several time-points within the ranges above, we took the last reported result.

Search methods for identification of studies

The Trials Search Co-ordinator of the Cochrane Ear, Nose and Throat Group carried out an independent search in August 2003 and March 2005.

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). Trials reported in conference proceedings or on posters have not been sought for this review, but will be sought for inclusion in an update of this review.

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register (code SR-ENT), and the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* Issue 1, 2005, for relevant trials up to March 2005. Full details of the Cochrane Ear, Nose and Throat Disorders Group methods and the journals handsearched are published in *The Cochrane Library* in the section on Collaborative Review Groups.

CENTRAL was searched using the terms shown in [Appendix 1](#). Using the CENTRAL search terms, in combination with the search strategy for identifying trials developed by The Cochrane Collaboration ([Clarke 2003](#)), we also searched the following databases:

- (1) MEDLINE (January 1951 to March 2005)
- (2) EMBASE (January 1974 to March 2005)
- (3) LILACS (www.bireme.br; January 1982 to March 2005)
- (4) AMED (1985 to March 2005)
- (5) CINAHL (January 1982 to March 2005)
- (6) OLDMEDLINE (January 1958 to December 1965)
- (7) PREMEDLINE
- (8) NNR
- (9) ZETOC

We searched the following potential sources of trials:

- *metaRegister of Controlled Trials* (mRCT accessible via the Internet: <http://controlled-trials.com/mrct/>)
- Cochrane Ear, Nose and Throat Disorders Group Trials Register for any relevant abstracts from conference proceedings
- Reference lists of all articles/trials identified by the above methods (includes searching of bibliographies for relevant citations)
- Previous published Cochrane review, 'Interventions for chronic suppurative otitis media' ([Acuin 1998](#))
- Other previously published (systematic) reviews: 'Chronic suppurative otitis media', in *Clinical Evidence* ([Acuin 2004](#)), and 'Systematic Review of Existing Evidence and Primary Care Guidelines on the Management of Otitis Media (Middle Ear

Infection) in Aboriginal and Torres Strait Islander Populations, March 2001 ([Couzos 2001](#))

- DARE using issues 2 and 3 of *The Cochrane Library* 2003 - searched for systematic reviews

We will explore the following potential sources of trials for future updates of this review:

- Other previously published (systematic) reviews identified by the above search strategy
- Organisations and individual researchers working in the field of otitis media (including authors of published trials and other experts who may know about additional trials)
- Pharmaceutical companies (see published notes for list of companies contacted) to locate additional studies, unpublished data, confidential reports, and raw data of published trials

Data collection and analysis

Selection of studies

Carolyn Macfadyen (CM) and Jose Acuin (JA) independently reviewed the titles and abstracts identified by the search strategy to identify potentially relevant trials.

CM retrieved the full papers for all potentially relevant studies, and assessed their eligibility to be included in the review using an eligibility form based on the stated inclusion criteria. We identified multiple publications from the same data set and reported these as one trial. Where outcomes are 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 do not meet the inclusion criteria for this review and stated the reason in the 'Characteristics of excluded studies' table. Where necessary, we contacted the study authors for clarification.

JA and Carrol Gamble (CG) provided a second opinion on trials CM had selected for inclusion, and the three authors resolved any disagreements through discussion.

Data extraction and management

CM extracted data of study characteristics, including methods, participants, interventions, and outcomes, and recorded these on standard forms. JA provided further information where this had been obtained from authors of trials included in the previous review 'Interventions for chronic suppurative otitis media' ([Acuin 1998](#)). In studies where data are insufficient or missing, we contacted the authors of the original studies for additional data and/or verification of methods, to clarify any uncertainties about the data and the way in which they were collected, and to try to obtain missing data.

CSOM can occur in one or both ears for each participant, which means participants can be counted more than once if ears are used

as the unit of analysis. Where outcomes were reported in number of ears only, we also attempted to obtain the values for number of participants; numbers of ears were used where this information could not be obtained. We checked the data and resolved any discrepancies by referring to the trial report, through discussion. 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 randomly assigned). If the number randomised and the numbers analysed were inconsistent, we calculated a per cent loss-to-follow-up and reported this information in [Table 1](#). For binary outcomes, we recorded total number of participants (or ears, where participant numbers were unavailable) 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. If the data were reported using geometric means, we planned to extract standard deviations on the log scale. We planned to extract medians and ranges, and report these in additional tables if any trials reported these.

Assessment of risk of bias in included studies

CM assessed the methodological quality of all the trials identified as eligible for inclusion. CG reviewed trials where there was any ambiguity about the methods used, and JA provided further information where this had already been obtained from authors of trials included in the previous review 'Interventions for chronic suppurative otitis media' ([Acuin 1998](#)). Any disagreements were resolved through discussion. Where necessary, we contacted the study authors for further clarification.

We assessed the methodological quality of the 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 inclusion of randomised participants as adequate, inadequate and unclear as outlined by [Juni 2001](#). Blinding is classified as double blind, single blind, or open.

Data synthesis

CM entered data into [Review Manager 4.2](#).

In studies that enrolled people with otitis externa, draining surgical cavities or acute otitis media, as well as CSOM, we only included the results for **just** CSOM participants if the authors reported accounting for diagnosis at randomisation (e.g. stratified by diagnosis) and presented results by diagnosis. Where information was not reported regarding whether alternative diagnostic groups were accounted for at randomisation, we included all participants (groups may be unbalanced, and decisions by trialists to report subgroups may have been linked to trend). We also included all participants where separate results were not available. See [Table](#)

[2](#) for details. For crossover trials, we have only taken the results before participants were crossed over to the alternative treatment, where possible; otherwise results for all participants combining pre and post-crossover data were used.

For binary data, we combined trials using relative risks (RR) and 95% confidence intervals (CI). We combined trials with continuous data using the weighted mean difference (WMD) and its 95% confidence interval. Where data have been reported using medians and ranges, or there is evidence of skewed data, we reported medians and ranges where possible (dividing 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 report on the original scale.

Quinolone and non-quinolone topical antibiotic treatments are not combined across trials. This was done to avoid counting patients in the antiseptic arm twice for trials that compared a quinolone with a non-quinolone and an antiseptic. There is also clinical interest in the difference in effectiveness of quinolones compared to non-quinolones, as quinolones are thought to be more effective and safer but more expensive.

Where heterogeneity is considered to be present, and it remained clinically appropriate to combine data, we also used the DerSimonian and Laird random-effects model, and reported both fixed-effect and random-effects results.

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), associated mopping (dividing studies into those with some form of ear toilet, 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 the 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' ([CochraneENTGuideline](#) 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.
- (4) Repeat the analysis excluding studies where people with CSOM are only a subgroup of the participants included in the study, for example, those that enrol people with otitis externa, draining

surgical cavities or acute otitis media, as well as CSOM.

Within this version of the review, trials where people with CSOM are only a subgroup of the participants included in the study are identified - see [Table 2](#).

For this version of the review, we visually examined forest plots, in conjunction with the χ^2 test, using a 5% level of statistical significance, and the I^2 statistic. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered substantial heterogeneity ([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

The electronic searches identified 649 citations in August and September 2003, plus 698 citations in March 2005, including four unpublished trials. Three additional trials were already known to the authors: [van Hasselt 1997](#); [van Hasselt 1998](#); [van Hasselt 2002](#). [Macfadyen 2005](#) was also already known to the authors. Trials with duplicate publications were identified and referred to under the main trial publication. Full texts of 127 trials were reviewed, and 14 included as eligible for this review - see breakdown of numbers below. We attempted to include all relevant studies regardless of language.

- 127 trials: full texts obtained for eligibility assessment (117 from the above sources, plus ten from reference lists and other searches). Of these, 85 were in English only, three had English and non-English publications, and 39 were in non-English languages only.

- 105 trials excluded: 74 English only, one English and non-English language, 30 only available in non-English language.

- Eight trials awaiting assessment: two English only [[Nawasreh 2001](#) is awaiting a response from the author as to whether this is the same trial as another trial already included in this review ([Tutkun 1995](#)); [McKelvie 1975](#) is awaiting full assessment for probable inclusion], and six trials only available in non-English language, awaiting translation to determine eligibility.

- 14 trials included: nine English only, two English and non-English language, three only available in non-English language.

The [Characteristics of excluded studies](#) table outlines reasons for excluding studies following review of their full texts. The [Characteristics of included studies](#) table provides information on

the included trials; also see tables: [Table 1](#) (Methodological quality of included studies); [Table 3](#) (Bilateral Disease: Numbers for Ears versus Participants); [Table 2](#) (Participant eligibility criteria, including CSOM diagnostic criteria); [Table 4](#) (Intervention regimens used); [Table 5](#) (Outcomes assessed).

Age, setting and location (for included studies)

See the [Characteristics of included studies](#) table for details.

Ages varied:

- Three studies were primarily in children, four included children and adults, five were in adults only, and two did not specify. Details are reported in the [Characteristics of included studies](#) table and [Table 2](#).

Setting:

- Two trials were community-based, and mainly in children: [Macfadyen 2005](#) (Kenyan primary schools, using child-to-child treatment) and [van Hasselt 1998](#) (rural Malawi). Two further trials in rural Malawi did not specify the setting ([van Hasselt 1997](#) and [van Hasselt 2002](#)).

- Eight were hospital-based (outpatient). Another two did not report the setting but appear to be based either in a hospital or private clinic ([Gyde 1978](#); [Gyde 1981](#)).

Location:

- Six trials in high-income countries (UK, Canada, Spain and Israel).

- Eight were in low or middle-income countries (Thailand, Turkey, India, Kenya and Malawi).

Diagnostic criteria for included participants

[Table 2](#) provides eligibility criteria and more detailed CSOM diagnostic criteria. Definitions used for CSOM varied, particularly for duration, and also whether positive bacterial culture or changes in mucosal appearance were assessed and/or required - see [Table 2](#). We accepted the authors' definitions when assessing eligibility. Three trials included otitis externa and draining mastoid cavities; all analysed and presented results separately, but two did not report how or whether randomisation was stratified by diagnosis ([Clayton 1990](#); [Gyde 1981](#)) and although one stated that type of infection was the principal criterion for randomisation by minimisation, it is not clear whether this relates to diagnosis or bacteriology ([Gyde 1978](#)); all participants are therefore included in this review. [Browning 1983a](#) also included participants with draining mastoid cavities, and [Fradis 1997](#) reported surgical perforations in three ears although prior middle-ear surgery was an exclusion criterion; neither trial reported the results separately, and all participants are

also included in this review. [Table 2](#) provides further details with numbers involved.

Interventions

[Table 4](#) provides details of the treatment regimens used in the trials. Treatment regimens (strength, dose, frequency of dose, duration, and treatment provider) and associated aural toilet were equivalent for all comparisons within each trial, unless specified below.

Ten trials tested non-quinolone antibiotics:

- seven tested aminoglycoside alone (five gentamicin, two tobramycin);
- two tested aminoglycoside-polymyxin combination (neomycin-polymyxin B);
- one tested chloramphenicol;
- two tested trimethoprim-sulphacetamide-polymyxin B (TSP);
- one tested trimethoprim-polymyxin B (TP).

In one trial, the choice of antibiotic (gentamicin or chloramphenicol) depended on baseline bacteriology ([Browning 1983a](#)).

Ten trials tested quinolone antibiotics:

- seven tested ciprofloxacin;
- three tested ofloxacin (although [van Hasselt 2002](#) used a single weak dose in a treatment delivery vehicle).

Seven trials tested antiseptics:

- two tested aluminium acetate (although [Fradis 1997](#) used a weak strength as the “placebo” group);
- one tested boric acid + iodine powder;
- one tested boric acid in alcohol;
- one tested acetic acid in spirit and glycerin;
- two tested povidone iodine (although [van Hasselt 2002](#) used a single weak dose in a treatment delivery vehicle).

Two trials tested placebo treatments:

- one tested normal saline solution;
- one tested a treatment delivery vehicle with no treatment, hydroxypropyl methyl-cellulose (hypromellose, HPMC).

Most treatments were self-administered two or three times daily, for between seven days and three weeks, usually with ear toilet at least once (by the participant or clinician). However, [Browning 1983a](#) compared daily antibiotics (self-treated) with weekly antiseptics (given by the otologist), both for four weeks. See [Table 4](#) for further exceptions and trial details. One trial included a crossover to the alternative treatment for failures at six months ([Gyde 1978](#)); we have only used results before crossover where possible. Nine

trials reported a treatment-free period before study entry (washout usually 10 days or two weeks), for antibiotics or other specified medicines. See [Table 4](#) for details and exceptions. Two trials also excluded participants who received antibiotics or any other treatment during the study.

Outcomes

The ‘Characteristics of included studies’ table indicates which review outcomes were covered by each trial. [Table 5](#) describes the definitions used by the trials, for each review outcome, and how and when outcomes were measured and reported.

Treatment failure (persistent discharge) - 14 trials:

All trials reported CSOM resolution for inclusion in the primary outcome of this review. However, definitions varied, and four only reported results before two weeks, not at or after two weeks - see [Table 5](#). Where trials reported separate categories for ‘cure’ and ‘improvement’, or ‘active’ and ‘mucoid’, we have classed ‘improvement’ or ‘mucoid’ as failure along with any other cases of failure reported. One trial ([Clayton 1990](#)) only categorised cases as improved or not improved - for this trial, improvement has been classed as success.

Healing of the perforation - one trial:

Numbers with complete healing at two and four weeks are presented for [Macfadyen 2005](#).

Time to resolution of CSOM - no trials:

However, [Gyde 1978](#) reported the mean duration of treatment, for successfully treated ears, but this includes crossed over times.

Improvement in hearing threshold - three trials:

See tables 7 to 11 for [Gyde 1978](#) ([Table 6](#)), [Tutkun 1995](#) ([Table 7](#), [Table 8](#), and [Table 9](#)), and [Macfadyen 2005](#) ([Table 10](#) and results text). [Gyde 1978](#) and [Tutkun 1995](#) also provided a summary statement for ototoxicity (see [Table 11](#)).

Five other trials assessed hearing, but reported no results ([Fradis 1997](#)) or only a summary statement regarding worsening in hearing or ototoxicity (four trials). [Table 11](#) (Safety) provides information regarding worsened hearing, where available.

Time to reappearance of discharge and perforation after its previous resolution - no trials:

However, [Gyde 1978](#) did report relapses.

Adverse events - seven trials:

Results of ototoxicity assessments and other adverse events collected are reported in [Table 11](#) (Safety). One further trial did not report safety in the outcomes, but did report a lack of additional side-effects when adding steroid to treatment, in the discussion ([Kaygusuz 2002](#)).

Other outcomes assessed but not specified in the protocol for this review - 10 trials:

See [Table 5](#) for details of these outcomes, which have not been analysed in this review.

Sources of Support

Pharmaceutical company support:

Three trials ([Gyde 1978](#); [Gyde 1981](#); [Lorente 1995](#)).

Trusts and charities:

Three trials ([Macfadyen 2005](#); [van Hasselt 1997](#); [van Hasselt 1998](#)).

Not mentioned:

Eight trials.

Risk of bias in included studies

[Table 1](#) provides details of the methodological quality of included studies.

Allocation

Six trials were “adequate”: these trials were also double-blind. Eight trials were “unclear”: allocation concealment was not discussed (four trials were described as double blind and one single blind).

Blinding

Ten trials were double-blinded. One trial was single-blinded (except the antiseptic group, which was given by the clinicians, after aural toilet; [Browning 1983a](#)). Three trials did not report on blinding.

Incomplete outcome data

For the primary outcome, resolution or treatment failure up to four weeks:

Five trials were “adequate” (> 90% included):

One trial reported following the intention-to-treat principle for the analyses ([Macfadyen 2005](#)).

One trial was adequate for ears, the unit of analysis (analysed 54/60 = 90%), but slipped to 88% (45/51) for participants ([Fradis 1997](#)).

One trial did not report any loss to follow-up or exclusions ([Kaygusuz 2002](#)).

Five trials were “unclear”:

These trials did not report numbers initially randomised or excluded from the analyses: three gave reasons but not numbers; two did not discuss at all.

Four trials were “inadequate”:

Overall rates for participants or ears analysed per trial were 68% to 75%. However follow-up rates for one trial varied widely between treatment groups (61% to 92%) ([van Hasselt 1997](#)).

Main reasons specified for exclusion were:

Lack of attendance (loss to follow-up) (most trials); participants who did not adhere to study treatment (five trials); participants who received antibiotics or any other treatment during the study (two trials); missing data (one trial); or consent withdrawn (one trial). See [Table 1](#).

Other potential sources of bias

Sequence generation

Two trials were “adequate”: [Gyde 1978](#), [Macfadyen 2005](#).

Twelve trials were “unclear”: described as randomised (five mentioned randomisation codes or coded treatments), but did not discuss how the sequence was generated, or how different diagnoses were accounted for during randomisation.

Balance of baseline characteristics across groups

This was not reported in five trials. The rest reported at least one characteristic by treatment group - see [Table 1](#) for details.

For the five trials that included a range of diagnoses, three reported numbers for each across treatment groups: two of these were mostly balanced (for ears) ([Gyde 1978](#); [Gyde 1981](#)), but one was not ([Clayton 1990](#)) - see [Table 1](#). The other two trials did not report baseline numbers or results for each diagnosis separately by treatment group ([Browning 1983a](#); [Fradis 1997](#)).

Bilateral disease

Trials were inconsistent in handling of bilateral disease, and have analysed and presented results either by ear or by participant. [Table 3](#) provides detailed information regarding bilateral disease, and reporting of ears versus participants, for each trial. Where available the number of participants with bilateral disease for each trial is also presented. Clarification has been requested from the authors for those where the unit of analysis is not clear, and for further information on handling bilateral cases.

Results for ears - six trials:

For bilateral disease each ear was treated and analysed as a separate case. Rates of bilateral disease in these trials, where available, varied widely from 9.9% of analysed participants (4.2% on gentamicin) in [Gyde 1978](#), to 41.1% of all randomised participants in [van Hasselt 1998](#). See [Table 3](#).

Results for participants - six trials:

Only two trials specified how bilateral cases were handled ([Browning 1983a](#) and [Macfadyen 2005](#)) - see [Table 3](#).

Unit of analysis unclear - two trials:

Bilateral disease was also not discussed ([Clayton 1990](#) and [Kasemsuwan 1997](#)).

Where available, we have reported results for number of participants rather than ears; otherwise results for number of ears have been taken. The concern is that a trial analysed by ears rather than number of participants will have an underestimated standard error (SE) and therefore receive an inappropriate increased weight in a meta-analysis. We will use the information in [Table 3](#) to attempt to address the issues of inflated weighting for trials reporting numbers of ears, in a later update of this review.

Effects of interventions

See also tables ([Table 3](#) for details regarding bilateral disease in each trial, [Table 4](#) for details of the treatment regimens used for each of the sets of comparisons discussed below, and [Table 5](#) for the definitions and timings of the outcomes assessed by trialists for each outcome category). Data relating to adverse events and ototoxicity have been summarised in [Table 11](#) for trials that mentioned this outcome. We have only presented outcomes below that the trial authors have reported - see [Table 5](#) for other outcomes. Clarification is being sought from the authors where uncertainties exist in the data and where outcomes are not reported. These responses will be incorporated in subsequent updates of the review. There were insufficient trials in each comparison to consider exploring heterogeneity or the sensitivity analyses outlined above; these will be considered in a subsequent update of the review

if there are sufficient trials. Meanwhile, trials where people with CSOM are only a subgroup of the participants included in the study are identified in this review - see [Table 2](#).

Do Topical Antibiotics Without Steroids Work?

Quinolone versus no treatment

Two trials compared quinolones with placebo; all groups received aural toilet at least once ([Kasemsuwan 1997](#); [van Hasselt 2002](#)). Follow-up in both trials was for one week only; the authors have been contacted to request longer follow-up data, if available. Results for [van Hasselt 2002](#) refer to number of ears, but it is not clear whether the results for [Kasemsuwan 1997](#) refer to ears or participants; further details have been requested.

Treatment failure (persistent discharge)

(Analysis 1.1)

Results were only provided at one week - see figure. The pooled RR is 0.45 (95% CI 0.34 to 0.59). However, there is a large amount of heterogeneity present ($I^2 = 72.5\%$ and χ^2 P value = 0.06), possibly because [Kasemsuwan 1997](#) used daily applications of ciprofloxacin versus saline solution while [van Hasselt 2002](#) used only one single application of ofloxacin in HPMC versus HPMC alone. The random-effects pooled result is 0.34 (95% CI 0.12 to 0.94).

Improvement in hearing threshold

One trial measured audiometry ([Kasemsuwan 1997](#)) before treatment and within 48 hours of completing seven days treatment. Data for these results were not provided but have been requested. The trial report provides a summary statement only '...no worsening of audiometry measurements related to this topical medication was detected in this study'. [van Hasselt 1997](#) did not mention this outcome and a request has been made for any available results.

Adverse Events

Data relating to adverse events have been summarised in [Table 11](#). [van Hasselt 2002](#) did not mention this outcome and a request has been made to the authors for any available results.

Non-quinolone versus no treatment

No trials were identified.

Which Topical Antibiotics (Without Steroids) Work Best?

Comparisons between topical non-quinolone antibiotics without steroids

Two trials compared non-quinolones. [Gyde 1978](#) compared trimethoprim-sulfacetamide-polymyxin B (TSP) with gentamicin, while [Gyde 1981](#) compared TSP with trimethoprim-polymyxin B (TP). [Table 4](#) gives more details of the treatment regimens. Both trials reported results for numbers of ears ([Table 3](#)).

Treatment failure

([Analysis 2.1](#))

Results for [Gyde 1978](#) at six months (before crossover) found no significant difference between TSP and gentamicin: RR was 2.00 (95% CI 0.64 to 6.22). Meanwhile [Gyde 1981](#) at three months showed a significant effect in favour of TSP over TP: RR was 0.29 (95% CI 0.11 to 0.80). However, both trials included participants with a range of diagnoses (see [Table 3](#) and [Table 2](#)), and cure rates varied between diagnoses; the figure shows the results for all participants. No meta-analysis has been undertaken for these trials due to different comparator drugs within the “non-quinolones only” comparison.

Time to resolution of CSOM; and Time to re-appearance of discharge and perforation after its previous resolution

No trials reported these outcomes, but two related outcomes reported by [Gyde 1978](#) were mean duration of treatment (for ears successfully treated only, including pre and post-crossover durations), and occurrence of relapses. The average successful treatment duration (for all diagnoses) was 19.3 days for TSP (range 7 to 32, N = 46), and 21.7 days for gentamicin (range 10 to 37, N = 51). There were no cases of relapse within the six to 12 month follow-up period.

Improvement in hearing threshold

Both trials reported recording this outcome, although [Gyde 1981](#) did not provide results. The results for [Gyde 1978](#) are shown in [Table 6](#). In a summary statement, the authors reported that “the majority of the participants tested showed an improvement of the auditory acuteness, and hearing results remained stable in all cases examined during the 3 to 12 month post-observation period”.

Adverse Events

Data relating to adverse events have been summarised in [Table 11](#).

Quinolone versus non-quinolone antibiotics without steroids

Six trials compared a quinolone antibiotic with a non-quinolone antibiotic, with follow-up at weeks one to three: [Lorente 1995](#) (day eight); [Tutkun 1995](#) (day 11); [Fradis 1997](#) (week three); [Kaygusuz 2002](#) (weeks one, two and three); [van Hasselt 1997](#) (weeks one and two), and [van Hasselt 1998](#) (week two). [van Hasselt 1998](#) also presented results at weeks one and eight (as percentage of ears cured), but did not report numbers analysed per group; this information has been requested from the authors. [van Hasselt 1998](#) had four treatment groups: the non-quinolone antibiotic delivered once weekly or twice daily and the same for the quinolone groups. For this trial we have entered data comparing the once weekly treatment regimens separately to the twice daily treatment regimens. [Table 4](#) indicates the treatment regimens used for each trial. Three trials reported results for ears ([Fradis 1997](#); [van Hasselt 1997](#); [van Hasselt 1998](#)); the other three reported for participants. [Table 3](#) provides further details.

Treatment failure

([Analysis 3.1](#))

The figure shows the results at weeks one, two and three separately, and combined for weeks two to three. No statistically significant difference was found between quinolones and non-quinolones at weeks one or three: RR were, 0.89 (95% CI 0.59 to 1.32) at week one and 0.97 (95% CI 0.54 to 1.72) at week three. However, a difference in favour of quinolones was seen at week two with a pooled RR of 0.65 (95% CI 0.46 to 0.92). Pooling the results for weeks two to three gives a RR of 0.76 (95% CI 0.55 to 1.04).

Results suggest moderate heterogeneity for results at two weeks, and for the overall two to three week results, mainly caused by [Tutkun 1995](#), which received 28% and 26% of the weight for results at two weeks and two to three weeks, respectively. The random-effects analyses are RR 0.64 (95% CI 0.35 to 1.17) for two weeks, and 0.78 (95% CI 0.48 to 1.26) for two to three weeks. Excluding [Tutkun 1995](#) gives pooled estimates detecting no difference between quinolone and non-quinolone antibiotics with a fixed RR of 0.84 (95% CI 0.57 to 1.23) ($I^2 = 0\%$, $\chi^2 P = 0.53$) at two weeks, and overall results at two to three weeks of 0.96 (95% CI 0.68 to 1.35) ($I^2 = 0\%$, $\chi^2 P = 0.90$) (figure not provided).

The two week data for [van Hasselt 1997](#) were discrepant between an internal report (CBM 1997) and a published report in 2002, which summarised the results in an introductory paragraph. The figure shows the results taken from CBM 1997. The results from the paper [van Hasselt 2002](#) are 3/14 (21%) with failure on quinolone (ofloxacin) and 6/35 (17%) with failure on non-quinolone (neomycin-polymyxin B) (RR is 1.25 (95% CI 0.36 to 4.32)). However, the pooled results for failure at two weeks and for two to three weeks do not change: RR is 0.65 (95% CI 0.46 to 0.92) ($I^2 = 58.0\%$, $\chi^2 P = 0.05$) and 0.76 (95% CI 0.55 to 1.04) ($I^2 = 49.7\%$, $\chi^2 P = 0.08$) respectively using the fixed-

effect model; or 0.64 (0.35 to 1.17) at two weeks and 0.78 (0.48 to 1.27) for two to three weeks using the random-effects model. The results when [Tutkun 1995](#) is excluded also remain unchanged (except heterogeneity for two to three weeks pooled results: $I^2 = 0\%$, $\chi^2 P = 0.89$). (Figure not provided for results using [van Hasselt 2002](#) paper.)

Improvement in hearing threshold

Three trials mentioned this outcome. [Fradis 1997](#) measured audiometry before treatment and after treatment but did not provide any results. [Lorente 1995](#) recorded audiometry measurements but only reported in a summary statement that one case (on gentamicin) of slight auditory disorder was detected on audiometry; the trialists considered this loss was only slight and without clinical relevance. A joint analysis of the two treatments was reported to show no statistically significant effects on the audiometry results, but details are not provided. Follow-up on this trial was for eight days only; however, results have been requested for completeness. [Tutkun 1995](#) looked at pre-treatment and post-treatment measurements for pure tone air and bone thresholds, air-bone gaps, speech reception threshold, and speech discrimination scores. These results are presented in tables: [Table 7](#) for pre and post-treatment pure tone thresholds (in dB HL); [Table 8](#) for pre and post-treatment air-bone gaps between 500 and 4000 Hz (in dB HL); and [Table 9](#) for pre and post-treatment speech reception thresholds (SRTs in dB HL) and speech discrimination scores (SDSs). No standard deviations were reported but have been requested. Bone conduction hearing thresholds were slightly elevated after treatment with gentamicin (non-quinolone); however, the authors reported that none of the differences in any of the assessments were significant (student's t-test $P > 0.01$).

Adverse Events

Only [Lorente 1995](#) and [Tutkun 1995](#) mentioned this outcome - data relating to adverse events have been summarised in [Table 11](#).

Comparisons between topical quinolone antibiotics

No trials were identified that compared different topical quinolone antibiotics against one another.

Comparisons between different treatment regimens of the same drug (e.g. method of delivery, or dose or frequency) have not been analysed in this review (e.g. excluded studies [Kiris 1998](#) and [de Miguel 1999](#); or included study, [van Hasselt 1998](#); see other comparisons).

Do Topical Antibiotics Without Steroids Work Better Than Antiseptics?

Non-quinolone versus antiseptic

Four trials compared a non-quinolone with an antiseptic ([van Hasselt 1997](#); [Clayton 1990](#); [Fradis 1997](#); [Browning 1983a](#)). Follow-up was at two, three, three and four weeks, respectively. [van Hasselt 1997](#) also reported results at one week. [Table 4](#) indicates the treatment regimens used by each trial, with potential sources of heterogeneity. [Browning 1983a](#) reported results for participants, while [Fradis 1997](#) and [van Hasselt 1997](#) presented by ears. [Clayton 1990](#) appears to report results for ears, although this is not clear in the paper and clarification has been requested. See [Table 3](#) for more details.

Treatment failure

([Analysis 4.1](#))

The figure shows results at weeks one and two to four ordered by length of follow-up. Note that [Clayton 1990](#) reports a success as an improvement and not a resolution. [Browning 1983a](#); [Clayton 1990](#) and [Fradis 1997](#) included participants with mastoid cavities or surgical perforations, while [Clayton 1990](#) also included otitis externa (see [Table 3](#) and [Table 2](#)). Only [Clayton 1990](#) presented results separately, but the authors did not specify whether the diagnostic groups were stratified for during randomisation; all participants are included in the figure.

Only one trial found a significant effect in favour of non-quinolone antibiotics ([van Hasselt 1997](#) at one and two weeks); [Fradis 1997](#) also found a non-significant result in favour of antibiotic at week three, although the antiseptic was a weak concentration used as a "placebo" group by the trialists. The possibility of any benefit decreased over time, and one trial found a non-significant trend in favour of antiseptics by week four ([Browning 1983a](#)). Results have not been pooled, due to the significant heterogeneity observed in these results, which may be partly explained by the length of follow-up and possibly also diagnostic criteria.

The two week data for [van Hasselt 1997](#) were discrepant between an internal report (CBM 1997) and a published report in 2002, which summarised the results in an introductory paragraph. The figure shows the results taken from CBM 1997. The results from the paper [van Hasselt 2002](#) are 6/35 (17%) with failure on non-quinolone antibiotic, and 35/39 (90%) with failure on antiseptic (RR was 0.19 (95% CI 0.09 to 0.40)). Clarification has been requested from the author.

Improvement in hearing threshold

[Fradis 1997](#) stated measurements were taken but did not provide results; these have been requested. None of the other authors mentioned this outcome and a request has been made for any available results.

Quinolone versus antiseptic

Five trials compared a quinolone antibiotic with an antiseptic (van Hasselt 2002; van Hasselt 1997; Fradis 1997; Jaya 2003; Macfadyen 2005). The longest length of follow-up for each of these trials was one, two, three, four and four weeks respectively. The antiseptic in Fradis 1997 was a weak concentration used as a “placebo” group by the trialists. Table 4 indicates the treatment regimens used by each trial. Jaya 2003 and Macfadyen 2005 report results for participants; the rest report numbers of ears. See Table 3 for more details.

Treatment failure

(Analysis 5.1)

The figure shows the results for week one, and weeks two to four ordered by length of follow-up. van Hasselt 2002 presented at week one only. The results indicate that quinolones are superior to antiseptics, with pooled results at one week of RR 0.52 (95% CI 0.41 to 0.67), and at two to four weeks of 0.58 (95% CI 0.47 to 0.72).

Macfadyen 2005 dominated the results at two to four weeks with 76% of the weight, due to its large size and narrow confidence intervals. Excluding Macfadyen 2005 increases the heterogeneity and confidence intervals with a non-significant effect after accounting for heterogeneity: the pooled results at two to four weeks become RR 0.46 (95% CI 0.28 to 0.75) using the fixed-effect model, but 0.50 (95% CI 0.22 to 1.16) using the random-effects model ($I^2 = 53.3\%$, $\chi^2 P = 0.12$) (figure not provided).

The two week data for van Hasselt 1997 were discrepant between an internal report (CBM 1997) and a published report in 2002, which summarised the results in an introductory paragraph. The figure shows the results taken from CBM 1997. The results from the paper van Hasselt 2002 are 3/14 (21%) with failure on quinolone antibiotic and 35/39 (90%) with failure on antiseptic (RR 0.24 (95% CI 0.09 to 0.65)). If these results are used then the pooled result becomes RR 0.58 (95% CI 0.47 to 0.71) (figure not provided). Clarification has been requested from the author.

Healing of the perforation

(Analysis 5.2)

Only one trial looked at healing of the perforation at two and four weeks (Macfadyen 2005). Results, expressed as RR, are 1.06 (95%CI 0.52 to 2.13) at two weeks, and 1.54 (95%CI 0.91 to 2.61) in favour of ciprofloxacin over boric acid at four weeks.

Improvement in hearing threshold

Three trials reported this outcome. Fradis 1997 and Jaya 2003 measured audiometry before treatment and after treatment but did not provide any results. These have been requested. However

Jaya 2003 provided a summary statement of results: “There is no deterioration of hearing as assessed by pure tone audiometry”.

Macfadyen 2005 showed greater hearing improvement on ciprofloxacin than boric acid at two and four weeks. Hearing threshold was averaged across four frequencies, 0.5, 1, 2 and 4 kHz (for one single reading for diseased ear, or averaged across the two ears in bilateral cases). Results from ANCOVA, controlling for baseline audio level, for the difference in mean improvement are: 2.17 (95%CI 0.09 to 4.24) at two weeks, and 3.43 (95%CI 1.34 to 5.52) in favour of ciprofloxacin at four weeks - see Table 10.

Adverse Events

Only two trials mentioned this outcome: Jaya 2003 (audiometry only) and Macfadyen 2005 - data relating to adverse events (and ototoxicity) have been summarised in Table 11.

DISCUSSION

This review considers alternative topical drug treatments, but does not compare treatment regimens or delivery methods. We also excluded comparisons with steroids (with or without antibiotics; see steroids review) or systemic treatments, and presented results for quinolone and non-quinolone antibiotics separately, to address focused and meaningful questions. These tighter comparisons and the addition of new trials, are why our conclusions differ to those of an earlier review (Acuin 1998). The earlier review included systemic non-quinolones and antibiotic-steroid combinations in this comparison, leading to a stronger effect in favour of topical quinolones than found here; meanwhile only three trials were included in the earlier antibiotic versus antiseptic comparison, one of which used steroids, and no statistically significant difference had been found. The following discusses the findings of this new review.

Topical antibiotics were superior to no drug treatment for curing CSOM at one week, when both groups received aural toilet. However, this was based on two small trials, both using quinolone antibiotics, with no longer-term follow-up.

Only two trials compared different topical non-quinolone antibiotics; no statistically significant difference was detected between trimethoprim-sulfacetamide-polymyxin B (TSP) and gentamicin (for cure rates or level of hearing), although TSP was better than trimethoprim-polymyxin B. However, these results included participants with a range of diagnoses, and rates differed between diagnoses.

Of the trials that compared topical quinolone and non-quinolone antibiotics, only one found an effect in favour of topical quinolones (Tutkun 1995, reporting at day 11); the other trials found no statistically significant difference at one week or up to three weeks,

although Kaygusuz 2002 did show a trend in favour of quinolones at two weeks but numbers were small with wide confidence intervals. Excluding Tutkun 1995 (which received 28% and 26% of the weight for results at two weeks and two to three weeks respectively) from the results for discharge gave pooled estimates detecting no statistically significant difference at any time-point. This trial also assessed hearing but found no significant difference between treatments in the level of hearing improvement at day 11.

When compared to topical antiseptics, topical quinolone antibiotics were more effective at curing CSOM. However, the findings for non-quinolones were more mixed, and any possible benefit decreased over time. Three of these trials included participants with a range of diagnoses, and treatment regimens varied widely. Other possible causes of the heterogeneity may be partly due to the different dropout rates between treatment groups for van Hasselt 1997 (see Table 1 for dropout rates), which was also the only study for the antiseptic comparisons that did not specify any blinding. Meanwhile Browning 1983a compared weekly insufflation of antiseptic after aural toilet by the otologist with daily non-quinolone antibiotics, and followed participants later than the other trials (four weeks). This was the only trial to find a result in favour of antiseptic, although the effect was not statistically significant, with confidence intervals crossing the line of no-effect.

Macfadyen 2005 dominated the quinolone versus antiseptic comparisons at two to four weeks, with 76% of the weight, due to its large size and narrow confidence intervals. Excluding Macfadyen 2005 from the quinolone versus antiseptics comparison increases the heterogeneity and confidence intervals, with a non-significant effect after accounting for heterogeneity. This trial reduced the heterogeneity and consolidated the results (with confidence intervals overlapping all the other trials), to pull the effect significantly in favour of quinolone antibiotics over antiseptics. The lack of heterogeneity in the results for this trial, and its impact on the pooled results, suggests the findings for this trial may be applicable to other settings. Using older dedicated children as 'ear monitors' to treat the participants at school, under teacher supervision, may have helped minimise treatment errors or sharing of the treatment with other members of the household or community. The effectiveness of the treatments may therefore be slightly higher than might be found in practice in resource-poor settings if treatment is to be applied at home. However, the resolution rates were lower than obtained by many trials in higher income settings, and/or in private clinics where treatment is done in the clinic. This may be partly due to better health and other environmental factors in richer settings, but also a reflection of the more pragmatic nature of this study than others, even with the child-to-child treatment approach. These rates are therefore more likely to reflect the actual resolution rates in developing countries than many other trials, and may also be more generalisable to higher-income settings than might be anticipated.

Macfadyen 2005 found low healing rates with both quinolones

antibiotic and antiseptic, although there was a trend towards a benefit of antibiotic over antiseptic by week two. This trial also reported improved hearing in both groups, with a greater improvement on antibiotic than antiseptic.

Antiseptics and non-quinolone antibiotics are often cheaper and more widely available than quinolone eardrops, and the findings presented here may have important implications in resource-poor settings.

Most trials did not report any adverse events. However, those that did discuss safety, supported a good profile for the topical treatments assessed; one trial also reported fewer local effects for quinolone antibiotic than for antiseptic in alcohol (Macfadyen 2005). None of the trials that assessed hearing in this review reported any evidence of ototoxicity; two reported a mild auditory disorder (Lorente 1995, one case) or increase in bone conduction thresholds (Tutkun 1995) after treatment with gentamicin (an aminoglycoside, non-quinolone, antibiotic), but stated that the hearing losses were not clinically (Lorente 1995) or statistically (Tutkun 1995) significant. However, ototoxicity has been observed for various non-quinolone antibiotics, and aminoglycoside antibiotics are not recommended in patients with a tympanic membrane perforation by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK (CSM 1997). One review of ototoxicity cases in humans reported that ototoxicity may be primarily due to vestibular damage (causing imbalance and dizziness) rather than cochlear (Marais 1998), so assessments of hearing thresholds for bone conduction alone would be unlikely to detect many cases (Marais 1998; Lancaster 1999).

The follow-up period in most trials included here was short, with few assessing the longer-term effects of treatment, and none reported time to resolution or to reappearance of discharge and perforation. As some conclusions changed over time, it may be important to investigate the longer-term effects in future trials.

Most of the trials in this review were poor quality, with short follow-up. Many included a range of participants (e.g. including otitis externa, or draining mastoid cavities; while some did not specify cholesteatomatous disease as an exclusion criterion). This may explain some of the heterogeneity found, since resolution rates may vary widely between diagnoses, and so make the results less applicable to any one type of disease. Trials were also inconsistent in approaches for handling and reporting bilateral disease. Where available, we have reported results for number of participants rather than ears; otherwise results for number of ears have been taken. The concern is that a trial analysed by ears rather than number of participants will have an underestimated standard error and therefore receive an inappropriate increased weight in a meta-analysis. We will use the information obtained to attempt to address the issues of inflated weighting for trials reporting numbers of ears, in a later update of this review.

AUTHORS' CONCLUSIONS

Implications for practice

Short courses of topical quinolone antibiotics are more effective than no drug treatment or topical antiseptics for the short-term resolution of otorrhoea from uncomplicated CSOM. The effects of non-quinolone antibiotics without steroids are less clear, when compared to antiseptics; studies were also inconclusive regarding any differences between quinolones and non-quinolones, although indirect comparisons suggest a benefit of topical quinolones cannot be ruled out. Less is known about longer-term outcomes (for dry ear, or to prevent complications, heal the eardrum, and improve hearing), or about treating complicated CSOM. Evidence regarding safety is also weak, and more research is needed to clarify the risk of ototoxicity with alternative topical treatments (about which there is much concern, particularly for aminoglycosides), and whether there may be fewer adverse events with topical quinolones. Treatment should therefore be accompanied by regular medical follow-up and clinical vigilance, also monitoring for adverse effects of treatment (particularly for local effects or signs of ototoxicity), or for complications of the disease. Clinical staff should also advise patients and their caregivers on appropriate ear care, with aural toilet and effective instillation of the drops, ensuring the drops reach the site of infection to work effectively.

Implications for research

Further trials should clarify the effects of non-quinolone antibiotics and what is the most appropriate topical treatment for CSOM. Adequately designed and powered clinical trials should focus on the effects on the longer-term natural history of CSOM, such as healing of the tympanic membrane, hearing improvement, prevention of complications, and also on further safety assessments. Other more comprehensive systematic reviews should also assess safety further, particularly to verify the risks of ototoxicity for alternative treatments. Trialists should also consider how they handle bilateral disease and also the type of participants included (or stratify randomisation by diagnosis if various diagnoses are included), to ensure the results are clinically relevant to a particular patient group. The cost effectiveness of alternative 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]

Browning 1983a

Methods	RCT	
Participants	See Table 03 75 adults over 16 years old, with active chronic otitis media randomised; 51 analysed 19/51 (37%) analysed participants had previously undergone modified radical mastoidectomy - results were not presented separately, so included in this review 38/51 analysed participants included in this review (receiving topical antibiotics or antiseptics); 13/51 receiving systemic antibiotics are not discussed here	
Interventions	See Table 04 1) Topical non-quinolone antibiotic eardrops: chloramphenicol or gentamicin, 3 or 4 times daily, respectively 2) Weekly insufflation of topical antiseptics (boric acid and iodine powder) after aural toilet * Other comparison not included in this review (n = 13/51 analysed participants) 3) Systemic non-quinolone antibiotics: oral cephalexin, flucloxacillin, cloxacillin or amoxicillin, 1 to 2g/day. * Duration (all treatments): 4 weeks. Aural toilet (all groups; confirmed by trial authors): weekly aural toilet by otologist, using microscopic vision and suction aspiration when necessary Participants with Pseudomonas species were randomised to topical antibiotic or antiseptics only (groups 1 or 2) Choice of antibiotics depended on sensitivity of bacteria isolated at baseline	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks)	
Notes	Setting: Secondary referrals at Department of Otolaryngology, Glasgow Royal Infirmary Location: Glasgow, UK. Trial in other CSOM reviews: systemic versus topical treatments	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Clayton 1990

Methods	RCT	
Participants	See Table 03 139 randomised ears (20 CSOM); 102 ears (15 CSOM) analysed. Participants with otorrhoea caused by otitis externa and mastoid cavities were also included in the trial. Randomisation was not described as stratified by diagnosis, so all cases are included in this review (although results were presented separately in the trial publication)	
Interventions	See Table 04 1) Topical non-quinolone antibiotic eardrops: gentamicin sulphate 0.3% 2) Topical antiseptic eardrops: Aluminium acetate 8% Both treatments: 3 times daily after self mopping, for 3 weeks	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks) NB: Trial reported improved or not improved only; numbers with complete cure were not reported Excluded participants who failed to attend clinics or failed to comply with treatment * Outcomes not included in this review were also assessed - see table 05 *	
Notes	Setting: ENT Department, Bradford Royal Infirmary. Location: UK.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Fradis 1997

Methods	RCT	
Participants	See Table 03 51 participants (aged 18 to 73), contributing 60 ears with purulent disease were randomised; 54 ears analysed. 3 ears had surgical perforations and no perforation could be seen in 8 ears due to granulation tissue - not analysed separately	
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: ciprofloxacin hydrochloride 2) Topical non-quinolone antibiotic eardrops: tobramycin 3) Topical antiseptic eardrops: 1% Burow aluminium acetate solution (weak antiseptic, as designated "placebo" by the trialists) All treatments: 3 times daily, for 3 weeks.	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks)	

Fradis 1997 (Continued)

	** 2) Improvement in hearing threshold ** * Outcomes not included in this review were also assessed - see table 05 *	
Notes	Setting: outpatient clinic of the otolaryngology department of a university teaching hospital Location: Haifa, Israel. Study time-period: 01 January 1994 - 01 December 1995.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gyde 1978

Methods	<p>RCT</p> <p>Individually randomised by Taves' minimisation method.</p> <p>Crossover design - failures at 6 months were crossed over to the alternative treatment and reassessed 6 months later</p>
Participants	<p>See Table 03</p> <p>91 analysed participants (all ages above 2 months) with otorrhoea, contributing 100 ears (CSOM 50 ears)</p> <p>11 participants (12 ears; 7 CSOM ears) then crossed over to the alternative treatment.</p> <p>Unless otherwise indicated, only numbers before crossover have been used for this review</p> <p>Participants with otorrhoea from post-operative or mastoid cavity infections, subacute otitis media, and otitis externa were also included in the trial. Type of infection was the principal criteria for randomisation (minimisation), but it is unclear whether this relates to diagnosis (balanced across treatments) or bacteriology, so all cases are included in this review (although results were presented separately in the trial publication)</p>
Interventions	<p>See Table 04</p> <p>1) Topical non-quinolone antibiotic eardrops: 0.1% trimethoprim-sulfacetamide-polymyxin B (TSP)</p> <p>2) Topical non-quinolone antibiotic eardrops: 0.3% gentamicin (Garamycin)</p> <p>Both treatments: twice daily with suction and mopping. Pneumatic otoscope sometimes used to instil the drops</p> <p>Duration: up to 3 weeks plus 3 more weeks if required. Failed ears or not dry at 6 months crossed over to the other treatment for 3 weeks; follow-up for 6 months as before</p>
Outcomes	<p>See Table 05</p> <p>Review outcomes assessed:</p> <p>1) CSOM resolution/failure (persistent discharge after 4 weeks)</p> <p>Results were at 6 months.</p> <p>Negative bacterial culture included in the definition of cure</p> <p>2) Improvement in hearing threshold</p> <p>3) Adverse events (including assessment of ototoxicity)</p> <p>Information relevant to the following were also reported:</p> <p>4) Time to resolution of CSOM</p> <p>5) Time to reappearance of discharge and perforation</p>

Gyde 1978 (Continued)

	* Outcomes not included in this review were also assessed - see table 05 *	
Notes	Setting: outpatient visit - appears to be a private clinic. Location: Winnipeg, Manitoba, Canada. Source of support: study conducted in conjunction with Burroughs Wellcome Ltd (manufacturer of TSP and collected details of Adverse Events) Article in French.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gyde 1981

Methods	RCT
Participants	See Table 03 60 eligible participants (all ages) with otorrhoea, contributing 68 ears were analysed (CSOM 27/68 ears) Participants with otorrhoea from post-operative or mastoid cavity infections, subacute otitis media, and otitis externa were also included in the trial. Randomisation was not described as stratified by diagnosis, so all cases are included in this review (although results were presented separately in the trial publication)
Interventions	See Table 04 1) Topical non-quinolone antibiotic eardrops: trimethoprim-polymyxin B-sulfacetamide (TSP) 2) Topical non-quinolone antibiotic eardrops: trimethoprim-polymyxin B (TP) Both treatments: twice daily with suction and mopping. Pneumatic otoscope sometimes used to instil the drops Duration: up to 14 days depending on response.
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge after 4 weeks) Results were at 3 months. Negative bacterial culture included in the definition of cure ** 2) Improvement in hearing threshold ** (Reported negative statement for no ototoxicity only) 3) Adverse events (including assessment of ototoxicity) * Outcomes not included in this review were also assessed - see table 05 *
Notes	Setting and location: not reported (appears to be a private clinic in Winnipeg, Canada) Conducted: October 1978 - March 1979. Sources of support: Burroughs Wellcome Ltd assisted in the compilation and statistical analysis of the data
Risk of bias	

Gyde 1981 (Continued)

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

Jaya 2003

Methods	RCT
Participants	See Table 03 40 randomised participants (over 10 years old), with actively discharging CSOM-tubotympanic disease; 36 assessed at week 4
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: 0.3% ciprofloxacin hydrochloride 2) Topical antiseptic eardrops: 5% Povidone-iodine (PVP-I, Betadine) Both treatments: 3 times daily, after dry-mopping, for 10 days Suction cleaning (both groups): before initial treatment for all participants; at weekly visits if discharge present
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks) ** 2) Improvement in hearing threshold ** (Reported negative statement for no ototoxicity only) 3) Adverse events (including assessment of ototoxicity) * Outcomes not included in this review were also assessed - see table 05 *
Notes	Setting: Academic tertiary medical centre - otolaryngology outpatient department Location: Vellore, India. Study time period: March - November 2000.

Risk of bias

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

Kasemsuwan 1997

Methods	RCT
Participants	See Table 03 50 adult participants randomised (aged 21 to 66), with perforated tympanic membranes (> 3 months) and mucopurulent otorrhoea; 35 were analysed

Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: ciprofloxacin (250 micrograms/mL) 2) Topical placebo eardrops: saline Both treatments: 3 times daily for at least 7 days, with ear cleaning at each visit (days 1, 4 and 7)	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge) Follow-up only reported to Day 7. ** 2) Improvement in hearing threshold ** (Reported negative statement for no ototoxicity only) 3) Adverse events (including assessment of ototoxicity) * Outcomes not included in this review were also assessed - see table 05 *	
Notes	Setting: Otolaryngology outpatient clinic at Ramathibodi Hospital Location: Bangkok, Thailand. Time period: October 1993 - December 1993.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kaygusuz 2002

Methods	RCT	
Participants	See Table 03 80 adults included (aged 18 to 60) contributing 103 ears with CSOM (perforated eardrum and discharge for over 3 months) 40/80 analysed participants included in this review (receiving topical antibiotics without steroids); 40/80 receiving topical antibiotics + steroids are not discussed here	
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: ciprofloxacin 0.3% 2) Topical non-quinolone antibiotic eardrops: tobramycin 0.3% * Other comparisons not included in this review (n = 40/80 participants)* *3) Topical quinolone antibiotic plus steroid eardrops: ciprofloxacin plus dexamethasone* *4) Topical non-quinolone antibiotic plus steroid eardrops: tobramycin plus dexamethasone* All treatments: 2 drops 3 times daily, with aspiration once daily, for 3 weeks	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks) Also reported results at Day 7. * Outcomes not included in this review were also assessed - see table 05 *	

Kaygusuz 2002 (Continued)

Notes	Setting: University hospital, outpatient clinic. Location: Firat University, Elazig, Turkey. Time period: 2000-2001. Article in Turkish. Trial in other CSOM reviews: steroids.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lorente 1995

Methods	RCT	
Participants	See Table 03 308 analysed adult participants (aged 18 to 65 years) with simple CSOM	
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: 0.3% ciprofloxacin 2) Topical non-quinolone antibiotic eardrops: 0.3% gentamicin Both treatments: 3 times daily for 8 days.	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge) Follow-up only reported to Day 8 ** 2) Improvement in hearing threshold ** (Reported negative statement for no ototoxicity only) 3) Adverse events (including assessment of ototoxicity) * Outcomes not included in this review were also assessed - see table 05 *	
Notes	Setting: Multicenter outpatient trial. Location: Barcelona, Spain. Sources of support: conducted with Laboratorios SALVAT, SA, Barcelona (manufacturer of ciprofloxacin 0.3% drops) Article in Spanish.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Macfadyen 2005

Methods	RCT	
Participants	See Table 03 427 randomised schoolchildren (at least 5 years old, but range was 4 to 19) with CSOM; 394 participants analysed for resolution at 4 weeks.	
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: ciprofloxacin hydrochloride (0.3%) 2) Topical antiseptic eardrops: 2% boric acid in 45% alcohol Both treatments: Child-to-child treatment twice daily with dry mopping for 10 schooldays (not weekends). Dry mop only for weeks 2 to 4 if discharge persists	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks) 2) Healing of the tympanic membrane 3) Improvement in hearing threshold 4) Adverse events Results were given for weeks 2 and 4. All analyses followed the intention-to-treat principle.	
Notes	Setting and location: 165 rural primary schools, Kisumu District, West Kenya Study time period: May to August 2002 school term. Sources of support: Wellcome Trust funded (but no role in any stage from design to submission for publication)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Tutkun 1995

Methods	RCT	
Participants	See Table 03 44 participants (at least 9 years old) with purulent chronic otorrhoea analysed for primary outcome 4 participants with normal flora at baseline (all ciprofloxacin) were excluded from the hearing analyses	
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: ciprofloxacin hydrochloride, 200 micrograms/mL 2) Topical non-quinolone antibiotic eardrops: gentamicin sulfate, 5mg/mL Both treatments: 3 times daily for 10 days.	
Outcomes	See Table 05 Review outcomes assessed:	

Tutkun 1995 (Continued)

	1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks). Result was for Day 11 Negative bacterial culture included in the definition of cure 3) Improvement in hearing threshold 4) Adverse events * Outcomes not included in this review were also assessed - see table 05 *	
Notes	Setting: Marmara University Hospital ENT and audiology departments Location, Istanbul, Turkey. Dates: Nov 1993 to June 1994 (Nov 1993 to March 1994 for Ozagar 1997)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Hasselt 1997

Methods	RCT	
Participants	See Table 03 96 children with CSOM randomised; 93 ears in 69 children analysed	
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: 0.3% ofloxacin 2) Topical non-quinolone antibiotic eardrops: 0.5% neomycin - 0.1% polymyxin-B 3) Topical antiseptic eardrops: 2% acetic acid in 25% spirit and 30% glycerin All groups: 3 times daily for 2 weeks; suction cleaning at weeks 0, 1 and 2 visits	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks) Also reported for 1 week. Discrepancies for results at week 2 existed between the 1997 CBM report (see graphs and results text) and 2002 paper (see results text)	
Notes	Location: Rural Nkota Kota District, Malawi. Sources of support: conducted for Christian Blind Mission.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Hasselt 1998

Methods	RCT	
Participants	See Table 03 Randomised 107 participants (mainly children) with 151 active ears (>2 months CSOM); analysed 138 ears at week 2	
Interventions	See Table 04 2 antibiotics, each with 2 alternative administration regimens, were compared: 1) Topical quinolone antibiotic eardrops, 0.3% ofloxacin: 1a) twice daily 1b) once weekly 2) Topical non-quinolone antibiotic eardrops, neomycin/polymyxin B: 2a) twice daily 2b) once weekly All treatments for 2 weeks with suction cleaning once weekly	
Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge at 2 to 4 weeks) Results at weeks 1, 2 and 8. * Outcomes not included in this review were also assessed - see table 05 *	
Notes	Setting: Community-based. Location: Rural area in Nkota Kota District, Malawi Sources of support: conducted for Christian Blind Mission	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Hasselt 2002

Methods	RCT	
Participants	See Table 03 253 analysed ears with CSOM.	
Interventions	See Table 04 1) Topical quinolone antibiotic eardrops: 0.075% ofloxacin in 1.5% HPMC 2) Topical antiseptic eardrops: 1% povidone iodine in 1.5% HPMC 3) 1.5% HPMC All treatments: Single application after suction cleaning. HPMC (hydroxypropyl methyl-cellulose, hypromellose): delivery vehicle providing prolonged contact with the middle ear mucosa and sustained release of antibiotic or antiseptic	

van Hasselt 2002 (Continued)

Outcomes	See Table 05 Review outcomes assessed: 1) CSOM resolution/failure (persistent discharge) Follow-up was for 1 week only.	
Notes	Setting: Pilot study in rural Malawi. Location: Malawi.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

VH 1998 daily

Methods	Dummy variable created for van Hasselt 1998 (comparisons tables/graphs)	
Participants		
Interventions		
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

VH 1998 weekly

Methods	Dummy variable created for van Hasselt 1998 (comparisons tables/graphs)	
Participants		
Interventions		
Outcomes		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Allocation concealment?	Unclear risk	D - Not used
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* Not included under any treatments/outcomes specified for this review *

** Measured but not reported results **

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adler 2000	PARTICIPANTS Participants had acute otitis media with effusion, with no perforation of the tympanic membrane. INTERVENTION No participants received topical treatment (systemic antibiotics only)
Akisada 1997	INTERVENTION No participants received topical treatment (oral antibiotics only)
Anon 1970a	ALLOCATION (Trial 1 of 2 reported in the paper): Included participants with chronic otorrhoea, but was not a randomised controlled trial (no comparator group)
Anon 1970b	PARTICIPANTS (Trial 2 of 2 reported in the paper): Randomised controlled trial for participants with acute otitis media only
Arguedas 1994	ALLOCATION Participants were not randomised. INTERVENTION No topical antimicrobial treatments were used (systemic antibiotics only)
Aslan 1998	ALLOCATION Participants were divided into two groups, but allocation not described as randomised
Baba 1982a	ALLOCATION Not a randomised controlled trial (no comparator group). INTERVENTION No participants received topical treatment (intravenous antibiotics only)
Baba 1982b	INTERVENTION No participants received topical treatment (oral antibiotics only)
Baba 1984	INTERVENTION No participants received topical treatment (systemic treatments only)

(Continued)

Baba 1995	INTERVENTION No participants received topical treatment (oral treatments only)
Blekher 1967	ALLOCATION No mention of how the decision was taken to assign individual participants to different treatment groups
Block 2000	PARTICIPANTS Participants had acute otitis media for one week or less, without tympanic membrane perforation. INTERVENTION No participants were allocated topical antibiotics (systemic antibiotics only)
Brook 2001	PARTICIPANTS Participants suffered from recurrent otitis media, not chronic suppurative otitis media. INTERVENTION Participants received oral antibiotics or no treatment - no participants were allocated topical antibiotics
Browning 1983b	ALLOCATION Participants were not described as randomised. INTERVENTION No topical treatments were allocated (systemic antibiotics only)
Browning 1984	ALLOCATION Editorial; not a randomised controlled trial.
Browning 1988	(INTERVENTION) For steroids review (topical gentamicin-hydrocortisone + steroid versus placebo)
Chaput 1982	PARTICIPANTS Participants had acute otitis media, not chronic suppurative otitis media. INTERVENTION No participants were allocated topical antibiotic treatment (systemic antibiotics only)
Coates 2002	This is an editorial, not a randomised controlled trial.
Coates 2003	ALLOCATION Not a randomised controlled trial - paper discusses 2 studies; 1 randomised controlled trial (Couzos 2003, for Steroids review) and a controlled clinical trial
Colletti 1983	ALLOCATION Not a randomised controlled trial - no comparator group. INTERVENTION All participants received intramuscular ribostamycin - no topical treatment group
Connolly 1997	(INTERVENTION) For review on delivery methods (compares alternative delivery methods of topical neomycin sulphate + dexamethasone (Otomize): drops versus spray)

(Continued)

Cooke 1974	INTERVENTION No participants were allocated topical treatment (given ear toilet with or without systemic (oral) antibiotics only)
Couzos 2003	(INTERVENTION) For steroids review (topical ciprofloxacin versus topical framycetin, gramicidin and dexamethasone (Sofradex))
Cronin 1974	ALLOCATION Participants were not described as randomised.
Crowther 1991	(INTERVENTION) For steroids review (topical antibiotic-steroid, gentamicin-hydrocortisone versus topical steroid, betamethasone)
Damoiseaux 2004	This is a letter regarding treatment of acute otitis media, not a randomised controlled trial for CSOM treatment
de Miguel 1999	(INTERVENTION) For other CSOM reviews: systemic versus topical treatments, and steroids (compares systemic quinolone versus systemic + topical quinolone versus topical quinolone alone (2 doses) versus non-quinolone + steroid drops. Does not compare 2 alternative topical antibiotics without steroids)
Deguchi 1985	ALLOCATION 'Double blind study' described in part of this paper does not appear to be a randomised controlled trial
Deguchi 1986	ALLOCATION Not a randomised controlled trial - five references described within the paper, one of which is apparently a double-blind test, but further information not available
Deguchi 1992	Review of several MIC studies, one of which is a phase III double-blind study, but reference not provided to confirm eligibility
Di Brino 1967	INTERVENTION No participants were allocated topical treatments (oral antibiotics only)
Eason 1986	(INTERVENTION) For other reviews instead: aural toilet, antiseptics, and steroids (comparisons are: no treatment; aural toilet alone; aural toilet + topical boric acid; aural toilet + topical Sofradex (antibiotic+steroid); aural toilet + topical Sofradex + oral clindamycin antibiotic)
Esposito 1990	(INTERVENTION) For systemic versus topical treatments review (comparisons: oral ciprofloxacin (quinolone) versus oral + topical ciprofloxacin, versus topical ciprofloxacin)
Esposito 1992	(INTERVENTION) For systemic versus topical treatments review (comparisons: intramuscular gentamicin sulfate (non-quinolone antibiotic) versus topical ciprofloxacin (quinolone))

(Continued)

Federspil 1969	ALLOCATION Not a randomised controlled trial - topical or systemic gentamicin administered to a series of unselected participants, with choice of allocation usually based on in vitro sensitivity tests
Fliss 1990	INTERVENTION No participants received topical antimicrobial agents (allocated 1 of 2 different systemic antibiotics or no treatment)
Fontanel 1998	ALLOCATION Not a randomised controlled trial.
Foshee 1992	PARTICIPANTS Two trials reported in this one article. In both trials, participants had acute otitis media with effusion, not chronic suppurative otitis media. INTERVENTION Participants were not allocated topical antibiotics in either trial (oral antibiotics only)
Garcia-Rodriguez 93a	ALLOCATION Participants divided into two treatment groups (0.2% or 0.5% ciprofloxacin drops) but allocation was not described as randomised
Garcia-Rodriguez 93b	ALLOCATION Participants divided into three treatment groups (oral and/or topical ciprofloxacin) but allocation was not described as randomised. INTERVENTION Only 1 group received topical antibiotic without systemic treatment
Gasmanne 1972	(INTERVENTION) For systemic antibiotics review? Comparisons were oral Bactrim or Ledermycin - no topical treatment group
Ghosh 2001	This is a review of studies assessing oral antibiotics vs placebo for acute otitis media, not a trial for CSOM
Gyde 1982	(INTERVENTION) For steroids review (comparisons: topical non-quinolone antibiotic (gentamicin) versus topical non-quinolone antibiotic + steroid (colistin, neomycin + hydrocortisone))
Halsted 1967	PARTICIPANTS Participants had acute otitis media, without a ruptured tympanic membrane, not chronic suppurative otitis media. INTERVENTION No participants were allocated topical treatment (oral antibiotics or placebo only)
Howard 1976	PARTICIPANTS Participants had acute otitis media, not chronic suppurative otitis media. INTERVENTION No participants were allocated topical treatment (systemic antibiotics only)

(Continued)

Howie 1971	PARTICIPANTS Participants had recurrent acute otitis media with presence of middle ear fluid. INTERVENTION No participants were allocated topical antibiotics (oral only)
Howie 1974	PARTICIPANTS Participants had acute otitis media with the presence of middle ear fluid. INTERVENTION No participants were allocated topical antibiotics (oral only)
Howie 1985	PARTICIPANTS Participants had acute or recurrent acute otitis media. INTERVENTION No participants were allocated topical treatment (systemic antibiotics only)
Indudharan 1997	(INTERVENTION) For Steroids review: comparisons were topical gentamicin (antibiotic) versus gentamicin-betamethasone (antibiotic-steroid) drops
Jang 2004	ALLOCATION Participants received topical vancomycin or gentamicin drops but allocation was not described as randomised
John 1983	PARTICIPANTS Participants were not described to have chronic suppurative otitis media. INTERVENTION Participants were randomised to oral antibiotic syrups; no participants received topical antibiotics
Johnston 2003	(INTERVENTION) (Unpublished trial) For steroids review - comparisons are: non-quinolone antibiotic + steroid (Otomize TM spray; dexamethasone 0.1%, neomycin sulphate 3250 units/ml), with antiseptic (glacial acetic acid 2%) versus antiseptic (Earcalm TM Spray; glacial acetic acid 2%)
Kaga 1997	INTERVENTION No participants were allocated topical treatments (oral antibiotics only)
Kantawala 1976	ALLOCATION Treatment allocation not described as random (cases were selected at random, but unclear how control group was selected). INTERVENTION Trial tests a mucolytic agent, Acetylcysteine; no comparisons with topical antibiotics or topical versus systemic treatment
Karabaev 1997	INTERVENTION All participants received oral antioxidants - no topical treatment or comparator drug

(Continued)

Kashiwamura 2004	ALLOCATION Not a randomised controlled trial - no comparator group. INTERVENTION No antibiotic group (topical antiseptic only).
Kawamura 1985	INTERVENTION No participants were allocated topical treatments (oral antibiotics only)
Khanna 2000	ALLOCATION Quasi-randomised trial. INTERVENTION No topical eardrops were prescribed except in participants with fungal infections
Kilcoyne 1973	ALLOCATION Not a randomised controlled trial - no comparator treatment group (topical gentamicin hydrocortisone only)
Kiris 1998	INTERVENTION Method of treatment delivery and aspiration daily or once only are compared, and not the actual treatment: daily topical ciprofloxacin following aspiration administered by clinic personnel at the clinic, versus topical quinolone self-administered at home after the first treatment with aspiration at the clinic only
Kriukov 1996	Study 1 of 2: ALLOCATION Not described as a randomised controlled trial - oral rovamycin compared to normal standard treatment Study 2 of 2: ALLOCATION Treatment allocation not described as randomised. INTERVENTION Bacterial study of oral amoxyclav compared to alternative oral treatments for a range of inflammatory ENT infections
Lancaster 1999	ALLOCATION Not a randomised controlled trial (all participants received topical gentamicin with comparisons made between their diseased and non-diseased ears before and after treatment)
Lancaster 2003	ALLOCATION Participants received antibiotic drops or spray, but treatment allocation was not described as randomised
Legent 1994	INTERVENTION No participants were allocated topical treatments (oral antibiotics only)
Leiberman 1989	(INTERVENTION) For systemic antibiotics review - participants were randomised to intravenous Mezlocillin or Cefazidime; no topical antimicrobials were used during the study

(Continued)

Lildholdt 1986	INTERVENTION For surgery review. No participants were allocated topical treatments (systemic antibiotics versus no drug treatment)
Linder 1997	Comment on two trials (one on otitis media with effusion, and Smith 1996 trial); not a randomised controlled trial itself
Mendonca 1969	ALLOCATION Not a randomised controlled trial - no comparator treatment group (topical gentamicin only)
Merifield 1993	ALLOCATION Participants were categorised into treatment groups, but not described as randomised. PARTICIPANTS Participants had tympanostomy tubes accompanied by chronic suppurative otitis media
Mesure 1973	(INTERVENTION) For systemic antibiotics review - participants were randomised to systemic Bactrim or demethylchlortetracycline; no topical treatment groups
Mira 1992	(INTERVENTION) For systemic versus topical treatments review (comparisons: intramuscular ceftizoxime (non-quinolone antibiotic) + topical saline versus intramuscular + topical ceftizoxime)
Miro 2000	(INTERVENTION) For steroids review (comparisons: topical quinolone, ciprofloxacin, versus topical non-quinolone antibiotic and steroid, polymyxin B, neomycin and hydrocortisone)
Miskovska 2004	PARTICIPANTS Participants had acute otitis media, not CSOM. INTERVENTION No topical treatment group; participants received systemic penicillin, surgery, or both
Moreno Martínez 1988	PARTICIPANTS Participants treated for a range of ENT infections, including otitis media with fever, not CSOM. INTERVENTION No topical treatment groups (systemic only).
Occhiuzzi 1972	INTERVENTION For systemic antibiotics review? Both groups of participants received intramuscular treatment (no topical treatment groups)
Ott 2001	(ALLOCATION) Not a randomised controlled trial (tutorial).
Papastavros 1989	(INTERVENTION) For systemic versus topical treatments review - participants received systemic antibiotic or topical antiseptic; no participants were allocated topical antibiotics

(Continued)

Picozzi 1983	(INTERVENTION) For steroids review (comparisons: topical non-quinolone antibiotic + steroid, gentamicin + hydrocortisone versus placebo; aural toilet both groups)
Picozzi 1984	(INTERVENTION) For steroids review (comparisons: topical non-quinolone antibiotic + steroid, gentamicin + hydrocortisone, versus topical gentamicin + hydrocortisone + systemic non-quinolone antibiotic, metronidazole; aural toilet both groups)
Povedano 1995	(INTERVENTION) For systemic versus topical treatments review - comparisons are: systemic versus topical quinolone, ciprofloxacin
Pugliese 1972	PARTICIPANTS Participants had acute otitis media. INTERVENTION No participants were allocated topical treatment (oral antibiotics only)
Quick 1975	PARTICIPANTS Participants suffered from a range of ENT disorders including acute otitis media, but none described to have chronic suppurative otitis media. INTERVENTION No participants were allocated topical treatments (systemic antibiotics only)
Rostein 1978	INTERVENTION No topical treatment group - all participants received oral sulfamethoxazol-trimethoprim
Roy 2003	(INTERVENTION) (Unpublished trial) For steroids review - comparisons are topical quinolone, ciprofloxacin ear drops, versus topical non-quinolone + steroid, Gentisone HC (hydrocortisone) ear drops
Salzberg 1972	ALLOCATION Not described as randomised. PARTICIPANTS Includes a range of upper respiratory tract infections, not specific to CSOM. INTERVENTION No participants were allocated topical treatments (oral antibiotics only)
Sambe 1977	INTERVENTION For systemic antibiotics review? Participants were allocated systemic Pipdemic acid or Aminobenzyl penicillin; no topical treatment groups
Schaad 1986	INTERVENTION No topical treatment group - participants were allocated oral bacterial lysate or placebo
Schechkin 1978	ALLOCATION Not a randomised controlled trial (no comparator group).

(Continued)

Shah 2000	Not a randomised controlled trial - analyses of bacteriology and drug sensitivity only; no treatment arm or effectiveness analyses of participants
Shenderey 1985	PARTICIPANTS Participants suffered from acute respiratory tract infections, including otitis media; none described to have chronic suppurative otitis media. INTERVENTION No participants were allocated topical treatments (oral antibiotics only)
Smith 1996	(INTERVENTION) For steroids review? (Comparisons: dry mopping alone; versus dry mopping plus topical non-quinolone antibiotic + steroid, framycetin, gramicidin + dexamethasone (Sofradex) plus systemic non-quinolone antibiotic, oral amoxicillin; versus no specific treatment)
Somekh 2000	INTERVENTION No participants were allocated topical antibiotics (both groups received intravenous antibiotics)
Steichenberg 1976	PARTICIPANTS Participants had acute otitis media, not chronic otitis media. INTERVENTION No participants were allocated topical treatments (systemic antibiotics only)
Sugiyama 1981	ALLOCATION Participants were divided into two groups (receiving oral or topical antibiotic), but not described as randomised. INTERVENTION Only one group received topical antibiotic without systemic treatment
Supiyaphun 1995	ALLOCATION Not a randomised controlled trial. INTERVENTION All participants received topical 0.3% ofloxacin, with no comparator group
Supiyaphun 2000	(INTERVENTION) For systemic versus topical treatments review (comparisons systemic + topical non-quinolone antibiotics, amoxicillin + chloramphenicol, versus topical quinolone, ofloxacin)
Tachibana 1986	INTERVENTION No participants were allocated topical treatment (administered intravenously in both groups)
Tong 1996	(INTERVENTION) For steroid review (comparisons: topical quinolone, ofloxacin, versus topical non-quinolone antibiotic + steroid, neomycin-polymyxin B-hydrocortisone drops)
Tong 2002	(Intervention) For surgery review - results before surgery were not provided

(Continued)

Van de Heyning 1988	ALLOCATION Not a randomised controlled trial. INTERVENTION All participants received oral ciprofloxacin, with no comparison group
Verhoeff 2003	INTERVENTION No topical treatment group (comparisons were systemic antibiotic versus placebo)
Wilde 1995	INTERVENTION Mode of delivery of treatment under investigation, not actual treatment (regular antibiotic-steroid ointment (Tri-Adcortyl) dressing versus Tri-Adcortyl ointment instilled into the ear once only)
Willis 1979	PARTICIPANTS The trial described within this discussion paper is for colorectal and bowel surgery, not otitis media
Yuen 1994	(INTERVENTION) For systemic versus topical treatments review (comparisons: systemic non-quinolone antibiotic, amoxicillin-clavulanic acid, versus topical quinolone, ofloxacin)
Zbären 1983	INTERVENTION Only systemic antibiotics were given; no topical treatment group

DATA AND ANALYSES

Comparison 1. Topical antibiotics versus no drug treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent discharge at 1 week	2	197	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.34, 0.59]
1.1 Quinolone versus no drug treatment (ear toilet both groups)	2	197	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.34, 0.59]

Comparison 2. Topical non-quinolones: trimethoprim-sulfacetamide-polymyxin B (TSP) versus other non-quinolone antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent discharge	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Topical TSP versus topical trimethoprim-polymyxin B (TP) after 3 months (all diagnoses)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.80]
1.2 Topical TSP versus topical gentamicin after 6 months (all diagnoses)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.64, 6.22]

Comparison 3. Topical quinolone versus topical non-quinolone antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent discharge	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Discharge at 1 week	3	402	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.32]
1.2 Discharge at 2 weeks	5	276	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.46, 0.92]
1.3 Discharge at 3 weeks	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.54, 1.72]
1.4 Discharge at 2-3 weeks	6	313	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.04]

Comparison 4. Topical non-quinolone antibiotic versus topical antiseptic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent discharge	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Discharge at 1 week	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Discharge at 2-4 weeks	4		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Topical quinolone antibiotic versus topical antiseptic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent discharge	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Discharge at 1 week	3	263	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.41, 0.67]
1.2 Discharge at 2-4 weeks	4	519	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.47, 0.72]
2 Healing of the tympanic membrane	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Healing at 2 weeks	1	411	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.52, 2.13]
2.2 Healing at 4 weeks	1	399	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.91, 2.61]

Analysis 1.1. Comparison 1 Topical antibiotics versus no drug treatment, Outcome 1 Persistent discharge at 1 week.

Review: Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations

Comparison: 1 Topical antibiotics versus no drug treatment

Outcome: 1 Persistent discharge at 1 week

Analysis 2.1. Comparison 2 Topical non-quinolones: trimethoprim-sulfacetamide-polymyxin B (TSP) versus other non-quinolone antibiotic, Outcome 1 Persistent discharge.

Review: Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations

Comparison: 2 Topical non-quinolones: trimethoprim-sulfacetamide-polymyxin B (TSP) versus other non-quinolone antibiotic

Outcome: 1 Persistent discharge

Analysis 3.1. Comparison 3 Topical quinolone versus topical non-quinolone antibiotic, Outcome 1 Persistent discharge.

Review: Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations

Comparison: 3 Topical quinolone versus topical non-quinolone antibiotic

Outcome: 1 Persistent discharge

(Continued ...)

Analysis 4.1. Comparison 4 Topical non-quinolone antibiotic versus topical antiseptic, Outcome 1 Persistent discharge.

Review: Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations

Comparison: 4 Topical non-quinolone antibiotic versus topical antiseptic

Outcome: 1 Persistent discharge

Analysis 5.1. Comparison 5 Topical quinolone antibiotic versus topical antiseptic, Outcome 1 Persistent discharge.

Review: Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations

Comparison: 5 Topical quinolone antibiotic versus topical antiseptic

Outcome: 1 Persistent discharge

Analysis 5.2. Comparison 5 Topical quinolone antibiotic versus topical antiseptic, Outcome 2 Healing of the tympanic membrane.

Review: Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations

Comparison: 5 Topical quinolone antibiotic versus topical antiseptic

Outcome: 2 Healing of the tympanic membrane

ADDITIONAL TABLES

Table 1. Methodological quality of included studies

Study ID	Sequence generation	Alloc. concealment	Balance at baseline?	Blinding	Follow-up
Browning 1983a	Unclear Treatment allocation described as random, using random numbered list kept by the pharmacist, who dispensed the medication, but method of sequence code generation was not stated.	Unclear Medication was supplied in the clinic by the pharmacist using the random numbered list, after eligibility assessments by the clinicians, who were blinded (except for antiseptic)	Unclear Baseline characteristics (including the distribution of participants with and without modified radical mastoidectomy) not reported	Single blind Allocation was kept blinded from the clinicians, with the necessary exception of antiseptic, given by the otologist after aural toilet	Inadequate 32% dropout: 24/75 participants were defaulters or non-compliers (ie used <75% of the medication). (Numbers excluded not given by treatment group or diag-

Table 1. Methodological quality of included studies (Continued)

	<p>The choice of antibiotic depended on sensitivity results of ear discharge isolates.</p> <p>Participants with <i>Pseudomonas</i> species isolated were randomised to topical antibiotics or antiseptics only - not to oral antibiotics due to resistance.</p> <p>Did not discuss whether randomisation was stratified by the different diagnostic groups (and results not reported separately in trial report)</p>	<p>tic). Whether treatment was concealed from the pharmacist is not discussed</p>			<p>nosis).</p> <p>Results given for the 51 participants who complied with treatment only (38 on topical antibiotics or antiseptics, included in this review)</p>
Clayton 1990	<p>Unclear</p> <p>Treatment allocation described as random, with medication codes; but no further details of sequence generation method were given.</p> <p>Did not discuss whether randomisation was stratified by the different diagnostic groups - therefore included all participants in this review</p>	<p>Adequate</p> <p>Patients were randomly allocated treatment in a double-blind fashion.</p> <p>Medication codes were known only by the pharmacy.</p>	<p>No</p> <p>The following imbalances were reported for analysed participants, after exclusions (due to failure to attend clinic or comply with treatment; exclusions were not reported by treatment group):</p> <p>Significant bias ($P=0.0002$) for more mildest disease score (score 1) in the antiseptic group (1/60) than antibiotic (11/42) - scores not presented by diagnosis;</p>	<p>Double blinded</p>	<p>Inadequate</p> <p>Dropout rates (numbers of randomised ears that were excluded; not reported by treatment group):</p> <p>25% (5/20) central perforations; 30% (9/30) mastoid cavity infections; 25.8% (23/89) otitis externa ; 26.6% (37/139) total.</p> <p>Patients who failed to attend clinics or to comply with treatment were excluded</p>

Table 1. Methodological quality of included studies (Continued)

			More ears with otitis externa (significant) and central perforations (not reported as significant) were analysed in the antibiotic group than antiseptic (see Table 02 for numbers)		
Fradis 1997	Unclear Participants were randomised to treatment, with coded bottles, but method of sequence code generation not described. Participants with otorrhoea in both ears were given two different bottles	Adequate All numbered treatment bottles were similar in appearance. Treatment bottles and code were retained in the hospital pharmacy; only the pharmacy department head knew what each bottle contained	Yes Groups comparable for age and bacteriology (although slight imbalance in numbers of positive cultures: 18 ciprofloxacin, 16 tobramycin, 12 antiseptic/placebo). No information was given for treatment groups of cases of surgical perforation or where no perforation could be seen	Double blind The treating physician and participants were blinded to treatment. The treatment code was only broken at the end of the study to summarise the results of the investigation	Adequate Adequate for ears, which were the unit of analysis, but slightly inadequate for participants: 6/60 (10%) randomised ears (6/51 participants, ie 12%) were unavailable for follow-up after three weeks. Excluded numbers by treatment group: Ciprofloxacin: 1/20 ears (5%) Tobramycin: 2/20 ears (10%) 1% Burow aluminium acetate: 3/20 ears (15%)
Gyde 1978	Adequate Used Taves' method of minimisation, with type of infection as the principal criteria. Minimisation is an alternative method to stratified randomisation for treatment allo-	Unclear Allocation concealment not mentioned, except that solutions were called 'A' (TSP) and 'B' (gentamicin) (trial was described as double blind). Taves' minimisation approach can lead	Yes Ears were balanced across treatments for diagnosis (equal numbers per treatment) before and after crossover. Balanced for age, sex, and diagnosis, with no great differences between the	Double-blind The solutions were called 'A' (TSP) and 'B' (gentamicin) to conserve the double blind. The treatment provider/outcome assessor was blinded until after the analysis of the	Unclear No withdrawal was reported - numbers analysed are the same as the reported numbers eligible for the study. But participants unable to continue the proposed length of treatment or return

Table 1. Methodological quality of included studies (Continued)

	<p>cation. It is sometimes recommended for small sample sizes, and can incorporate more prognostic factors (Scott 2002).</p> <p>Unclear whether 'type of infection' relates to diagnosis or bacteriology - therefore included all participants in this review</p>	<p>to predictability of treatment allocation in some situations</p>	<p>seriousness of infections in the two groups, according to the trialists.</p> <p>These results are for all ears including crossed-over cases, so some participants are counted twice (bilateral disease or crossover) and 1 was counted 4 times (bilateral disease and crossed over).</p> <p>But there was more bilateral disease in the TSP group (7/43 participants = 16.3%) than on gentamicin (2/48 = 4.2%), for all participants before crossover</p>	<p>results. Participants were also blinded</p>	<p>for follow-up visits were excluded.</p> <p>Appears to be only per protocol population reported and analysed; number of excluded noncompliers was not reported</p>
Gyde 1981	<p>Unclear</p> <p>Participants were randomly assigned to one treatment group using coded medications, but method of generation of random codes was not described.</p> <p>Did not discuss whether randomisation was stratified by the different diagnostic groups - therefore included all participants in this review</p>	<p>Adequate</p> <p>Medications were coded and identically labelled, and used sequentially starting with the lowest number; no number was skipped or used more than once</p>	<p>Mostly</p> <p>Comparable across treatment groups (for ears) for diagnosis.</p> <p>Overall results for age and bacteria were also comparable (not broken down by diagnosis).</p> <p>But there was a slightly higher proportion of males in the TP group (17/33 ears, 51.5%) than the TSP group (25/35 ears, 71.4%)</p>	<p>Double blind</p>	<p>Unclear</p> <p>No withdrawal was reported - number analysed is the same as the reported number of ears eligible for the study.</p> <p>But participants unable to continue the proposed length of treatment or return for follow-up visits were excluded.</p> <p>Appears to be only per protocol population reported and analysed; number of excluded noncompliers was not reported</p>

Table 1. Methodological quality of included studies (Continued)

Jaya 2003	Unclear Treatment allocation described as random, with coded bottles, but method of generation of random codes was not described	Adequate Both drugs were coloured identically and were dispensed in identical bottles, labelled with code numbers only - given to participants after baseline assessments	Mostly Comparable for a range of demographic and disease related (prognostic) factors, except more participants receiving PVP-I were male (10/19, 52.6%), than on ciprofloxacin (4/21, or 19.0%). Other prognostic criteria were assessed and found to have no significant effect on the outcomes for the compared treatments	Double blinded The randomisation code was only decoded at the end of the study	Adequate 10% dropout rate: 4/40 randomised participants were excluded by week 4 (1/21 ciprofloxacin; 3/19 PVP-I). Reasons for exclusion from the analysis were not given.
Kasemsuwan 1997	Unclear Treatment allocation was described as random, with coded medications, but method of generation of random codes was not specified	Adequate Participants were randomly allocated treatment in a double blind method. The medication codes were known only in the pharmaceutical laboratory	Unclear Baseline characteristics not reported for each group.	Double blind	Inadequate 30% dropout: 15/50 participants were excluded due to lack of attendance. Participants who received other antibiotics during the trial were also excluded
Kaygusuz 2002	Unclear Treatment allocation described as random, but randomisation method was not stated	Unclear Allocation concealment not reported - nor was blinding.	Yes for bacteriology Baseline characteristics only reported for infective organism, which was comparable across groups	Unclear Blinding not mentioned.	Adequate No loss to follow-up or exclusions were reported. 80 participants were reported as included in the study and analysed
Lorente 1995	Unclear Treatment allocation described	Unclear Allocation concealment methods were	Yes Comparable for age sex, otorrhoea, itch-	Double-blind	Unclear Not clear how many people

Table 1. Methodological quality of included studies (Continued)

	as randomised, but randomisation method was not stated	not stated - but trial was double blind	ing, stinging, pain, irritation, and tinnitus		ple were originally randomised into the trial. (No exclusion was reported.)
Macfadyen 2005	<p>Adequate</p> <p>Treatment was prepared according to computer generated block randomisation schedule, stratified by school</p>	<p>Adequate.</p> <p>Treatment was identical in appearance, and identically labeled and packaged in treatment boxes, identifiable by school name and trial number only. Treatment packs remained sealed until sequentially allocated to a child</p>	<p>Yes</p> <p>Comparable for age*, sex, duration of current episode*, proportion of bilateral cases*, size of perforation*, cause of current episode, whether previous ear treatment had ever been used, and hearing level.</p> <p>* Logistic regression adjusting for these factors did not significantly alter the treatment effect</p>	<p>Double blind</p> <p>Participants, care-givers, and outcome assessors remained blind to the treatment allocated throughout the study</p>	<p>Adequate</p> <p>Number with missing data and so excluded from analysis for resolution of discharge at four weeks: 33/427 (7.7%) total; 20/216 (9%) ciprofloxacin; 13/211 (6%) boric acid.</p> <p>Some of these were due to missing data for participants seen at that visit.</p> <p>The rest were due to withdrawals or lost to follow up: 25/427 (5.9%) total; 16/216 (7.4%) ciprofloxacin (15 lost to follow-up; 1 consent withdrawn); 9/211 (4.3%) boric acid (all lost to follow-up).</p> <p>All analyses followed the Intention To Treat principle.</p>
Tutkun 1995	<p>Unclear</p> <p>Participants were randomly divided into two groups but randomisation method</p>	<p>Unclear</p> <p>Allocation concealment not reported - nor was blinding.</p>	<p>Unclear?</p> <p>Only reported baseline data for bacteriology - comparable apart from "normal flora" isolated</p>	<p>Unclear</p> <p>Blinding not mentioned.</p>	<p>Unclear</p> <p>It is not clear how many people were originally randomised into the trial - an un-</p>

Table 1. Methodological quality of included studies (Continued)

	was not stated		in the ciprofloxacin group only (4 cases; excluded from hearing analyses in Ozagar 1997		<p>reported number of non-compliers (participants who did not use the topical solutions regularly and those who had taken any other medication during the study period) were excluded from study.</p> <p>4 participants were excluded from the hearing analysis (and clinical response in Ozagar 1997)</p>
van Hasselt 1997	<p>Unclear</p> <p>Described as a randomised trial in 2002 paper, but randomisation method was not stated</p>	<p>Unclear</p> <p>Allocation concealment not reported - nor was blinding.</p>	<p>Unclear</p> <p>Baseline characteristics were not provided.</p>	<p>Unclear</p> <p>Blinding not mentioned.</p>	<p>Inadequate</p> <p>28% dropout: 27/96 participants did not complete the trial.</p> <p>Ofloxacin: 8% dropout (1/12 participants)</p> <p>Neomycin/polymyxin B: 21% dropout (8/38 participants)</p> <p>Acetic acid/spirit: 39% dropout (18/46 participants)</p> <p>Only children completing the trial fully (ie attended at both review dates) were included in the analysis</p>
van Hasselt 1998	<p>Unclear</p> <p>Described as a randomised trial, but randomisation method was not</p>	<p>Unclear</p> <p>Allocation concealment not reported - but trial was double-blind</p>	<p>Unclear</p> <p>Baseline characteristics were not provided.</p>	<p>Double-blind</p>	<p>Adequate (except week 8)</p> <p>Number excluded from the analysis:</p> <p>Week 1: 12/151 ears</p>

Table 1. Methodological quality of included studies (Continued)

	stated				(8%); Week 2: 13/151 ears (9%) ; Week 8: 23/151 ears (15%). 'Defaulting ears' were excluded.
van Hasselt 2002	Unclear Described as a randomised trial, but randomisation method was not stated	Unclear Allocation concealment not reported - but trial was double-blind	Unclear Baseline characteristics were not provided.	Double-blind	Unclear Not clear how many people were originally randomised into the trial

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria

Study ID	CSOM diagnosis	Otitis exclusions	Other elig criteria	Disease duration	Bacteriology?	Mucosal appearance?	Other diagnoses?	Other diags: sep?
Browning 1983a	Active chronic otitis media including previous modified radical mastoidectomy participants	1) Cholesteatoma 2) Aural polyp	Non-otitis inclusion criteria: 1) Over 16 years old Exclusions - see otitis exclusions; no other exclusions were specified	Not specified - but all participants were secondary referrals	Yes. Sensitivity of isolated aerobic flora determined the choice of antibiotic. Participants with Pseudomonas spp were not randomised to oral (systemic) antibiotic	Not reported	19/51 (i.e. 37%) analysed participants had previously undergone modified radical mastoidectomy (not provided by treatment group). NB: only 38/51 on topical antibiotics or antiseptics included in this review (2 of 3 treatment groups)	No

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

Clayton 1990	Otorrhoea caused by: a) discharging central perforation; b) mastoid cavity; c) otitis externa.	1) Acute middle ear disease 2) Cholesteatom 3) Clinical evidence of fungal ear infection	Exclusion criteria - treatment related: 1) Topical or systemic antibiotic use in previous three weeks; 2) History of drug sensitivity to any of the agents used in the study	Not specified - but excluded acute middle ear disease	Indicated; Not required for inclusion: 11.7% had no bacteria isolated.	Yes: scoring system of severity included presence and degree of oedema obscuring the tympanic membrane or mastoid cavity, or of oedematous mucosa lining the mastoid cavity	Included otor-rhoea from mastoid cavity and otitis externa. a) Discharging central perforation: 15 ears + 5 excluded b) Mastoid cavity: 21 ears + 9 excluded c) Otitis externa: 66 ears + 23 excluded Participants who failed to attend clinic or comply with treatment were excluded (numbers not given by treatment group)	Not separate in review: randomisation not reported to stratify by diagnosis. But results were given by diagnosis separately in trial publication
Fradis 1997	CSOM was defined as a chronic inflammation of the middle ear and mastoid process with a perforated tympanic membrane and discharge. All cases had	1) Prior middle-ear surgery 2) Suspected cholesteatoma	Other inclusion criteria: 1) Signed consent 2) Discontinued all other medications two weeks before study entry. Exclusion criteria - treatment	Disease duration: mean (range): 24 months (1 to 240 months).	Indicated; Not required for inclusion: 23/60 cultures were negative for organisms before treatment.	In 8/60 ears granulation tissue meant no perforation could be seen	a) 3/60 ears: surgical perforations; b) 8/60 ears: no perforation seen due to granulation tissue	No

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

	purulent disease.		related 1) History of allergy to aminoglycosides or fluoroquinolone derivatives. Exclusion criteria - other 1) General health problems 2) Younger than 18 years (range was 18 to 73 years)					
Gyde 1978	1) Otorrhoea from: a) recurrent benign chronic otitis media with tympanic membrane perforation (CSOM); b) postoperative infections (mastoidectomy or tympanoplasty) and mastoid cavity infections; c) subacute otitis media (with small or medium perforation) ; d) external otitis.	1) Otorrhoea not caused by bacteria 2) 'Unsafe' ears (active atticofacial disease, accompanied by cholesteatoma , with adjacent area extension)	Inclusion criteria - other: 1) Adults or children - includes paediatric cases (under 12 years old) and geriatric cases (over 60 years old) . 2) Informed consent Exclusion criteria - treatment related: 1) Known allergy to any components of the trial drugs. 2) Use of	Not specified	Indicated with results; Required for inclusion.	Not reported	Total 100 analysed ears before crossover; 12 ears crossed over to the alternative treatment (8/50 TSP to gentamicin; 4/50 gentamicin to TSP) ; a) 50 CSOM (25 TSP, 25 gentamicin); 7 ears then crossed over (2 from gentamicin to TSP, 5 from TSP to gentamicin)	Not separate in review: type of infection was the principal criteria for randomisation (minimisation) , but unclear whether this relates to diagnosis or bacteriology. But results were given by diagnosis separately in trial publication (for number of ears)

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

			<p>high doses of local (topical) corticosteroid preparations.</p> <p>3) Previous use of ototoxic drug therapy.</p> <p>4) Use of general or topical antibiotics within two weeks before study entry.</p> <p>5) Unable to continue the proposed length of treatment or return for follow-up visits due to distance or inconvenience.</p> <p>Exclusion criteria - other:</p> <p>1) Pregnant or lactating.</p> <p>2) Infants under 2 months old.</p>				<p>b) 10 post-operative and mastoid cavity infections (5 TSP, 5 gentamicin); 3 ears then crossed over (3 from TSP to gentamicin)</p> <p>c) 16 subacute otitis media (8 TSP, 8 gentamicin); 2 ears then crossed over (2 from gentamicin to TSP)</p> <p>d) 24 external otitis (12 TSP; 12 gentamicin) 0 ears crossed over.</p>	
Gyde 1981	<p>1) Otorrhoea from</p> <p>a) recurrent otitis media with tympanic membrane perforation (CSOM);</p> <p>b) in-</p>	<p>1) Acute otitis media</p> <p>2) 'Unsafe' ears (active atticofurunculosis, with adjacent area extension)</p>	<p>13/68 ears were paediatric (< 12 years old), 12/68 ears were geriatric (> 70 years old). Concurrent medica-</p>	<p>Disease duration (for all diagnoses) ranged from just under 1 month to 5 years</p>	<p>Indicated; Required for inclusion: Presence of gram-negative or gram-positive organisms from a specified list</p>	<p>Not reported</p>	<p>Numbers for analysed ears (68 total: 35 TSP, 33 TP)</p> <p>a) 27 CSOM (13 TSP, 14 TP);</p> <p>b) 6 infected</p>	<p>Not separate in review: randomisation not reported to stratify by diagnosis.</p> <p>But results</p>

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

	<p>fects mastoid cavities and post-operative tympanoplasties;</p> <p>c) subacute otitis media;</p> <p>d) external otitis.</p> <p>2) Presence of gram-negative or gram-positive organisms from a specified list</p>		<p>tions, such as analgesics and decongestants etc were allowed.</p> <p>Exclusion criteria - treatment related:</p> <p>1) History of sensitivity to any components of the trial drugs.</p> <p>2) Use of extensive ototopical corticosteroid preparations within the past four weeks.</p> <p>3) Previous use of ototoxic drug therapy.</p> <p>4) Use of oral or parenteral antibiotics within two weeks before study entry.</p> <p>5) Unable to continue the proposed length of treatment or return for follow-up visits due to distance or inconvenience.</p>				<p>mastoid cavities and post-operative tympanoplasties (2 TSP, 4 TP);</p> <p>c) 4 subacute otitis media (2 TSP, 2 TP);</p> <p>d) 31 external otitis (18 TSP, 13 TP)</p> <p>.</p>	<p>were given by diagnosis separately in trial publication</p>
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Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

			Exclusion criteria - other: 1) Pregnant or lactating. 2) Tuberculosis, fungal or viral diseases.					
Jaya 2003	Actively discharging CSOM with moderate to large central perforation (i.e. active CSOM-tubotympanic disease)	1) Cholesteatom 2) Aural polyp 3) Impending complications of CSOM	Other inclusion criteria: 1) Older than 10 years Exclusion criteria - treatment related: 1) Known allergy to iodine or fluoroquinolone 2) Prior systemic or topical antibiotic therapy within 10 days of study entry Exclusion criteria - other 1) Debilitating illness (e.g. diabetes mellitus, tuberculosis, renal failure or AIDS)	Total duration of disease: ≤ 5 years: n = 13 > 5 years: n = 27 Current episode of discharge was < 2 weeks for many participants: < 1 week: n = 15 1 to 4 weeks: n = 20 > 4 weeks: n = 5 The trialists reported that this duration did not significantly alter the outcome in both treatment groups	Indicated; Not required for inclusion: 8/40 swabs did not yield potential bacterial pathogen	Status of middle ear at baseline (number of participants): 20 hyperemic 18 pale and edematous 2 granular	None specified - see otitis exclusions	n/a
Kasemsuwan 1997	1) Perforated tympanic membrane for	1) Cholesteatom 2) Underly-	Other inclusion criteria: 1) Adult	Perforated tympanic mem-	Indicated; Not required for	Not reported	Not specified - see otitis exclu-	n/a

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

	longer than 3 months; 2) Mucopurulent otorrhoea (Assessed on microscopic examination)	ing diseases	(age range was 21 to 66) Exclusion criteria - treatment related: 1) Receiving antibiotics in the previous two weeks and during the study. Exclusion criteria - other: 1) Pregnant women 2) Underlying diseases	brane for longer than 3 months	inclusion: no bacteria were isolated for 26% of participants		sions	
Kaygusuz 2002	Chronic suppurative otitis media with: 1) perforated eardrum, and 2) discharge in the ears for > 3 months	1) Suspected or confirmed cholesteatoma (on otoscopy) 2) Previous history of ear surgery	Other inclusion criteria: None reported other than adults with CSOM (age range was 18 to 60 years, mean, (SD) 31 (+/- 11.5) years) Exclusion criteria - treatment related: 1) Allergy to aminoglycosides or fluoroquinolones Exclusion criteria	Discharge for > 3 months (average duration was 44.4 years +/- 40.9 months; range 3 to 10 years)	Indicated; Not required for inclusion: 5.8% of pre-treatment cultures were negative	Not reported	Not specified - see otitis exclusions.	n/a

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

			- other: 1) Under 18 years old 2) General health problems					
Lorente 1995	Simple chronic otitis media in the suppurative phase (CSOM): purulent otitis of > 3 months duration, with perforated tympanic membrane	1) Cholesteatom or attic disease 2) Otomycosis 3) Bilateral hypacusia higher than 60 dB	Inclusion criteria - other: 1) Age 18 to 65 (mean 42 years) 2) Either gender 3) No evidence of physical or psychological (psychiatric) illness, with laboratory tests (biochemical and haematological) within reference ranges 4) Consent to participate Exclusion criteria - treatment related: 1) Topical or systemic antibiotic use in the previous 48 hours 2) Allergy to quinolones or aminoglycosides	Purulent otitis of > 3 months duration	Indicated: Not specified in inclusion criteria: 304 microorganisms isolated before treatment were reported	Not reported	Not specified - see otitis exclusions	n/a

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

			Exclusion criteria - other: 1) Pregnant or breast feeding 2) Severe kidney or liver deficiency					
Macfadyen 2005	1) Purulent aural discharge for 14 days or longer, with pus seen in the external canal on otoscopy 2) Perforated tympanic membrane (on otoscopy)	Other ear problems: 1) Pre-existing disease, e.g. otomycosis, polyp, impacted foreign body, or previous ear surgery 2) Complicated otitis media, e.g. cholesteatoma, mastoiditis, requires treatment other than study treatment 3) Anatomical abnormalities	Inclusion criteria - other: 1) School children (enrolled at Kisumu rural primary schools visited) 2) Age five years or older (range was 4 to 19 years) 3) Informed consent (parental consent for affected children; school staff and parent-teacher-association representatives consented to school participation). Exclusion criteria - treatment related: 1)	Purulent aural discharge for 14 days or longer	Assessed but results not provided Not required for inclusion	Not assessed	No - see otitis exclusions	n/a

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

			Treated for ear infection or received antibiotics for any other disorder in the previous 2 weeks 2) Allergy to study drugs.					
Tutkun 1995	History of purulent otorrhoea lasting > 1 year	Cholesteatom	<p>Inclusion criteria - treatment related: 1) All participants stopped taking any medication at least 10 days prior to treatment.</p> <p>Inclusion criteria - other: 1) Informed consent.</p> <p>Exclusion criteria - treatment related: 1) History of allergy to fluoroquinolone derivatives or aminoglycosides, or to topical agents</p> <p>2) Did not use the topical solutions</p>	History of purulent otorrhoea lasting > 1 year	Indicated Not specified in inclusion criteria: 4 participants had normal flora	Not reported	Not specified	n/a

Table 2. Participant eligibility criteria, including CSOM diagnostic criteria (Continued)

			regularly, or had taken any other medication during the study. Exclusion criteria - other: 1) Younger than 9 years 2) History of general health problems.					
Van Hasselt 1997	CSOM ('typically... affected ears were filled with mucoid pus.... Most perforations were medium or large. Granulations were present in most cases')	Not reported	Inclusion criteria - other: Children Exclusion criteria: Not reported.	Not specified	Not specified	Not reported	Not specified	n/a
Van Hasselt 1998	> 2 months CSOM for inclusion as an active ear (CSOM not described)	Not reported	Participants were mainly children. Exclusion criteria: 1) Uncooperative with suction cleaning	> 2 months CSOM	Not specified	Not reported	Not specified	n/a
Van Hasselt 2002	CSOM (not described)	Not reported	Other eligibility criteria: Not reported	Not specified	Not specified	Not reported	Not specified	n/a

Table 3. Bilateral disease: numbers for ears versus participants

Study ID	# of participants	# of ears	% bilateral cases	Handling bilat cases	Results: pt or ears?
Browning 1983a	75 randomised - all treatments; not reported by group 51 analysed: 18 topical antibiotics 20 topical antiseptics * 13 systemic antibiotics; not included in this review * 19/51 (37%) were post modified radical mastoidectomy - numbers and results were not presented separately	Not reported	Not reported	One ear was chosen at random by the pharmacist (method of choice unknown)	Participants
Clayton 1990	Not reported	Randomised ears: 139 total: 20 central perforation; 30 mastoid cavity; 89 otitis externa Completed (analysed) + excluded cases: Total: 102 completed (42 antiseptic; 60 antibiotic) + 37 excluded; Central perforation: 15 completed (4 antiseptic; 11 antibiotic) + 5 excluded; Mastoid cavity: 21 completed (13 antiseptic; 8 antibiotic) + 9 excluded; Otitis externa: 66	Not reported	Unclear - report for ears only, but baseline characteristics table uses term 'patients' instead, although totals match number of ears reported in text	Ears? But baseline characteristics table uses term 'patients' (text uses 'ears')

Table 3. Bilateral disease: numbers for ears versus participants (Continued)

		completed (25 anti-septic; 41 antibiotic) + 23 excluded			
Fradis 1997	51 randomised participants; 45 analysed	60 randomised ears (20 per treatment group) 54 analysed ears: 19 ciprofloxacin 18 tobramycin 17 Burow aluminium acetate	Randomised bilateral rates: 9/51 (17.6%) Analysed bilateral rates: 9/41 (20.0%).	Treated both ears (each ear given a different bottle in bilateral cases), and report number of ears	Ears
Gyde 1978	Randomised participants: not reported Analysed participants before crossover (all diagnoses reported only): 91 total; 43 TSP; 48 gentamicin. Analysed participants crossed over to other treatment (all diagnoses): 11/91 total; 7/43 from TSP to gentamicin; 4/48 from gentamicin to TSP. NB the trialists reported the combined crossover plus pre-crossover numbers	Randomised ears: not reported Analysed ears before crossover: 100 total (50 TSP; 50 gentamicin); 50 CSOM (25 TSP; 25 gentamicin); 10 post-operative and mastoid cavity infections (5 TSP; 5 gentamicin); 16 subacute otitis media (8 TSP; 8 gentamicin); 24 otitis externa (12 TSP; 12 gentamicin). Analysed ears crossed over to other treatment: 12/100 total (8/50 from TSP to gentamicin; 4/50 from gentamicin to TSP)	Randomised participants: rates not reported Analysed participants bilateral rates (all diagnoses only): Before crossover: Total: 9/91 (9.9% bilateral); TSP: 7/43 (16.3% bilateral); Gentamicin: 2/48 (4.2% bilateral). Crossed over to alternative treatment: Total: 1/11 (9% bilateral); TSP to gentamicin: 1/7 (14% bilateral); Gentamicin to TSP: 0/4 (0% bilateral). ie this crossover participant is counted 4 times in the combined figures presented by the trialists (twice per treatment)	Both ears treated and analysed separately - reported number of ears	Ears

Table 3. Bilateral disease: numbers for ears versus participants (Continued)

		<p>;</p> <p>7/50 CSOM (5/25 from TSP to gentamicin; 2/25 from gentamicin to TSP)</p> <p>;</p> <p>3/10 post-operative and mastoid cavity infections (3/5 from TSP to gentamicin)</p> <p>;</p> <p>2/16 subacute otitis media (2/8 from gentamicin to TSP)</p> <p>;</p> <p>0/24 otitis externa.</p> <p>NB the trialists reported combined pre- plus post-crossover numbers. Where possible, we have used pre-crossover cases only</p>			
Gyde 1981	<p>60 participants were eligible and included in the analyses</p> <p>Not available by treatment group or diagnosis.</p>	<p>Eligible ears included in the analyses:</p> <p>68 total (35 TSP; 33 TP);</p> <p>27 CSOM (13 TSP; 14 TP);</p> <p>6 post-operative and mastoid cavity infections (2 TSP; 4 TP);</p> <p>4 subacute otitis media (2 TSP; 2 TP);</p> <p>31 otitis externa (18</p>	<p>Total: 8/60 (13.33%)</p> <p>Not available by treatment group or diagnosis.</p>	Treated both eligible ears and report number of ears.	Ears

Table 3. Bilateral disease: numbers for ears versus participants (Continued)

		TSP; 13 TP)			
Jaya 2003	40 randomised participants (21 ciprofloxacin; 19 PVP-I) 36 assessed at week 4 (20 ciprofloxacin; 16 PVP-I)	Not reported; but only 40 ear swabs taken at baseline	Not reported	Unclear - reported at participant level.	Participants
Kasemsuwan 1997	Main text states participants: 50 randomised 35 completed study and analysed (19 ciprofloxacin; 16 normal saline)	Abstract states ears: 50 ears randomised 35 completed study and analysed	Not reported	Unclear - used term 'ears' in abstract, but mostly 'patients' in main text	Participants? 'Participant' in main text, but used term 'ears' in abstract
Kaygusuz 2002	80 participants included and analysed (20 per treatment group; i.e. 40 for this review)	103 ears included (not reported by treatment group)	23/80 (28.75%)	Appears to have taken success when both ears had resolved only (treatment was successful when there was no discharge)	Participants
Lorente 1995	308 analysed participants (159 ciprofloxacin; 149 gentamicin) Numbers originally randomised, not provided	Not reported	Not reported	Not reported	Participants
Macfadyen 2005	427 randomised participants (216 ciprofloxacin; 211 boric acid) 394 analysed for resolution at four weeks (196 ciprofloxacin; 198 boric acid)	533 randomised ears (264 ciprofloxacin; 269 boric acid)	Rates for randomised participants: Total: 106/427 (25%) Ciprofloxacin: 48/216 (22%) Boric acid: 58/211 (27%)	Report at participant level. Both ears treated and assessed for bilateral cases - success when both ears had resolved or healed. Sensitivity analysis conducted -	Participants

Table 3. Bilateral disease: numbers for ears versus participants (Continued)

				success for bilateral cases when either or both ears resolved or healed.	
				Audiometry results were averaged over the study ear(s) for one overall reading	
Tutkun 1995	44 analysed participants (24 ciprofloxacin; 20 gentamicin) 40 analysed for hearing (20 ciprofloxacin; 20 gentamicin) (Ozagar 1994)	Not reported	Not reported	Unclear - reported at participant level; bilateral disease or numbers of ears not discussed	Participants
van Hasselt 1997	96 children randomised: 12 ofloxacin; 38 neomycin/polymyxin B 46 acetic acid/spirit 69 children completed and included in analysis: 11 ofloxacin 30 neomycin/polymyxin B 28 acetic acid/spirit	Number ears randomised: not reported 93 ears included in analysis: (or 88?) 14 ofloxacin 40 neomycin/polymyxin B (35 in Van Hasselt 2002 paper) 39 acetic acid/spirit.	Randomised rates: not available Analysed participants: Total: 24/69 (34.78%) Ofloxacin: 3/11 (27.27%) Neomycin/polymyxin B: 10/30 (33.33%) (or 5/30, 16.67% from Van Hasselt 2002 publication) Acetic acid/spirit: 11/28 (39.29%)	Treated both ears and report % ears dry. CBM Report: provided number and proportion of ears dry and wet at each visit. 2002 paper: reported proportion of ears dry at two weeks.	Ears
van Hasselt 1998	107 participants randomised Number analysed: not reported	151 randomised ears Analysed ears: 139 ears at week 1 138 ears at week 2: 32 ofloxacin twice daily; 39 ofloxacin once	Total randomised: 44/107 (41.12%) Analysed participants: not available	Report proportion of analysed ears dry; numbers of ears per group reported for week two only	Ears

Table 3. Bilateral disease: numbers for ears versus participants (Continued)

		weekly; 36 neomycin polymyxin B twice daily; 31 neomycin polymyxin B once weekly. 128 ears at week 8.			
van Hasselt 2002	Not reported	253 analysed ears: 79 ofloxacin + HPMC 91 povidone iodine + HPMC 83 HPMC	Not reported	Reported % of number of ears dry.	Ears

Table 4. Intervention regimens used

Study ID	Intervention	Strength	Dose and frequency	Duration	Ear Toilet	Concurrent meds
Do topical antibiotic eardrops work?						
Quinolone versus placebo:						
Kasemsuwan 1997	1) Quinolone: ciprofloxacin in saline solution 2) Placebo: normal saline solution	1) Ciprofloxacin: 250 microgram/mL 2) Saline: n/a	Both treatments: 5 drops three times daily.	Both treatments: At least 7 days.	Both groups: Ear cleaning at each visit (treatment days 1, 4 and 7).	Excluded if received antibiotics in the previous two weeks or during the study
van Hasselt 2002	1) Quinolone: ofloxacin in HPMC 2) Placebo: HPMC HPMC = hydroxypropyl methyl-cellulose (hypromellose) -	1) 0.075% Ofloxacin in 1.5% HPMC 2) 1.5% HPMC	All treatments: 1 single topical application after suction cleaning.	Both treatments: Once only.	Both groups: Suction cleaning once.	Not reported.

Table 4. Intervention regimens used (Continued)

	a treatment de- livery vehicle					
Which an- tibiotic eardrops work best?						
Non- quinolone versus non-quinolone						
Gyde 1978	1) Non- quinolone: trimethoprim- sulfacetamide- polymyxin B (TSP) (Bur- roughs Wellcome Ltd). 2) Non- quinolone: gen- tamicin sulphate (Garamycine)	1) 0.1% TSP (Trimetho- prim 1 mg/mL; Polymyxin B 10, 000 U/mL; Sul- facetamide 5mg/ mL). 2) 0.3% gen- tamicin sulphate	Both treatments: 8 drops twice daily (morning and evening).	Both treatments: De- pended on clini- cal and bacterio- logical response: Up to 3 weeks initially, plus 3 weeks if required. Failed ears or not dry at 6 months crossed over to the other treatment for 3 weeks; 6 month follow-up as be- fore: 11 partici- pants (12 ears; 7 CSOM ears). Average du- ration (including crossovers) (days): All successfully treated ears: TSP 19.3 days (range 7 to 32) (N = 46); gentamicin 21.7 days (range 10 to 37) (N = 51).	Both groups: Suction and dry mop- ping before each treatment appli- cation. Pneumatic oto- scope sometimes also used to en- sure the eardrops reached the mid- dle ear and mas- toid cavity	Two-week washout period if used any an- tibiotics before study entry. Excluded if used high doses of ototopical corti- costeroids, or ever used oto- toxic drug ther- apy

Table 4. Intervention regimens used (Continued)

				CSOM: TSP 16.4, gentamicin 22.8; Post-operative or mastoid infections: TSP 24.0, gentamicin 24.3; Subacute otitis media: TSP 21.3, gentamicin 22.7 Otitis externa: TSP 17.1, gentamicin 17.5.		
Gyde 1981	1) Non-quinolone: Trimethoprim-sulfacetamide-polymyxin B (TSP) 2) Non-quinolone: Trimethoprim-polymyxin B (TP)	1) 0.1% TSP 2) 0.1% TP Concentrations of treatment components: Trimethoprim 1 mg/mL; Polymyxin B 10,000 U/mL; Sulfacetamide 5 mg/mL	Both treatments: 8 drops twice daily (morning and night).	Both treatments: Up to 14 days maximum, depending on response to treatment and bacterial culture results	Both groups: Suction and dry mopping before each treatment application. Pneumatic otoscope sometimes also used to ensure the eardrops reached the middle ear and mastoid cavity	Two week washout period if used any antibiotics before inclusion. Excluded if used extensive ototopical corticosteroids within 4 weeks, or ever used ototoxic drug therapy. Concurrent medications such as analgesics and decongestants etc were allowed
Quinolone versus non-quinolone						
Fradis 1997	1) Quinolone: ciprofloxacin hydrochloride solution	1) Ciprofloxacin: Not specified 2) Tobramycin:	All treatments: 5 drops, 3 time daily.	All treatments: 3 weeks.	Not specified.	All other medication discontinued two weeks before study entry.

Table 4. Intervention regimens used (Continued)

	2) Non-quinolone: tobramycin	Not specified				(34 participants previously received systemic antibiotics; 12 had used neomycin-polymyxin B eardrops without success)
Kaygusuz 2002	1) Quinolone: ciprofloxacin hydrochloride 2) Non-quinolone: tobramycin	1) 0.3% Ciprofloxacin hydrochloride 2) 0.3% Tobramycin	All treatments: 2 drops 3 times daily.	All treatments: 3 weeks.	All groups: Aspiration once daily.	Not reported.
Lorente 1995	1) Quinolone: ciprofloxacin 2) Non-quinolone: gentamicin	1) 0.3% Ciprofloxacin 2) 0.3% Gentamicin	Both treatments: 5 drops (0.75 mg) 3 times daily.	Both treatments: 8 days (awaiting confirmation that this was not continued to day 30)	Not specified.	Excluded if received antibiotic treatment (topical or systemic) in the last 48 hours
Tutkun 1995	1) Quinolone: ciprofloxacin hydrochloride 2) Non-quinolone: gentamicin sulfate	1) Ciprofloxacin hydrochloride: 200 microgram/mL 2) Gentamicin sulfate: 5 mg/mL	Both treatments: 5 drops 3 times daily.	Both treatments: 10 days.	Not specified.	All other medication stopped at least 10 days prior to treatment. Excluded if used any other medication during the study.
van Hasselt 1997	1) Quinolone: ofloxacin (Exocin R from Allergan) 2) Non-quinolone: neomycin-polymyxin B	1) 0.3% Ofloxacin; 2) 0.5% Neomycin, 0.1% polymyxin B	All treatments: 3 drops, 3 times daily.	All treatments: 2 weeks.	All groups: Suction cleaning at the beginning of the trial, and at weeks 1 and 2 visits	Not reported.

Table 4. Intervention regimens used (Continued)

VH 1998 daily	1) Quinolone: ofloxacin 2) Non-quinolone: neomycin-polymyxin B	1) 0.3% Ofloxacin 2) Neomycin-polymyxin B: not specified	Both treatments: 6 drops twice daily.	All treatments: 2 weeks.	All groups: Once weekly suction cleaning.	Not reported.
VH 1998 weekly	1) Quinolone: ofloxacin 2) Non-quinolone: neomycin-polymyxin B	1) 0.3% Ofloxacin 2) Neomycin-polymyxin B: not specified	Both treatments: Once weekly.	All treatments: 2 weeks.	All groups: Once weekly suction cleaning.	Not reported.
Do topical antibiotics work better than topical antiseptics?						
Non-quinolone versus antiseptic						
Browning 1983a	1) Non-quinolone: chloramphenicol (Chloromycetin), or gentamicin (Genticin) (self treated). Choice of antibiotics depended on sensitivity of bacterial isolated at baseline. 2) Antiseptics: insufflation of boric acid and iodine powder after aural toilet (otologist treated)	1) Antibiotics: not specified 2) Antiseptic: not specified	1) Topical Antibiotics (self treat): a) Chloramphenicol: 1 or 2 drops, 3 times daily; b) gentamicin: 3 or 4 drops, 4 times daily. 2) Antiseptic: once weekly (insufflation after aural toilet, by otologist) (dose not reported)	All treatments: 4 weeks.	All groups: Weekly aural toilet by otologist, using microscopic vision and suction aspiration when necessary	Not reported.
Clayton 1990	1) Non-quinolone: gentamicin sulphate	1) 0.3% Gentamicin sulphate	All treatments: 5 drops, 3 times daily.	All treatments: 3 weeks.	All groups: Self mopping before each treat-	No antibiotics in the preceding 3 weeks.

Table 4. Intervention regimens used (Continued)

	2) Antiseptic: aluminium acetate	2) 8% Aluminium acetate			ment administration.	
Fradis 1997	2) Non-quinolone: tobramycin 3) Antiseptic: Burow aluminium acetate solution	2) Tobramycin: Not specified 3) 1% Aluminium acetate (weak antiseptic, used as a “placebo” by the trialists).	All treatments: 5 drops, 3 times daily.	All treatments: 3 weeks.	Not specified.	All other medication discontinued two weeks before study entry. (34 participants previously received systemic antibiotics; 12 had used neomycin-polymyxin B eardrops without success)
van Hasselt 1997	2) Non-quinolone: neomycin-polymyxin B 3) Antiseptic: acetic acid in spirit and glycerin	2) 0.5% Neomycin, 0.1% polymyxin B 3) 2% Acetic acid in 25% spirit and 30% glycerin	All treatments: 3 drops, 3 times daily.	All treatments: 2 weeks.	All groups: Suction cleaning at the beginning of the trial, and at weeks 1 & 2 visits	Not reported.
Quinolone versus antiseptic						
Fradis 1997	1) Quinolone: ciprofloxacin hydrochloride solution 3) Antiseptic: Burow aluminium acetate solution	1) Ciprofloxacin: Not specified 3) 1% Aluminium acetate (weak antiseptic, designated as the “placebo group” by the trialists)	All treatments: 5 drops, 3 times daily.	All treatments: 3 weeks.	Not specified.	All other medication discontinued two weeks before study entry. (34 participants previously received systemic antibiotics; 12 had used neomycin-polymyxin B eardrops without success)
Jaya 2003	1) Quinolone: ciprofloxacin hydrochloride	1) 0.3% Ciprofloxacin hydrochloride	All treatments: 3 drops three times daily.	All treatments: 10 days.	Both groups: Dry mopping before each treatment occasion.	No prior systemic or topical antibiotic therapy within 10

Table 4. Intervention regimens used (Continued)

	2) Antiseptic: povidone (polyvinyl pyrrolidone)- iodine (PVP-I, Betadine)	2) 5% Povidone iodine			Aural suctioning performed before initial treatment for all participants, and at subsequent weekly visits if discharge was present	days of study entry
Macfadyen 2005	1) Quinolone: ciprofloxacin hydrochloride (Ciloxan, from Alcon) 2) Antiseptic: boric acid in alcohol (powder from UK but manufactured locally)	1) 0.3% Ciprofloxacin hydrochloride 2) 2% Boric acid in 45% alcohol	Both treatments: Drops given twice daily (morning registration and lunch time). Child-to-child treatment: older children trained to clean and treat infected ears (at school) , under supervision of trained teachers	Both treatments: 10 consecutive school days (ie excluding week-ends).	Both groups: Dry mop-ping before each treatment administration. Dry mop only for weeks 2-4 if persistent discharge at week 2	Excluded if treated for ear infection or received antibiotics for any other disorder in the previous 2 weeks
van Hasselt 1997	1) Quinolone: ofloxacin (Exocin R, from Allergan) 3) Antiseptic: acetic acid in spirit and glycerin	1) 0.3% Ofloxacin 3) 2% Acetic acid in 25% spirit and 30% glycerin	All treatments: 3 drops, 3 times daily.	All treatments: 2 weeks.	All groups: Suction cleaning at the beginning of the trial, and at weeks 1 & 2 visits	Not reported.
van Hasselt 2002	1) Quinolone: ofloxacin in HPMC 2) Antiseptic: povidone iodine in HPMC HPMC = hydroxypropyl	1) 0.075% Ofloxacin in 1.5% HPMC 2) 1% Povidone iodine in 1.5% HPMC	All treatments: 1 single topical application after suction cleaning	Both treatments: Once only.	All groups: Suction cleaning once.	Not reported.

Table 4. Intervention regimens used (Continued)

	methyl-cellulose (hypromellose) - a treatment delivery vehicle						
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Table 5. Outcomes assessed

Study ID	CSOM Resolution	Healing	Time to resolution	Time to reappear-ance	Hearing improve-ment	Safety	Other outcomes?	Other notes	Par-ticipant or ears?
Browning 1983a	1) Partici-pants with active, mu-coid or in-active ears after 4 weeks of treatment								Participant
Clayton 1990	1) Im-proved ears (i.e. dry or dis-charge im-proved by a score of 2 or more) at treatment days 9 and 21. Scor-ing system for severity of infec-tion: de-gree of ot-or-rhoea and of oedema or oedema-tous mucosa. Numbers with com-plete						1) Antibiotic or an-tiseptic re-sistant bac-terial strains at treat-ment days 9 and 21. (Reported resistant strains for 21 days.) 2) Com-pliance to treatment, monitored at assess-ments ev-ery 3 days	Resolution reported as 'improved' or 'not im-proved'; complete cure not re-ported. Excluded partic-ipants who failed to at-tend clin-ics or failed to comply with treat-ment (ex-clusions per di-agnosis re-ported but not by treatment group)	Unclear - ears?

Table 5. Outcomes assessed (Continued)

	cure not reported. Presented results for day 21 only.								
Fradis 1997	1) Clinical efficacy: cessation of otorrhoea on microscopic examination 24 hours after end of 3 weeks treatment. Reported as cure, improvement or failure - improvement has been grouped with failure for this review				** 1) Hearing assessment: audiology assessed before and 24 hours after 3 weeks treatment. Results were not reported. **		1a) Bacteriological efficacy: eradication, persistence or superinfection, 24 hours after end of treatment; Reported pre and post-treatment microorganisms isolated (including fungi, Candida). 1b) Sensitivity of pre and post (24 hrs)-treatment bacteria to ciprofloxacin and tobramycin		Ears
Gyde 1978	1) Ears with clinical cure or failure at 6 months: Success: dry ear		1) Mean duration of treatment (days). Reported for successful ears only;	1) Relapse	1) Hearing assessment in 50 participants: pre and post-treatment audiometry	1) Ototoxicity: pre and post-treatment audiometry, with a follow-up audiometry	1) Bacteriology - reported cure, improvement or failure according to pre-	Negative bacterial culture was included in the definition of cure	Ears

Table 5. Outcomes assessed (Continued)

within 3 weeks of treatment, or sufficiently improved after 3 weeks that 3 weeks further therapy allowed the discharge to stop; with negative post-treatment culture; and no return of the same strain of causative organism within 6 months of stopping treatment.		includes crossed over treatment times		etry, with a follow-up audiogram by a certified audiologist.	diogram by a certified audiologist. Post-treatment observations	treatment bacteria cultured; Results include crossed over cases.		
Failure: evidence of exudate after 3 weeks, with a positive culture and little hope of further improvement. Failures at 6 months were allocated the alterna-				Results for average hearing loss before and after treatment, average improvement, and variation in improvement, are reported for each treatment group and treatment + 'intervention' (unclear what this is - possibly surgery).	were 3 to 12 months after medical treatment or surgery, to detect any delayed ototoxicity.			
				Post-treatment observations were 3 to 12 months after medical treatment or surgery, to detect any delayed ototoxicity.	Audiometry (or an assessment of impedance, or both) assessed for a subset of 50 subjects only (not reported separately by diagnosis).			
					2) Adverse reactions: open-ended question with further questioning for intensity of reaction. No specific or sugges-			

Table 5. Outcomes assessed (Continued)

	<p>tive treatment, and followed-up for 6 months as before.</p> <p>Results at 6 months, before crossover, have been taken for this review</p>				<p>Audiometry (or an assessment of impedance, or both) assessed for a subset of 50 subjects only.</p> <p>Results were not reported separately by diagnosis; all analysed cases are included in this review</p>	<p>tive questions were asked</p>			
Gyde 1981	<p>1) Ears with clinical cure or failure at 3 months:</p> <p>Success: dry ear clinically within 3 weeks of treatment, with negative post-treatment culture, and no return of the same strain of causative organism within 3 months of stopping treatment.</p>				<p>** 1) Hearing assessment: pre and post-treatment audiometry, with a follow-up audiogram by a certified audiologist. Only reported negative findings in relation to ototoxicity - see safety column.**</p>	<p>1) Ototoxicity: pre and post-treatment audiometry, with a follow-up audiogram by a certified audiologist.</p> <p>2) Adverse reactions: open-ended question with further questioning for intensity of reaction. No specific</p>	<p>1) Bacteriology - reported cure or failure according to pre-treatment bacteria cultured</p>	<p>Negative bacterial culture was included in the definition of cure.</p> <p>Participants were examined at Days 7 and 14, and 3 months after completing therapy to detect any delayed toxicity.</p> <p>Clarification has</p>	Ears

Table 5. Outcomes assessed (Continued)

	Failure: evidence of exudate after 3 weeks, with a positive culture and little hope of further improvement					or suggestive questions were asked		been sought regarding the timings of the outcomes (2 weeks, 3 weeks or 3 months)	
Jaya 2003	1) State of discharge (actively discharging or inactive) on microscopy. Assessed at study start and weeks 1, 2, 3, and 4 (results presented for all 4 weeks)				** 1) Hearing assessment: pure tone audiometry (PTA) measured at study start and week 4. Only stated a lack of cases with deteriorated hearing on PTA; improvement not reported **	1) Pure tone audiometry (PTA) measured at study start and week 4. Reported lack of cases with deteriorated hearing on PTA only. 2) Ototoxic effects or allergy to the drug; specific inquiries for symptoms at weeks 1, 2, 3, and 4	1) Bacteriology and sensitivity of pus culture at study start, and week 4 (if still discharging)		Participant
Kasemsuwan 1997	1) Clinical response (no discharge on microscopic exam-				** 1) Hearing assessment: audiometric measurements before treat-	1) Adverse effects of medication: recorded at each visit (treat-	1) Bacteriological response after 7 days (eradication; only performed		Unclear - participants?

Table 5. Outcomes assessed (Continued)

	ination) after 7 days				ment and within 48 hours post therapy. Only presented results in relation to ototoxicity, and not improvement in hearing.**	ment days 1, 4 and 7) 2) Ototoxicity: audiometric measurements assessed before treatment and within 48 hours post-treatment	aerobic culture). Sensitivity analysis also conducted.		
Kaygusuz 2002	<p>1) Clinical response - subjective assessment according to scale of discharge: complete improvement (no discharge); partial improvement (moist/wet); or unsuccessful (discharge filled the middle ear or external canal).</p> <p>Partial improvement has been classified as failure for this review.</p> <p>Participants were as-</p>					<p>** Not reported as an outcome, although a lack of additional side-effects when adding steroid to treatment, was reported in the discussion.**</p>	1) Bacteriology before and after treatment, and resistance of pre-treatment cultures to ciprofloxacin and tobramycin		Participant

Table 5. Outcomes assessed (Continued)

	essed daily for three weeks. Results were reported for Days 7, 14 and 21								
Lorente 1995	1) Number and proportion of participants with dry ears (presence or absence of otorrhoea, assessed on otoscopy) at Day 8				**1) Hearing assessment: audiometry to detect deterioration in hearing in relation to ototoxicity; Not reported improvement or degree of change. **	1) Ototoxicity: assessment of audiometry results and report of tinnitus to detect deterioration in hearing, and of balance to detect damage to the labyrinth. 2) Adverse events: local (pain, pruritis, stinging etc) and general	1) Participants with negative bacterial cultures (pre and post-treatment bacteriology assessed) ; only reported proportions, not numbers. 2) Changes in mean scores for otorrhoea, pruritus (itching), stinging, pain, irritation and tinnitus at days 8 and 30. Scoring was on a scale of 0 (absent) to 3 (severe)	All outcomes were assessed at visits on Days 0 (before treatment), 8 and 30. Telephone contact on Day 3, to collect details of adverse events only	Participant
Macfadyen 2005	1) Resolution of aural discharge on otoscopy at two and	1) Healing of the tympanic membrane on otoscopy			1) Change in hearing threshold (pure tone audiometry)	1) Adverse event probe - reported adverse		Participants were followed-up at weeks 2 and 4; re-	Participant

Table 5. Outcomes assessed (Continued)

	four weeks (resolution at two weeks was the primary outcome)	at 2 and 4 weeks			etry) from baseline at 2 and 4 weeks.	events of interest only (local symptoms of pain, irritation and bleeding on mopping) at weeks 2 and 4		ported results for both visits.	
					Hearing threshold in dB HL was averaged across 0.5, 1, 2 and 4 kHz.			All analyses followed the intention-to-treat principle.	
					Unilateral cases: 1 single reading taken from the diseased ear; Bilateral disease: calculated average across both ears.			For bilateral cases, success was defined as when both ears resolved or healed; sensitivity analysis used success for bilateral cases when either or both ears resolved or healed	
					Presented results for mean improvements in hearing threshold, and the difference in improvement between treatments, controlling for baseline threshold				

Table 5. Outcomes assessed (Continued)

					<p>with analysis of covariance (AN-COVA). Adding background noise as an additional covariate did not change the conclusions.</p> <p>Also described hearing impairment levels using WHO classifications; considered changes between levels using Fishers exact test</p>				
Tutkun 1995	1) Clinical success 24 hours after 10 days treatment: cessation of otorrhoea on otoscopy and eradication of microorganisms in post-treatment culture (aero-				<p>Differences between average pre-treatment and post-treatment (24 hours after 10 days treatment) mean values of:</p> <p>1) speech reception thresh-</p>	<p>1) Ototoxicity: pure tone threshold, and speech discrimination scores assessed before and 24 hours post-treatment.</p> <p>2) Safety: absence of side-effects</p>	<p>1) Sensitivity to gentamicin and ciprofloxacin of aerobic culture taken 24 hours before treatment and 24 hours after completing treatment</p>	<p>Participants were assessed on Days 2, 5, 7 and 10. Final assessment 24 hours after completing 10 days treatment.</p> <p>Negative bacterial culture</p>	Participant

Table 5. Outcomes assessed (Continued)

	bic culture only)				olds; 2) speech discrimination scores; 3) pure tone thresholds for air conduction (dB HL, at 250 to 8000 Hz); 4) pure tone thresholds for bone conduction (dB HL, at 500 Hz to 4000 Hz). Also: 6) Pre-treatment and post-treatment air-bone gaps (dB HL at 500 Hz to 4000 Hz (dB HL). For all hearing analyses, only averages have been reported, with no standard deviation or other in-	reported in results but not specified as an outcome for assessment		was included in the definition of cure	
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Table 5. Outcomes assessed (Continued)

					dicators of variation or range of results				
van Has- selt 1997	1) Dry or wet ear af- ter 1 and 2 weeks.							Results for cure at week 2 were dis- crepant be- tween the 1997 CBM report (see figures and re- sults text) and 2002 paper (see results text) for acetic acid and neomycin- polymyxin B	Ears
van Has- selt 1998	1) Resolu- tion of ot- orrhoea at weeks 1, 2 (end of treatment) and week 8: inactive when com- pletely dry middle ear; active when otor- rhoea still present. Presented % ears cured at each visit, but only reported						1) Medicine cost per healed ear after week 8.		Ears

Table 5. Outcomes assessed (Continued)

	numbers per group at week 2								
van Has- selt 2002	1) Dry ears after 1 week.								Ears

Table 6. Gyde 1978 Hearing analysis measured in dB (TSP versus gentamicin at 3-12 months

Intervention	Number exam- ined	Number improved	Ave dB loss be- fore	Ave dB loss after Rx	Average hearing gain	dB variation in gain
Topical non- quinolone antibiotic:						
Trimethoprim- polymyxin-B- sulfacetamide (TSP)	19 (any diagno- sis)	17	31.3	13.5	17.8	? to 43
TSP + interven- tion (not speci- fied)	25 (any diagno- sis)	24	35.7	16.1	20.0	-6 to 53
Topical non- quinolone antibiotic:						
Gentamicin	26 (any diagno- sis)	23	35.9	19.6	16.4	0 to 35
Gentam- icin + interven- tion (not speci- fied)	22 (any diagno- sis)	20	37.9	19.6	18.2	-3 to 34

Table 7. Tutkun 1995 Hearing analysis: pre and post-treatment pure tone thresholds (dB HL

Frequency	Ciprofloxacin - air	Ciprofloxacin - bone	Gentamicin - air	Gentamicin - bone
250 Hz				
Difference (dB HL)	-1.2		2.0	
500 Hz				

Table 7. Tutkun 1995 Hearing analysis: pre and post-treatment pure tone thresholds (dB HL) (Continued)

Pre-treatment (dB HL)	38.3	14.5	34.8	11.8
Post-treatment (dB HL)	35.4	12.7	31.7	13.3
Difference (dB HL)	+2.9	+1.8	+3.1	-1.5
1000 Hz				
Pre-treatment (dB HL)	32.3	13.3	35.8	10.1
Post-treatment (dB HL)	31.7	10.4	30.3	14.0
Difference (dB HL)	+0.6	+2.9	+5.5	-3.9
2000 Hz				
Pre-treatment (dB HL)	30.5	13.1	31.5	12.5
Post-treatment (dB HL)	29.5	14.0	27.5	14.6
Difference (dB HL)	+1.0	-0.9	+4.0	-2.1
4000 Hz				
Pre-treatment (dB HL)	36.0	22.2	37.6	23.9
Post-treatment (dB HL)	31.3	19.5	40.6	24.6
Difference (dB HL)	+4.7	+2.7	-3.0	-0.7
8000 Hz				
Difference (dB HL)	+7.7		+4.0	

Table 8. Tutkun 1995 Hearing analysis: pre and post-treatment air-bone gaps (in dB HL)

Group	500 Hz	1000 Hz	2000 Hz	4000 Hz
Ciprofloxacin				
Pre-treatment (dB HL)	25.0	23.0	18.0	15.7
Post-treatment (dB HL)	24.5	18.2	15.7	12.3
Gentamicin				
Pre-treatment (dB HL)	21.4	25.7	17.1	15.1

Table 8. Tutkun 1995 Hearing analysis: pre and post-treatment air-bone gaps (in dB HL) (Continued)

Post-treatment (dB HL)	22.5	20.0	16.4	17.8
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Table 9. Tutkun 1995 Hearing analysis: pre and post-treatment SRTs and SDSs

Assessment	Ciprofloxacin	Gentamicin	student's t-test p
Speech Reception Threshold (SRT) (dB HL)			
Pre-treatment	34.3	34.4	
Post-treatment	30.8	30.2	
Difference (dB HL)	+3.5	+4.2	P > 0.01
Speech Discrimination Score (SDS)			
Pre-treatment	96.3%	96.0%	
Post-treatment	96.6%	98.4%	
Difference (%)	-0.3%	-2.4%	P > 0.01

Table 10. Macfadyen 2005 Hearing analysis: average change from baseline at 2 and 4 weeks

Week	Treatment Group	N	dB Mean Improve (SD)	Dif 95%CI: cip-boric	p
				(ANCOVA controlling for baseline audio level)	(ANCOVA controlling for baseline audio level)
2 weeks	Ciprofloxacin Boric acid	201 202	4.32 (11.18) 2.69 (11.67)	2.17 (0.09 to 4.24)	0.0410
4 weeks	Ciprofloxacin Boric acid	196 194	5.42 (11.03) 2.63 (12.18)	3.43 (1.34 to 5.52)	0.0014

Table 11. Safety

Study ID	Treatment comparison	Allergic reaction	Ototoxicity	Other AE
Gyde 1978	1) Topical non-quinolone antibiotic: trimethoprim-polymyxin B-sulfacetamide eardrops.	The treatments did not cause any allergic reactions.	The results of audiometry (tested on 50 subjects, 3 to 12 months after treatment or addi-	There were no unfavourable reactions nor side effects following the administration

Table 11. Safety (Continued)

	2) Topical non-quinolone antibiotic: gentamicin 0.3% eardrops		<p>tional surgery) showed no signs of ototoxicity either immediately after the treatment, or later on, for either treatments (see separate table for results).</p> <p>The majority of the participants tested showed an improvement of the auditory acuteness, and hearing results remained stable in all cases examined during the 3 to 12 month post-observation period</p>	<p>of either treatment.</p> <p>The participants did not complain about pain, itching or of burn.</p> <p>The treatment did not cause allergic reactions not excessive fungal growth</p>
Gyde 1981	<p>1) Topical non-quinolone antibiotic: trimethoprim-polymyxin B-sulfacetamide eardrops.</p> <p>2) Topical non-quinolone antibiotic: trimethoprim-polymyxin B eardrops</p>		<p>There were no signs of ototoxicity.</p> <p>[From abstract only - data not presented]</p>	<p>There were no incidences of side-effects/local sensitivity, or fungal infection overgrowth.</p> <p>[From abstract and discussion only - data not presented]</p>
Jaya 2003	<p>1) Topical quinolone: 0.3% ciprofloxacin hydrochloride eardrops.</p> <p>2) Topical antiseptic: 5% povidone-iodine eardrops.</p>	No patients developed allergic manifestations.	<p>No patients developed ototoxic effects.</p> <p>There was no deterioration of hearing as assessed by pure-tone audiometry</p>	
Kasemsuwan 1997	<p>1) Topical quinolone: ciprofloxacin in saline eardrops.</p> <p>2) Topical placebo: normal saline eardrops.</p>		No worsening of audiological measurements (taken 24 hours after completing treatment) was detected	No medical side-effects related to the topical medication were detected in the study
Lorente 1995	<p>1) Topical quinolone: ciprofloxacin eardrops 0.3%</p> <p>2) Topical non-quinolone: gentamicin 0.3%</p>		<p>One case (on gentamicin) of slight auditory disorder was detected on audiometry; the loss was considered to be only slight and without clinical relevance by the trialists.</p> <p>One case of loss of bal-</p>	<p>Both treatments were reported to be very well tolerated with respect to general side effects.</p> <p>No cases of superinfection with fungus (<i>Candida albicans</i> or <i>Aspergillus</i>) were observed</p>

Table 11. Safety (Continued)

			<p>ance was reported before treatment in a patient randomised to ciprofloxacin; this disappeared during the course of treatment.</p> <p>A joint analysis of the action of both treatments showed no statistically significant effects on the audiometry results ($P = 0.21$)</p>	
Macfadyen 2005	<p>1) Topical quinolone: ciprofloxacin eardrops (after dry mopping)</p> <p>2) Topical antiseptic: boric acid in alcohol eardrops (after dry mopping)</p>			For adverse events of ear pain, irritation and bleeding on mopping, there was a higher frequency in the boric acid group (30/206) than in the ciprofloxacin group (17/210)
Tutkun 1995	<p>1) Topical quinolone: ciprofloxacin eardrops</p> <p>2) Topical non-quinolone: gentamicin eardrops</p>		<p>Audiometric evaluation yielded no evidence of ototoxicity as reflected by the pure tone threshold and speech discrimination scores in either group.</p> <p>Instead, hearing thresholds were slightly better than pre-treatment levels in both groups (Ozagar 1997)</p>	There were no side effects.

APPENDICES

Appendix I. Search strategy for CENTRAL

#1 OTITIS MEDIA SUPPURATIVE single term (MeSH)
#2 OTITIS MEDIA explode all trees (MeSH)
#3 otitis media
#4 #2 OR #3
#5 SUPPURATION explode all trees (MeSH)
#6 suppurat* OR purulen* OR PUS
#7 #5 OR #6
#8 #4 AND #7
#9 CHRONIC DISEASE explode all trees (MeSH)
#10 CHRONIC* OR PERSIST*
#11 #9 OR #10
#12 #1 AND #11
#13 #8 AND #11
#14 #12 OR #13
#15 CHRONIC* NEAR DISCHARG*
#16 PERSIST* NEAR DISCHARG*
#17 #15 OR #16
#18 #4 AND #17
#19 CSOM OR OTORRH* OR OTORH*
#20 #14 OR #18 OR #19
#21 MASTOIDITIS single term (MeSH)
#22 MASTOIDITIS
#23 TYMPANIC MEMBRANE PERFORATION single term (MeSH)
#24 EAR* NEAR DRUM* OR EARDRUM* OR TYMPANIC
#25 PERFORAT* OR RUPTUR*
#26 #24 AND #25
#27 #20 OR #21 OR #22 OR #23 OR #26
#28 ANTI INFECTIVE AGENTS explode all trees (MeSH)
#29 ACETIC ACID explode all trees (MeSH)
#30 BORIC ACIDS explode all trees (MeSH).
#31 antibiot* OR antibact* OR antisept* OR antiinfect* OR
microbides OR bacteriocid* OR antimicrobial* OR
antimycobact*
#32 anti ADJ (biot* OR bact* OR sept* OR infect* OR
mycobact* OR microbial*)
#33 borax OR boric OR hydrogen peroxide OR iodine OR acetic acid
OR burow* OR acetate* OR acetyl
#34 #28 OR #29 OR #30 OR #31 OR #32 OR #33
#35 #27 AND #34
#36 OTITIS-MEDIA-SUPPURATIVE-QT.DE.
#37 #35 OR #36

WHAT'S NEW

Date	Event	Description
30 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 4, 2005

Date	Event	Description
24 August 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Jose Acuin (JA) was the primary author for the Cochrane Review 'Interventions for chronic suppurative otitis media', that this review replaces.

Carolyn Macfadyen (CM) designed the current review, in consultation with JA.

CM and JA worked with Gemma Healy (GH) and Carolyn Doree (CD), the Cochrane ENT Group Trials Search Co-ordinators, for the search strategy development. GH ran the initial electronic searches, and performed a preliminary screen of the search results; CD ran the search update in March 2005. Both searches were carried out independently.

CM and JA independently reviewed the titles and abstracts identified during the search for preliminary assessment, and CM retrieved and reviewed the full papers for all potentially relevant studies. CM will organise retrieval of future unpublished studies, and will contact authors for additional information or clarifications where needed.

CM assessed the methodological quality of all trials identified for inclusion, extracted data, and entered data into Review Manager 4.2 for analysis. JA and Carrol Gamble (CG) provided a second opinion on trials CM had selected for inclusion; CG reviewed those where there was any ambiguity about the methods used, for the methodological quality and data extraction; and JA provided further information where this had been obtained from authors of trials included in the previous review 'Interventions for chronic suppurative otitis media' (Acuin 1998). The three authors resolved any disagreements through discussion.

CM and CG have worked on one trial in the review (Macfadyen 2005); no third party input was enlisted for this trial.

CM wrote the final review, with statistical and clinical input from CG and JA. All three authors provide the methodological perspective; CG also provides the statistical perspective and JA the clinical perspective.

DECLARATIONS OF INTEREST

None known. However, Carolyn Macfadyen and Carrol Gamble conducted and analysed a trial comparing a topical aural antiseptic, boric acid, with a topical aural antibiotic, ciprofloxacin (Macfadyen 2005).

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- Cochrane Infectious Diseases Group, UK.

External sources

- Cochrane Ear, Nose and Throat Disorders Group, UK.
- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following changes were made to the eligibility criteria and outcome measures from those stipulated in the protocol:

1. ELIGIBILITY CRITERIA

Types of studies: quasi-randomised controlled trials were specified in the protocol but excluded from the review.

Types of participants:

Protocol: People of any age with a diagnosis of CSOM meeting the WHO definition

Review: any diagnosis of CSOM as defined by the trial authors.

Types of interventions - the following were stipulated in the protocol:

Intervention: topical (aural) antibiotics (all and individual)

Comparator: no intervention; placebo; other topical antibiotics with and without steroids; systemic antibiotics (all and individual); combination of topical and systemic antibiotics; antiseptics.

However, we have divided these trials into the following three reviews:

* Topical treatment with antibiotics (THIS REVIEW)

comparisons: no treatment or aural toilet, topical antiseptics, various topical antibiotics, excluding steroids

* Systemic versus topical treatments for CSOM

comparisons: any systemic treatment against any topical treatment excluding steroids

* Systemic or topical steroids, as monotherapy or combination therapy

comparisons: no treatment or aural toilet, topical antiseptics, topical antibiotics, systemic antibiotics

2. OUTCOMES

Types of outcome measures - the following primary outcomes have been changed:

Protocol:

* Resolution of CSOM at 2 to 4 weeks and after 4 weeks, according to the following findings:

a) No report of otorrhoea

- b) Disappearance of discharge on otoscopy
- c) Healing of the eardrum perforation on otoscopy
- d) Time to resolution of CSOM according to any other definition of resolution made by the authors, including improvement in mucosal appearance

Review:

* Resolution of CSOM at 2 to 4 weeks, and after 4 weeks, according to the investigators' criteria.

We have also analysed results for treatment failure rather than success.

The others were analysed as separate, secondary outcomes (where reported by trialists):

* Healing of perforation at 2 to 4 weeks, and after 4 weeks;

* Time to resolution of CSOM as defined by the investigators.

The other protocol outcomes were unchanged, except that results before 2 weeks were also included and reported separately.

3. SEARCH STRATEGY

The protocol stated that we would obtain all relevant studies regardless of publication status. However, trials reported in conference proceedings or on posters have not yet been sought, but will be sought for inclusion in an update of this review. Additionally, the further potential sources that we will search for future updates of this review, were also specified in the protocol for this review.

4. METHODS - REVIEWERS' CONTRIBUTIONS

The protocol stated that we would follow the statistical guidelines in the Cochrane ENT Group Guidelines for Reviewers (Cochrane ENT Guideline, updated November 2000), and that two reviewers (CM and JA) would independently:

* select trials (at least for electronic searches), review the titles and abstracts of articles identified by the search strategy, and assess full texts for eligibility;

* assess the methodological quality of all trials identified as eligible for inclusion (and report the level of agreement between the two reviewers);

* extract data of study characteristics, including methods, participants, interventions and outcomes, and record these on standard forms; and

* enter data onto Review Manager 4.2.

However, while CM and JA independently reviewed titles and abstracts of articles identified by the search strategy, only CM assessed the full texts for eligibility and methodological quality, extracted data, and entered data onto Review Manager 4.2. JA and CG provided a second opinion on trials CM had selected for inclusion; CG reviewed those where there was any ambiguity about the methods used, for the methodological quality and data extraction; and JA provided further information where this had been obtained from authors of trials included in the previous review 'Interventions for chronic suppurative otitis media' (Acuin 1998). The three authors resolved any disagreements through discussion.

5. MINIMISING CONFLICTS OF INTERESTS

The protocol also stated that where one of the authors has worked on a trial in the review, we will seek help from another person at the ENT editorial base, to minimise bias due to potential conflict of interests. However, CM and CG both worked on one trial, Macfadyen 2005; no third party input was enlisted.

6. ASSESSMENT OF METHODOLOGICAL QUALITY

The protocol stated that allocation concealment, and inclusion of randomised participants, would be assessed as inadequate if an allocation concealment approach was not reported, or it was not clear how many people were originally randomised into the trial, respectively. However, we have classed these as unclear.

We assessed the methodological quality of the trials using the following dimensions and criteria based on four methodological aspects.

- a) Generation of allocation sequence

Adequate: if sequences are suitable to prevent selection bias and the method used is described.

Adequate methods include random numbers generated by computer, table of random numbers, drawing of lots or envelopes, tossing a coin, shuffling cards, throwing dice, or other methods of allocation that appear to be unbiased.

Unclear: stated but method not described.

The trial describes itself as being randomised but no further information is given.

Inadequate: if sequence could be related to prognosis.

Inadequate methods include case record number, date of birth, time, day, month or year of admission.

b) Allocation concealment

Adequate: if participants and investigators enrolling participants cannot foresee assignment. Adequate measures include a priori numbered or coded containers of identical appearance, central randomisation; sequentially numbered, opaque, sealed envelopes; or other descriptions that contained convincing elements of concealment.

Inadequate: trials in which the authors reported an approach that could not be considered adequate (e.g. methods of allocation such as alternation methods or use of case record numbers are not concealed).

Unclear: trials in which the authors either did not report an allocation concealment approach at all or allocation concealment was stated but method not described.

Baseline comparison of experimental groups will confirm whether treatment arm allocation appears to be unbiased.

c) Blinding

Double blind: the trial uses a placebo, or a double dummy technique such that neither the participant or care provider/assessor know which treatment is given.

Single blind: the participant or care provider/assessor is aware of the treatment given.

Open: all parties are aware of treatment.

d) Inclusion of all randomised participants

Adequate: More than 90% of people randomised in the trial were included in the analysis.

Inadequate: Less than 90% of those randomised in to the trial were included in the analysis.

Unclear: It is not clear how many people were originally randomised into the trial or analysed.

7. DATA ANALYSIS

The protocol stated that we would only include the results for CSOM participants where available, for studies that also enrolled people with otitis externa, draining surgical cavities or acute otitis media. However, we only did so if the authors reported stratifying randomisation by diagnosis. Where information was not reported regarding whether alternative diagnostic groups were stratified at randomisation, we included all participants (groups may be unbalanced, and decisions by trialists to report subgroups may have been linked to trend).

NOTES

This review, 'Topical antibiotics for chronically discharging ears with underlying eardrum perforations' is one in a series of reviews, which replaces the review 'Interventions for chronic suppurative otitis media'. Reviews of other interventions will follow.

REVIEW HISTORY

Issue review first published: 1998/4 (Interventions for chronic suppurative otitis media).

Date of most recent amendment: Information not available.

Date of most recent SUBSTANTIVE amendment: 12 February 1998.

Most recent changes:

February 1998.

October 2001: Cochrane review 'Interventions for chronic suppurative otitis media' split into a series of Cochrane review titles, each focusing on particular interventions.

Issue 1, 2004: Publish protocol for component review 'Topical antibiotics for chronically discharging ears with underlying eardrum perforations'.

DEVIATIONS FROM THE PROTOCOL: see [Differences between protocol and review](#).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Anti-Infective Agents, Local [therapeutic use]; Chronic Disease; Developing Countries; Hearing Disorders [drug therapy; etiology]; Otitis Media, Suppurative [complications; *drug therapy]; Quinolones [therapeutic use]; Randomized Controlled Trials as Topic; Tympanic Membrane Perforation [complications; *drug therapy]

MeSH check words

Humans