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Systemic corticosteroids for acute otitis media in children

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[Intervention Review]

Systemic corticosteroids for acute otitis media in children

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ABSTRACT

Background

Acute otitis media (AOM) is a common acute infection in children. Pain is its most prominent and distressing symptom. Antibiotics are commonly prescribed for AOM, although they have only a modest effect in reducing pain at two to three days. There is insufficient evidence for benefits of other treatment options, including systemic corticosteroids. However, systemic corticosteroids are potent anti-inflammatory drugs, and so theoretically could be effective, either alone or as an addition to antibiotics.

Objectives

To assess the effects of systemic corticosteroids (oral or parenteral), with or without antibiotics, for AOM in children.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) which contains the Cochrane ARI Group's Specialised Register, MEDLINE (Ovid), Embase (Elsevier), CINAHL (EBSCO), Web of Science (Thomson Reuters), and LILACS (BIREME) for published studies, and ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for completed and ongoing studies, to 20 February 2018. We checked the reference lists of all primary studies and review articles for additional references and contacted experts in the field to identify additional unpublished materials.

Selection criteria

We included randomised controlled trials of children with AOM that compared any systemic corticosteroid (oral or parenteral) with placebo, either with antibiotics (corticosteroid plus antibiotic versus placebo plus antibiotic) or without antibiotics (corticosteroid versus placebo).

Data collection and analysis

Three review authors (EDS, RR, YP) independently screened the titles and abstracts and retrieved the full texts of potentially relevant studies. We independently extracted study characteristics and outcome data from the included studies, and assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. We assessed study quality using the GRADE method.

Systemic corticosteroids for acute otitis media in children (Review)

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Main results

We included two studies involving 252 children with AOM aged from three months to six years receiving hospital ambulatory care who were treated with intramuscular ceftriaxone, and who were then randomised to the corticosteroid group (corticosteroid and corticosteroid plus antihistamine) or the placebo group (antihistamine and double placebo). In one study, children also had a needle aspiration of middle ear fluid. Both studies were at unclear risk of bias for allocation concealment, and unclear to high risk of bias for selective reporting.

One study (N = 179) included pain as an outcome, but we were unable to derive the proportion of children with persistent pain at Day 5 and Day 14. Reduction of overall or specific symptoms was presented as improvement in clinical symptoms and resolution of inflamed tympanic membranes without the need for additional antibiotic treatment: at Day 5 (94% of children in the treatment group (N = 89) versus 89% in the placebo group (N = 90); risk ratio (RR) 1.06, 95% confidence interval (CI) 0.97 to 1.16) and Day 14 (91% versus 87%; RR 1.05, 95% CI 0.95 to 1.17). Low-quality evidence meant that we are uncertain of the effectiveness of corticosteroids for this outcome.

The second study (N = 73) reported a reduction of overall or specific symptoms without additional antibiotic treatment during the first two weeks as a favourable outcome. Children in the treatment group had more favourable outcomes (adjusted odds ratio 65.9, 95% CI 1.28 to 1000; P = 0.037), although the numbers were small. We were unable to pool the results with the other study because it did not report the proportion of children with this outcome by treatment group. Only one study reported adverse effects of corticosteroids (e.g. drowsiness, nappy rash), but did not quantify incidence, so we were unable to draw conclusions about adverse effects. Neither study reported a reduction in overall or specific symptom duration.

Authors' conclusions

The evidence for the effect of systemic corticosteroids on AOM is of low to very low quality, meaning the effect of systemic corticosteroids on important clinical outcomes in AOM remains uncertain. Large, high-quality studies are required to resolve the question.

PLAIN LANGUAGE SUMMARY

Systemic corticosteroids for improving symptoms in children with acute middle ear infection

Review question

We reviewed the evidence on the effects of corticosteroids given by mouth or injection for acute middle ear infection (acute otitis media (AOM)) in children, particularly in improving symptoms such as ear pain, fever, irritability, lack of sleep, and lack of appetite. We also looked at the side effects of corticosteroids.

Background

Acute otitis media is common in children and causes ear pain and non-specific symptoms such as fever, irritability, and deafness. It is often treated with antibiotics, although ear pain generally resolves within two days, and antibiotics help symptoms only slightly. Other treatments (such as over-the-counter antihistamines and decongestants) do not help very much.

Corticosteroids are often prescribed to reduce inflammation in children for other illnesses, and so may also help symptoms of AOM, which is an inflammatory process. We investigated whether using corticosteroids was better or worse than nothing in improving AOM-related symptoms.

Search date

Our evidence is current to 20 February 2018.

Study characteristics

We included two studies involving 252 children with AOM, aged from three months to six years, receiving hospital ambulatory care. Children were treated with an antibiotic injection and either oral corticosteroid or a placebo (treatment with no effect). In one study, fluid from the middle ear was collected by inserting a needle through the eardrum to measure the level of inflammation.

Study funding sources

The National Institutes of Health (NIH) and the National Center for Research Resources, NIH, US Public Health Service funded both studies. Pharmaceutical companies provided the drug but did not contribute any other scientific or financial support.

Key results and quality of evidence

Corticosteroids did not make a significant difference in improving the symptoms and inflammation of the eardrum(s) at Day 5 and Day 14, but we are unsure of this effect due to the small numbers of children in the studies. There were no significant differences between the corticosteroid and placebo groups in terms of resolving fluid in children's middle ears (at 1, 2, and 3 months) and experiencing new episodes of AOM (at 1, 2, 3 months, and 4 and 6 months). Neither study reported a reduction in the duration of overall or specific symptoms, rupture of eardrum(s), the occurrence of middle ear inflammation in the other ear following the current ear infection, or serious complications. Only one study reported the overall side effects identified during the trial (e.g. drowsiness, dry mouth, diaper rash, nervousness).

We could not draw any conclusions regarding the effects of corticosteroids for AOM in children.

The quality of evidence included in this review was low to very low due to few children included in two small studies. We are uncertain about whether or not corticosteroids are useful in relieving pain from AOM.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Systemic corticosteroids versus placebo for children with acute otitis media						
Patient or population: children with acute otitis media Setting: paediatric outpatient clinics Intervention: systemic corticosteroids Comparison: placebo						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with systemic corticosteroids				
Proportion of children with pain at various time points						
<i>Day 5</i>	Study population		Not estimable	(0 studies)	-	Only pre-treatment data were available. We could not retrieve post-treatment data
	0 per 1000	0 per 1000 (0 to 0)				
<i>Day 14</i>	Study population		Not estimable	(0 studies)	-	Only pre-treatment data were available. We could not retrieve post-treatment data
	0 per 1000	0 per 1000 (0 to 0)				
Reduction of overall or specific symptoms at various time points						
<i>Day 5</i>	Study population		RR 1.06 (0.97 to 1.16)	179 (1 RCT)	⊕⊕○○ LOW ¹	This outcome was represented as the proportion of children for whom symptoms and inflamed eardrum(s) resolved and who did not require additional antibiotic treatment

	889 per 1000	942 per 1000 (862 to 1000)				
<i>Day 14</i>	Study population		RR 1.05 (0.95 to 1.17)	179 (1 RCT)	⊕⊕○○ LOW ¹	This outcome was represented as the proportion of children for whom symptoms and inflamed eardrum(s) resolved and who did not require additional antibiotic treatment
	867 per 1000	910 per 1000 (823 to 1000)				
Reduction in overall or specific symptom duration	Study population		Not estimable	(0 studies)	-	No study provided data for this outcome.
	0 per 1000	0 per 1000 (0 to 0)				
Adverse effects	Study population		Not estimable	(0 studies)	-	The available data were reported as an overall result. We could not retrieve data from each individual group (overall side effects across all groups: drowsiness (22% to 34%), dry mouth (16% to 27%), increased urine amount (14% to 27%), nappy rash (7% to 32%), nervousness (7% to 20%), and decreased urine amount (0% to 11%).
	0 per 1000	0 per 1000 (0 to 0)				

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Downgraded one level due to study limitations (unclear description of the allocation concealment and evidence of selective reporting) and one level due to indirectness (differences between the outcome of interest (i.e. in reporting, measurements) and reported outcomes).

BACKGROUND

Description of the condition

Acute otitis media (AOM) is a common complication of acute respiratory infections. A prospective, longitudinal cohort study found an overall incidence of 37% over one year for AOM following an acute respiratory infection usually caused by viruses, in children aged six months to three years (Chonmaitree 2008). Before the age of three years, approximately 80% of children experience at least one episode of AOM, mostly affecting those younger than two years old (Lieberthal 2013; SACHCN 2014; Vergison 2010). Immaturity and the anatomy of the Eustachian tube may contribute to AOM (SACHCN 2014).

Clinicians commonly diagnose AOM in children who present with ear pain (holding, tugging, rubbing of the ear in a non-verbal child) or intense erythema of the tympanic membrane, or moderate-to-severe bulging of the tympanic membrane, or ear discharge not from otitis externa (NSW Health 2014; Pichichero 2015).

Acute symptoms (pain and systemic symptoms) resolve in 60% of children within 24 hours and 80% within 72 hours (Morris 2009; Venekamp 2015). Children aged up to two years often experience more severe and protracted illness (Chonmaitree 2008). Studies have reported that 62% of children aged up to 12 months experience at least one episode of AOM. Acute otitis media is recurrent in 10% to 30%, and 2% to 25% of children experience persistent middle ear effusion for three months, which may require ventilation tube (grommet) insertion to relieve the accompanying deafness (Gribben 2012; Kitamura 2015).

The prevalence of AOM varies across Asian countries. In Korea, a 1991 national survey reported a point prevalence of 0.08% for AOM in children aged up to 15 years (Lee 2012); in Malaysia, 9% of children aged three months to 12 years experienced AOM over the previous three years (Tikaram 2012). A 2005 study in Taiwan found that 13.2% of children aged up to seven years had experienced AOM (Ting 2012). In East Jakarta, Indonesia, the point prevalence of AOM in children aged less than 18 years was 5.4% (Umar 2013).

The risk of AOM is high in Australian indigenous populations: a cluster survey in Indigenous versus non-Indigenous children found that severe otitis media was more prevalent in Indigenous children (7.9%) compared to non-Indigenous children (1.7%) (Gunasekera 2007).

Pain is the most common symptom of AOM. Guidelines recommend analgesics such as paracetamol or ibuprofen (Lieberthal 2013; NSW Health 2014; SACHCN 2014). Analgesics have been trialed against placebo in AOM, with ibuprofen (7% versus 25.3%; risk ratio (RR) 0.28, 95% confidence interval (CI) 0.11 to 0.71) and paracetamol (9% versus 25.3%; RR 0.38, 95% CI 0.17 to 0.85) both significantly reducing ear pain 48 hours after treatment (Bertin 1996; Bradley-Stevenson 2007). However, there

is insufficient evidence of efficacy for topical analgesics reducing ear pain in AOM (Foxlee 2011).

Antibiotics are also commonly prescribed in the treatment of AOM. Antibiotics have a modest effect in reducing pain at two to three days, with a number needed to treat for an additional beneficial outcome (NNTB) of 20 children (Venekamp 2015), and yet 11% to 19% of children still experience symptoms to Day 6 (Chonmaitree 2003; Lieberthal 2013). Antibiotics have no effect on deafness caused by middle ear effusion, which persists in 30% to 60% of children one month following AOM, and three months in 15% to 25% (Chonmaitree 2003).

Recurrent AOM after an initial attack is common, with about one-third of children experiencing recurrence within a month (Chonmaitree 2003).

Antibiotics are not considered mandatory. An alternative strategy is observation (Lieberthal 2013; Pichichero 2015).

There is limited evidence for the use of decongestant/antihistamine combinations for AOM in children: a Cochrane Review found a small statistical benefit from the combination medication, but the clinical significance was minimal and the contributing studies may have been biased (Coleman 2008).

Description of the intervention

Corticosteroids are natural steroid hormones produced by the adrenal cortex, which can be synthetically manufactured. Corticosteroids have many physiological effects, including an anti-inflammatory role (Gupta 2008), which is exploited for many acute and chronic inflammatory illnesses in adults and children (Coutinho 2011).

How the intervention might work

The pathophysiology of AOM is complex. However, inflammation is an important mechanism. This mechanism is induced by both cellular and chemical mediators, such as cytokines, chemokines, mast cells, prostaglandins, and leukotrienes (Juhn 2008). Corticosteroids could act by suppressing inflammation. Corticosteroids are effective in some other acute respiratory infections, for example when combined with antibiotics for sore throat (Hayward 2012), acute sinusitis (Venekamp 2014), and acute bacterial meningitis (Brouwer 2015). A Cochrane Review on the use of topical intranasal steroids for otitis media effusion in children found no evidence of benefit in terms of symptom relief (including ear symptoms that are crucial in the management of AOM) either at short- or longer-term follow-up (Simpson 2011).

Several studies have investigated corticosteroids for chronic otitis media with effusion (OME). A Cochrane Review on the use of topical intranasal steroids for OME in children found no evidence of benefit in improving ear symptoms, either at short- or longer-term follow-up (Simpson 2011). However, a recent randomised

controlled trial on the use of oral steroids, with and without intranasal steroids, compared to watchful waiting in children with OME demonstrated that fewer children had incomplete resolution or persistent middle ear effusion, or both, with corticosteroids compared with the watchful-waiting group at six weeks after treatment, but not in the longer term (three to nine months) (Hussein 2017). These findings demonstrate that corticosteroids may work for middle ear inflammation.

There are theoretical risks associated with corticosteroids, especially with long-term use, including Addisonian crisis after stopping treatment abruptly. However, short-term use (≤ 1 week) has not been found to cause adverse effects, nor require dose-tapering (Chonmaitree 2003; Deshmukh 2007; Venekamp 2014).

Why it is important to do this review

Antibiotics for treating AOM in children are weakly effective, but are used very often in the absence of a more effective treatment. Treatment with antibiotics also risks antibiotic resistance. Alternative, more effective treatments are therefore needed. Systemic corticosteroids may fill that role, either as a monotherapy or in addition to antibiotics. However, there is insufficient evidence to support corticosteroid treatment for AOM (Principi 2013). A Cochrane Review is important to assess studies that have not been systematically reviewed.

OBJECTIVES

To assess the effects of systemic corticosteroids (oral or parenteral), with and without antibiotics, for AOM in children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included children aged up to 15 years with AOM (this upper age being the limit for adolescence) (UNICEF 2011). We defined AOM as "...the rapid onset of ear pain accompanied with bulging and/or hyperaemic tympanic membrane and the presentation of middle ear effusion" (Lieberthal 2013; Pichichero 2015). We included both unilateral and bilateral AOM. We included children from all recruitment settings.

We excluded children with contraindications to corticosteroid therapy (e.g. immunodeficient or immunocompromised); children with anatomic or physiological disorders of the ear (including those with ventilation tubes, because this procedure is principally used for non-acute (chronic) otitis media with effusion) or nasopharynx; and those with chronic middle ear effusion.

Types of interventions

We included studies that compared any type of systemic corticosteroid (e.g. oral or parenteral) with placebo, either without antibiotics (i.e. corticosteroid versus placebo) or with antibiotics (i.e. corticosteroid plus antibiotic versus placebo plus antibiotic).

We excluded studies using topical corticosteroid such as intranasal spray.

Participants could have used paracetamol as an antipyretic analgesic (Bertin 1996).

Types of outcome measures

Primary outcomes

1. Proportion of children with pain at various time points (24 hours; 2 to 3 days; and 4 to 7 days (time points taken from Venekamp 2015)).
2. Reduction of overall or specific symptoms (e.g. ear discomfort, hearing loss, irritability, sleep disturbance, diminished appetite). Reduction of overall or specific symptoms may have been measured using visual analogue scales or validated symptom scales specific to otitis media such as the Acute Otitis Media Severity of Symptoms Scale (AOM-SOS), Otitis Media Outcome-22 questionnaire (OMO-22), Otitis Media-6 quality of life survey (OM-6), or others (Timmerman 2007).
3. Reduction in overall or specific symptom duration.
4. Adverse effects.

Secondary outcomes

1. Changes in tympanometry measurements at various time points as an objective assessment of the resolution of AOM (e.g. middle ear pressure, tympanogram curve types).
2. Tympanic membrane perforation. This is considered to be a mild complication of AOM (Principi 2017), usually spontaneously healing in a few days (four to six days) (Principi 2017; Slovik 2008).
3. Contralateral otitis (in children with unilateral infection).
4. AOM recurrence, which was defined as the occurrence of AOM episodes within one month after completion of antibiotic therapy (Pichichero 2000).
5. Serious complications related to AOM such as mastoiditis and meningitis.

Search methods for identification of studies

Electronic searches

We searched the following databases up to 20 February 2018:

- Cochrane Central Register of Controlled Trials, which contains the Cochrane ARI Group's Specialised Register, (CENTRAL; Issue 1, 2018, in the Cochrane Library) using the strategy in [Appendix 1](#);
- MEDLINE via Ovid (from 1946 to 20 February 2018) using the strategy in [Appendix 2](#);
- EMBASE via Elsevier (from 1974 to 20 February 2018) using the strategy in [Appendix 3](#);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) via EBSCO (from 1981 to 20 February 2018) using the strategy in [Appendix 4](#);
- Web of Science via Thomson Reuters (from 1900 to 20 February 2018) using the strategy in [Appendix 5](#); and
- LILACS (Latin American and Caribbean Literature in Health Sciences) via BIREME (from 1985 to 20 February 2018) using the strategy in [Appendix 6](#).

We searched the following trials registries on 20 February 2018:

- ClinicalTrials.gov (www.clinicaltrials.gov); and
- the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

We did not restrict results by language or publication status (published, unpublished, in press, or in progress).

We combined the MEDLINE (Ovid) search strategy ([Appendix 2](#)) with the Cochrane Highly Sensitive Search Strategy to identify randomised trials in MEDLINE: sensitivity and precision-maximising version (2008 revision) ([Lefebvre 2011](#)). We adapted these search terms to search other databases (Embase, CENTRAL, CINAHL, Web of Science and LILACS). We planned to assess whether we would need to apply a filter for retrieving studies in children ([Boluyt 2008](#)). (This was not required because searches identified relatively few records). We imposed no language or publication restrictions.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We contacted experts in the field to identify additional unpublished materials.

Data collection and analysis

Selection of studies

Three review authors (EDS, RR, YP) independently screened the titles and abstracts of all studies identified by the searches. We retrieved full-text study reports of potentially relevant studies. Three review authors (EDS, RR, YP) independently screened the retrieved reports to identify studies for inclusion, and the reasons for exclusion of ineligible studies were recorded. Any disagreements were resolved through discussion and consulting with a fourth review author (EMB). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was assessed in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Moher 2010](#)).

Data extraction and management

We used a data collection form that had been piloted to collate study characteristics and outcome data. Three review authors (EDS, RR, YP) independently extracted study characteristics from the included studies. We extracted the following study characteristics:

1. methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study;
2. participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria;
3. interventions: intervention, comparison, concomitant medications, and excluded medications;
4. outcomes: primary and secondary outcomes specified and collected, and time points reported; and
5. notes: funding for the trial and notable conflicts of interest of trial authors.

We noted if outcome data were not reported in a usable way in the [Characteristics of included studies](#) table. Any disagreements were resolved by consensus. A review author (RR) entered data into Review Manager 5 ([Review Manager 2014](#)). We double-checked that data were entered correctly by comparing data presented in the systematic review with the study reports. Two review authors (EDS, YP) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Three review authors (EDS, RR, YP) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Any disagreements were resolved by discussion with another review author (EMB). We assessed the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;

5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

We took into account the risk of bias for the studies that contributed to that outcome when considering treatment effects.

Measures of treatment effect

We entered outcome data for each study into data tables in Review Manager 5 to calculate the treatment effects (Review Manager 2014). We intended to use the risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and the mean difference (MD) or standardised mean difference (SMD) for continuous outcomes. Because several outcomes were incompletely reported or unavailable for pooling, we did not undertake meta-analysis. Nonetheless, we used RR with 95% CI in reporting both our primary and secondary outcomes reported by one study (i.e. the proportion of children with pain, reduction of overall or specific symptoms, changes in tympanometry measurements, and AOM recurrence at various time points).

Unit of analysis issues

We did not expect any trials to have applied cross-over or cluster-randomised designs.

For studies with more than two intervention groups, where more than two groups were eligible for our review, we planned to follow the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), that is in studies with more than one control group or more than one intervention group, we would combine the results of the control or intervention groups, respectively.

Dealing with missing data

We contacted trial authors to verify key study characteristics and to obtain missing numerical outcome data (i.e. numbers of children in each group for several outcomes). However, the trial authors were unable to provide these data.

We were unable to locate missing numerical outcome data such as standard deviations or correlation coefficients. We thus did not calculate the missing parameters from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not impute values (e.g. correlation coefficients), therefore

we did not perform sensitivity analyses to assess how sensitive the results were to reasonable changes in the assumptions that were made in the imputation.

Assessment of heterogeneity

We planned to use the Chi² test and I² statistic to measure heterogeneity among the studies in each analysis. If we identified substantial heterogeneity (over 50% as specified in the *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2011), we would report this and explore the possible causes by conducting prespecified subgroup analysis. We were aware that when there are few studies in a meta-analysis there is uncertainty in the I² statistic measurement. In such case, we planned to use a P value of 0.10 rather than 0.05 in the Chi² test to determine statistical heterogeneity (Higgins 2011). However, due to insufficient numbers of studies and available outcome data, we were unable to pool the included studies and assess their heterogeneity.

Assessment of reporting biases

We had planned to use funnel plots to explore possible small-study and publication biases if we were able to pool more than 10 trials. However, the small number of included studies precluded this.

Data synthesis

We had planned to pool data from studies that we judged to be clinically homogeneous using Review Manager 5 (Review Manager 2014), employing a fixed-effect model. If a single true effect was not plausible due to variation in populations and interventions or substantial heterogeneity, we would use a random-effects model instead (DerSimonian and Laird method) (Higgins 2011). If more than one study provided usable data in any single comparison, we would perform a meta-analysis. However, we could not do so because there were only includable data from one study.

GRADE and 'Summary of findings' table

We had planned to create a 'Summary of findings' table using the following primary outcomes: proportion of children with pain at various time points (24 hours; 2 to 3 days; 4 to 7 days); reduction of overall or specific symptoms; reduction in overall or specific symptom duration; and adverse effects of corticosteroids. However, due to insufficient available outcome data, we were only able to report one primary outcome, that is reduction of overall or specific symptoms.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004; GRADE 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins

2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We justified all decisions to downgrade or upgrade the quality of studies using footnotes and made comments to aid readers' understanding of the review.

Subgroup analysis and investigation of heterogeneity

We had planned to carry out the following subgroup analyses using the Chi² test to test for subgroup interactions (Review Manager 2014):

1. short- versus long-term use of corticosteroids (≤ 1 week versus > 1 week);
2. type of corticosteroids (i.e. prednisolone, dexamethasone, etc.); and
3. corticosteroids as monotherapy versus adjuvant to antibiotics.

However, the small number of included studies precluded this.

Sensitivity analysis

We had planned to carry out sensitivity analyses by identifying and excluding studies with high risk of bias or low methodological quality based on the Cochrane 'Risk of bias' assessment. However, the small number of included studies precluded this.

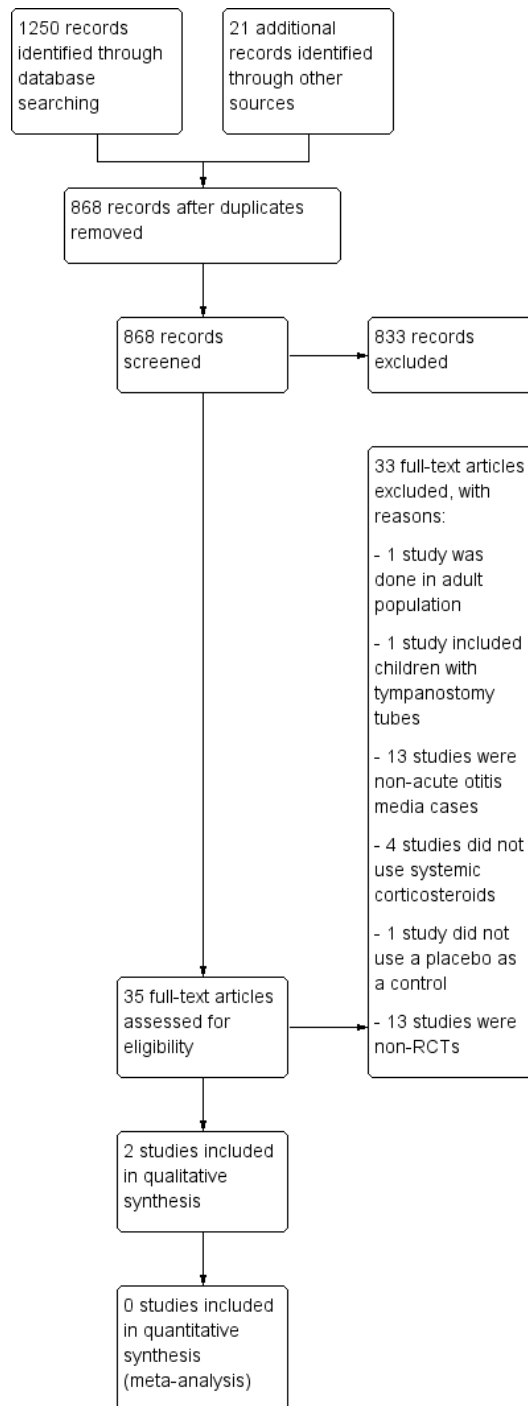
RESULTS

Description of studies

Results of the search

We retrieved 1250 records from electronic databases and 21 records from clinical trial registry searches (Figure 1). After removing duplicates, three review authors (EDS, RR, YP) independently assessed 868 records based on titles and abstracts, and then reviewed the full-text reports. After reviewing the full-text reports based on the eligibility criteria, we identified 35 articles. We excluded 33 articles: one included only adults (Arusgamov 1966); one included children with tympanostomy tubes (Ruohola 1999); 13 included chronic otitis media (Califano 2014; Chinski 2003; Choung 2008; Daly 1991; Endo 1997; Hearey 1990; Hussein 2017; Persico 1978; Puhakka 1985; Saffar 2001; Schwartz 1979; Schwartz 1981; Woodhead 1986); four included non-systemic corticosteroids (Cajgfinger 1967; Chirileanu 1978; Martin 1975; Terjung 1967); 13 included non-RCTs (Albernaz 2001; Capella 1984; Carvalho 1984; Crysdale 1984; Fradis 1983; Han 2009; Matsubara 2007; Oppenheimer 1968; Pulkki 2006; Rosenfeld 1992; Roydhouse 1978; Seehusen 2012; Sergienko 1975); and one did not include a placebo (Wang 2007).

Figure 1. Study flow diagram.



We included two studies in the review (Chonmaitree 2003; McCormick 2003).

Included studies

We included two studies with a total of 252 children with AOM (Chonmaitree 2003; McCormick 2003). We contacted both trial authors and obtained additional information regarding the randomisation and allocation concealment procedures, and the blinding of the outcome assessors for these two studies. Methods, participants, interventions, and outcomes of the included studies are presented in the [Characteristics of included studies](#) table.

Design

Chonmaitree 2003 and McCormick 2003 were 2 x 2 factorial, double-blind, randomised, placebo-controlled trials.

Participants and settings

Chonmaitree 2003 and McCormick 2003 included 198 and 80 children, respectively, aged from three months to six years with AOM. Both studies analysed children who had at least 70% adherence to the treatment measured by diary entries, weight of medicine bottles, and the availability of outcome data on the second visit and subsequent other visits. Chonmaitree 2003 analysed 179 of 198 children, and McCormick 2003 analysed 73 of 80 children due to their adherence to the trial. We therefore analysed these studies based on available cases instead of intention-to-treat. The two studies had similar exclusion criteria. Children were excluded if they had:

- anatomic or physiologic ear and/or nasopharyngeal defects;
- major medical or immunology disorders;
- current treatment with other medication;
- antibiotic use in the previous week;
- history of allergy to cephalosporin drugs;
- tympanostomy tube or perforated tympanic membrane;
- previous exposure to chickenpox in preceding three weeks.

Both studies were conducted at the paediatric outpatient clinic of the University of Texas Medical Branch at Galveston, USA.

The main difference between the studies was that McCormick 2003 performed tympanocentesis to measure the level of histamine and leukotriene B (LTB₄) in the middle ear in all children, whereas Chonmaitree 2003 did not. Because all children in McCormick 2003 underwent tympanocentesis, any confounding effect of this procedure was eliminated. However, the potential pain relief effect of tympanocentesis, which might modify outcomes for both groups, made McCormick 2003 more difficult to generalise.

Interventions and comparators

Children in both Chonmaitree 2003 and McCormick 2003 were randomly allocated to one of four groups:

1. corticosteroid (prednisolone 2 mg/kg/day) and placebo;
2. antihistamine (chlorpheniramine maleate 0.35 mg/kg/day) and placebo;
3. corticosteroid plus antihistamine;
4. two placebos of corticosteroid and antihistamine.

All medicines were given in three divided doses for five days, including the placebos, which were matched with prednisolone and chlorpheniramine maleate for their colour and taste. Following the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we therefore combined the results of these groups into corticosteroid group (corticosteroid and the combination of corticosteroid and antihistamine groups) and placebo group (antihistamine and double placebo groups). All children in these studies received a single-dose antibiotic intramuscular injection of ceftriaxone (50 mg/kg) at the baseline visits.

Outcomes

Chonmaitree 2003 reported the main outcomes as:

1. the rate of treatment failure during the first two weeks (Day 5 and Day 14);
2. duration of middle ear effusion (1, 2, and 3 months); and
3. rate of recurrence of AOM (at 1, 2, 3, and 4 to 6 months).

Treatment failure was defined as the persistence of any clinical symptom(s) and the inflammation of tympanic membrane requiring antibiotic treatment. Chonmaitree 2003 also reported the reduction of symptoms and signs severity score during the first two weeks, persistent middle ear effusion measured using pneumatic otoscope and tympanometry during the first three months, and the side effects (i.e. drowsiness, dry mouth, excitability, diaper rash, increased or decreased urine amount) measured using symptom diaries. Recorded symptoms consisted of nine clinical symptoms that were scored ranging from zero (no symptom), one (mild symptom) to two (severe symptom). The symptoms were: fever (> 38 °C rectally), ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, and watery eyes. The severity of the signs was measured and scored based on the otoscopic examination of three characteristics of the tympanic membrane: position, colour/transparency, and mobility of the tympanic membrane. Each sign was scored ranging from zero (normal, shiny) to two (bulging, red/yellow, immobile) with a maximum score of six. McCormick 2003 assessed:

1. clinical outcome (improvement or failure) at visit 2 (Day 4 to Day 6) and visit 3 (Day 14) and bacterial outcome at visit 2;
2. the changes of histamine and leukotriene B₄ (LTB₄) of the middle ear fluid taken by tympanocentesis at the baseline and

visit 2 (Day 4 to Day 6);

3. the duration of middle ear effusion; and
4. AOM recurrence during the first four months.

Clinical improvement was defined as an improvement in clinical symptoms, clinical signs (reduced/absent of redness and bulging of tympanic membrane), and no drainage of middle ear fluid. Clinical failure was defined as persistent clinical symptoms and signs indicated by redness and bulging of tympanic membrane, purulent drainage of middle ear, with or without a positive bacterial culture. Bacterial failure was defined as the persistence of pathogen bacterial from middle ear fluid collected at visit 2 and the requirement of another cycle of antibiotic treatment. Children were considered to have a satisfactory or favourable total outcome if they experienced clinical improvement at visit 2 and visit 3 without bacterial failure and did not require antibiotic treatment during the first two weeks.

Funding sources

Both [Chonmaitree 2003](#) and [McCormick 2003](#) were funded by National Institutes of Health (NIH) Grant R01 DC 2620 and National Center for Research Resources, NIH, US Public Health Service (USPHS) Grant M01 RR 00073. The prednisolone oral liquid was supplied by Fisons Pharmaceuticals, Rochester, NY, and the chlorpheniramine maleate was supplied by Schering-Plough, Kenilworth, NJ. There was no other scientific or financial contribution from these pharmaceutical companies.

Excluded studies

We excluded 33 studies ([Characteristics of excluded studies](#)):

- one included only adults ([Arusgamov 1966](#));
- one included children with tympanostomy tubes ([Ruohola 1999](#));
- 13 included chronic otitis media ([Califano 2014](#); [Chinski 2003](#); [Choung 2008](#); [Daly 1991](#); [Endo 1997](#); [Hearey 1990](#); [Hussein 2017](#); [Persico 1978](#); [Puhakka 1985](#); [Saffar 2001](#); [Schwartz 1979](#); [Schwartz 1981](#); [Woodhead 1986](#));
- four included non-systemic corticosteroids ([Cajgfinger 1967](#); [Chirileanu 1978](#); [Martin 1975](#); [Terjung 1967](#));
- one did not include a placebo ([Wang 2007](#));
- 13 included non-RCTs ([Albernaz 2001](#); [Capella 1984](#); [Carvalho 1984](#); [Crysdale 1984](#); [Fradis 1983](#); [Han 2009](#); [Matsubara 2007](#); [Oppenheimer 1968](#); [Pulkki 2006](#); [Rosenfeld 1992](#); [Roydhouse 1978](#); [Seehusen 2012](#); [Sergienko 1975](#)).

Risk of bias in included studies

Overall, the risk of bias in the included studies was unclear to high (see [Figure 2](#) and [Figure 3](#)). The two concerning biases were: 1) unclear description of allocation concealment, and 2) unclear to high risk of selective reporting due to insufficient information provided in published papers and clinical trial registries and unavailability of the trial protocols. [McCormick 2003](#) reported the favourable total outcomes during the first two weeks as a P value, adjusted odds ratio, and 95% confidence intervals, and not as the proportion of children who had favourable or unfavourable total outcome by their treatment groups ([Characteristics of included studies](#)). However, both studies had unclear to high risk of bias for other domains, and we therefore assessed both studies at high risk of bias overall ([Chonmaitree 2003](#); [McCormick 2003](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

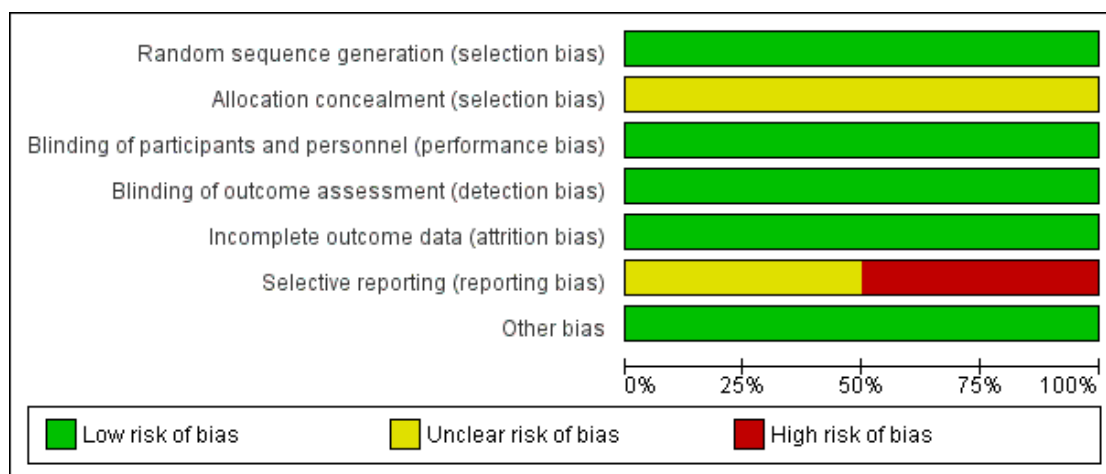


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chonmaitree 2003	+	?	+	+	+	?	+
McCormick 2003	+	?	+	+	+	-	+

Allocation

Neither study clearly described the randomisation process and the allocation concealment. We contacted the trial authors and were informed that the randomisation in both studies used computer-generated block randomisation. There was no clear description regarding allocation concealment. Based on information provided by the trial author, only the statistician who generated the randomisation schedule knew the code, but it is unclear whether this was a group code or individual codes. We therefore assessed both studies as at unclear risk of bias for allocation concealment (Chonmaitree 2003; McCormick 2003).

Blinding

In Chonmaitree 2003 and McCormick 2003, the parents/caregivers and the examining clinicians were unaware of the type of treatment allocation. Furthermore, placebos for both corticosteroid and antihistamine were prepared similarly to the active medicine based on colour and taste. This blinding method also prevented the children and their parents/caregivers from being aware of the treatment that they had received. This information was not provided in the papers, and was obtained by contacting the trial authors. We therefore graded this as low risk for performance bias and detection bias (blinding of participants, personnel, and

outcome assessors).

Incomplete outcome data

In [Chonmaitree 2003](#), of 198 children who were enrolled and randomised, 179 children (90.4%) were analysed for the outcomes; in [McCormick 2003](#), of 80 children, 73 children (91.2%) were analysed for the outcomes. The requirement for being included in final analyses was at least 70% adherence to the treatment measured by the diary, the weight of medicine bottles, and the availability of the outcome data on the second visit and after. Based on the low rate of missing outcome data due to non-compliance to the study (< 10%), which was found to be mostly even in each treatment group, we graded this as low risk for attrition bias or incomplete outcome data.

Selective reporting

We were unable to retrieve the protocols for either study. Although both were registered on a clinical trial registry, there was no information regarding the primary or the secondary outcomes for both studies. In addition, [McCormick 2003](#) did not provide the results of clinical outcome at visit 2 and visit 3. We therefore judged [Chonmaitree 2003](#) as at unclear risk and [McCormick 2003](#) as at high risk for reporting bias or selective reporting.

Other potential sources of bias

We identified no other potential sources of bias. We contacted the trial authors ([Chonmaitree 2003](#); [McCormick 2003](#)), who declared that there was no scientific or financial contribution from the pharmaceutical industry. We therefore judged this domain as at low risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Systemic corticosteroids compared to placebo for children with acute otitis media](#)

Primary outcomes

1. Proportion of children with pain at various time points

[Chonmaitree 2003](#) recorded pain as one of nine clinical symptoms. However, the trial authors only reported the proportion of children with pain before treatment (at the baseline visit) and not the proportion of children with pain after treatment. We contacted the trial authors but they could not provide the data (the study was conducted 15 years ago).

2. Reduction of overall or specific symptoms

[Chonmaitree 2003](#) recorded nine clinical symptoms: fever > 38 °C rectally, ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, and watery eyes, based on three grading scores. The author only reported the proportion of children with pre-treatment symptoms in each group. The post-treatment symptoms were reported as overall results of reduction in symptom severity score and otoscopic sign scores. There were no significant differences between groups at each follow-up visit. We contacted the trial authors but they could not provide the data.

[Chonmaitree 2003](#) reported clinical failure as a main outcome at various time points: visit 2 (Day 5) and visit 3 (Day 14). We converted the outcome to clinical improvement in order to represent the reduction of overall or specific symptoms. At visit 2, there were 84 children in the corticosteroid group (N = 89) compared to 80 children in the placebo group (N = 90) with improvement of clinical symptom(s) and otoscopic signs of AOM (94% versus 89%; risk ratio (RR) 1.06, 95% confidence interval (CI) 0.97 to 1.16), whilst at visit 3, there were 81 children in the corticosteroid group compared to 78 children in the placebo group (91% versus 87%; RR 1.05, 95% CI 0.95 to 1.17; [Analysis 1.1](#)). Although these results reflected the benefit of corticosteroids, there were no statistically significant differences between the two groups at these time points.

[McCormick 2003](#) defined favourable total outcome as the improvement of clinical outcomes (e.g. reduced or absence of tympanic membrane inflammation, no ear discharge) at visit 2 (Day 4 to Day 6) and visit 3 (Day 14) without bacterial finding in the middle ear fluid at visit 2, without the need for additional antibiotic treatment during the first two weeks. The favourable total outcome was more likely to be found in the corticosteroid group compared to other groups (adjusted odds ratio 65.9, 95% CI 1.28 to 1000; P = 0.037). As the trial author did not report the proportion of children who had favourable total outcome in the other groups (i.e. corticosteroid plus antihistamine group, corticosteroid plus placebo group, antihistamine plus placebo group, double placebo group), we could not pool the data from this study with [Chonmaitree 2003](#).

We rated the evidence from these studies as low quality due to serious risk of bias (unclear description of the allocation concealment) and indirect results, which was caused by the difference between the outcome of interest (i.e. reduction of overall or specific symptoms) and the outcomes reported (i.e. combination of persistent clinical symptom(s) and signs of inflammation of the tympanic membrane(s) that required another cycle of antibiotic treatment) ([Summary of findings for the main comparison](#)). Systemic corticosteroids may therefore make little or no difference to clinical outcomes.

3. Reduction in overall or specific symptom duration

Neither included trial reported the reduction in overall or specific symptom duration.

4. Adverse effects

[Chonmaitree 2003](#) recorded unfavourable effects in symptom diaries daily. However, the trial authors reported adverse effects as overall side effects across all groups: drowsiness (22% to 34%), dry mouth (16% to 27%), increased urine amount (14% to 27%), nappy rash (7% to 32%), nervousness (7% to 20%), and decreased urine amount (0% to 11%). No correlation was reported between the use of corticosteroid and the risk of viral infection by comparing the persistence and the occurrence of new viral infections in the two weeks following the baseline visit. We contacted the trial authors, but outcome data by individual group were not available.

Secondary outcomes

1. Changes in tympanometry measurements at various time points

[Chonmaitree 2003](#) represented changes in tympanometry measurement at various time points as the proportion of children with persistent middle ear effusion measured by pneumatic otoscope and tympanometry. We converted this to the proportion of children who had resolution of middle ear effusion. Resolution of middle ear effusion was reported at three different time points as follows: at one month, 45 children in the corticosteroid group (N = 89) versus 38 children in the placebo group (N = 90) (50% versus 42%; RR 1.20, 95% CI 0.87 to 1.64); at two months, 62 versus 52 children in the corticosteroid and placebo groups, respectively (70% versus 58%; RR 1.21, 95% CI 0.96 to 1.51); and at three months, 61 versus 61 children in the corticosteroid and placebo groups, respectively (76% versus 68%; RR 1.13, 95% CI 0.94 to 1.35; [Analysis 1.2](#)). None of these results showed statistically significant differences between the two groups. [McCormick 2003](#) did not report this outcome.

We rated this evidence as very low quality due to serious risk of bias from unclear allocation concealment; imprecision because the CI included both the possibility of resolution and persistent middle ear effusion during these time points; and indirect results due to the difference between the outcome of interest (i.e. changes in tympanometry measurements) and those reported (i.e. proportion of children with persistent middle ear effusion). It therefore remains uncertain whether systemic corticosteroids improve middle ear effusion.

2. Tympanic membrane perforation

Neither included trial reported tympanic membrane perforation.

3. Contralateral otitis (in children with unilateral infection)

Neither included trial reported contralateral otitis.

4. AOM recurrence

[Chonmaitree 2003](#) reported recurrence cumulatively during the six-month period of follow-up: at one month, there were 15 children in the corticosteroid group versus 12 children in the placebo group with recurrence of AOM (17% versus 13%; RR 1.26, 95% CI 0.63 to 2.55); at two months, 20 versus 24 children in corticosteroid and placebo groups, respectively (22% versus 27%; RR 0.84, 95% CI 0.50 to 1.41); at three months, 19 versus 29 children in corticosteroid and placebo groups, respectively (21% versus 32%; RR 0.66, 95% CI 0.40 to 1.09); and at four to six months, 33 and 36 children in corticosteroid and placebo groups, respectively (37% versus 40%; RR 0.93, 95% CI 0.64 to 1.34; [Analysis 1.3](#)).

[McCormick 2003](#) reported that there were no statistically significant differences in terms of AOM recurrence at the first or fourth month between the groups.

We rated this evidence as low quality due to serious risk of bias from unclear allocation concealment and imprecise results. The wide CIs may include favourable and unfavourable effects of corticosteroids on AOM recurrence. It is therefore uncertain whether corticosteroids improve or reduce the recurrence of AOM.

5. Serious complications

Neither included trial reported serious complications.

DISCUSSION

Summary of main results

We included two small randomised, double-blind, placebo-controlled studies with a total of 252 participants ([Chonmaitree 2003](#); [McCormick 2003](#)). Low- to very low-quality evidence demonstrated that corticosteroids did not make a significant difference in improving clinical outcomes (e.g. symptoms, inflammation of the eardrum), resolution of middle ear effusion, and AOM recurrence. However, we are uncertain of these results due to wide confidence intervals around the estimates.

Although [McCormick 2003](#) reported a significant difference between the children in the corticosteroid and placebo groups who had clinical improvement during the first two weeks, we were unable to meta-analyse the results due to insufficient information from the published paper and incompleteness of outcome reporting. This study also reported that there was no significant difference between corticosteroid and placebo groups in AOM recurrence at the first or fourth month.

Adverse effects, as one of our primary outcomes, was reported by [Chonmaitree 2003](#) as an overall result (i.e. drowsiness, nervousness, dry mouth, diaper rash, increased and decreased urine amount) but not by treatment group. Neither of the included studies reported reduction of overall or specific symptom duration, tympanic membrane perforation, contralateral otitis, or serious complications related to AOM.

Overall completeness and applicability of evidence

All participating children in both studies received antibiotics at their baseline visits; this was because only children with high-risk AOM were included in [Chonmaitree 2003](#), but no reason was provided for [McCormick 2003](#). These results are therefore best generalised to children with high-risk AOM.

Pain is one of the most common symptoms of AOM and is distressing for both children and their parents. Although for more than 50% of children with AOM, symptoms resolve within 24 hours with or without antibiotic treatment, almost one-fifth of children with AOM treated with antibiotics have symptoms that persist for up to six days ([Chonmaitree 2003](#); [Venekamp 2015](#)). To date, physicians tend to prescribe medication for AOM to relieve pain and other distressing symptoms, including antibiotics, despite the self-limiting nature of AOM. Antibiotics are still commonly prescribed for AOM, although evidence demonstrates that they are most likely beneficial for severe cases (i.e. fever ≥ 39 °C, moderate to severe ear pain), bilateral AOM in young children, or AOM with perforated tympanic membrane(s) ([Lieberthal 2013](#); [NSW Health 2014](#); [Venekamp 2015](#)). Due to the modest benefits of antibiotics and their potential side effects and risk of antibiotic resistance ([Venekamp 2015](#)), alternative treatment for AOM, such as corticosteroids as an anti-inflammatory medication, could improve clinical symptoms of AOM, particularly pain. The proportion of children with pain (a primary outcome of this review) was evaluated by [Chonmaitree 2003](#). However, this outcome was only reported before treatment, therefore we could not assess the effect of corticosteroids in improving pain alone.

Aside from the beneficial effects of corticosteroids on clinical outcomes, assessing adverse effect or harm is also very important. Unfortunately, we could not assess data for this outcome due to incomplete outcome reporting ([Chonmaitree 2003](#)).

This review demonstrated insufficient and low- to very low-quality evidence for the effects of systemic corticosteroids. We are uncertain whether corticosteroids improve important clinical outcomes of AOM (i.e. pain and overall symptoms, middle ear effusion, AOM recurrence) due to the small number of included studies. Consequently, the overall completeness and applicability of evidence is very low.

Quality of the evidence

We judged the evidence as low to very low quality.

We downgraded the quality of the evidence to low for the primary outcomes due to serious risk of bias and indirectness of the results. Serious risk of bias was due to unclear allocation concealment and unclear to high risk of selective reporting. Indirectness was due to the differences between the outcomes of interest and those reported in the included studies.

Potential biases in the review process

A potential bias inherent in this review was the difference in outcome reporting and measurement for both our primary and secondary outcomes. For the outcome of reduction of overall or specific symptoms, we presented results as the proportion of children who had clinical improvement measured using symptoms and signs severity score, and not the absolute change of the scores. Similarly, we presented the results for changes in tympanometry measurement as the proportion of children who had resolution of middle ear effusion measured using pneumatic otoscope and tympanometry, rather than the absolute changes of middle ear pressure or the tympanogram curve types. This resolution was determined by the normalisation of tympanogram curve to type A curve (the absence of middle ear effusion).

Agreements and disagreements with other studies or reviews

A literature review of the effectiveness of corticosteroids in several acute respiratory infections (i.e. acute pharyngitis, community-acquired pneumonia, and AOM) similarly concluded that the effect of corticosteroids for AOM is still unknown due to insufficient evidence ([Principi 2013](#)). This review poorly reported the searching method or eligibility criteria, and the conclusion was based on only one RCT ([Chonmaitree 2003](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Our review did not demonstrate that systemic corticosteroids improve important clinical outcomes in acute otitis media, and therefore has no implication for clinical practice.

Implications for research

Large, high-quality randomised controlled trials are needed to evaluate the effectiveness of corticosteroids in uncomplicated acute otitis media.

ACKNOWLEDGEMENTS

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The methods section of this protocol is based on a standard template developed by Cochrane Airways and adapted by the Cochrane Acute Respiratory Infections Group.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chonmaitree 2003

Methods	<p>Randomised: yes, it was computer-generated with block randomisation (RCT)</p> <p>Concealment of allocation: yes, the list of randomisation was in codes and only the statistician who had generated the randomisation was aware of the code</p> <p>Double-blind: yes, syrups similar in taste and colour to prednisolone were used as placebo</p> <p>Intention-to-treat: not an ITT analysis. Analysis was done on children who had more than 70% adherence. Adherence to treatment was assessed by diary and the weight of medication bottles (available-case analysis)</p> <p>Loss to follow-up: unclear</p> <p>Design: 2 x 2 factorial design</p>
Participants	<p>N: 198 children (N = 179 children included in analysis)</p> <p>Age: 3 months to 6 years</p> <p>Setting: the paediatric outpatient clinic of the University of Texas Medical Branch at Galveston, USA</p> <p>Inclusion criteria: (1) children who had experienced 2 or more previous AOM episodes (with the first AOM episode before 1 year of age) or (2) infants younger than 6 months of age having the first or second episode of AOM</p> <p>Exclusion criteria: children who had: (1) anatomic or physiologic defect of the ear or nasopharynx; (2) major medical condition; (3) other concurrent medication; (4) received antibiotic treatment within 1 week; (5) history of previous allergic reaction to cephalosporin drugs; (6) indwelling tympanostomy tube; (7) history of exposure to an individual with chickenpox in the previous 3 weeks</p> <p>Baseline characteristics: most of the baseline characteristics were balanced except for breastfeeding and fever. There were fewer numbers of children in the corticosteroid group compared to the placebo group in terms of breastfeeding (16% versus 34%) and clinical symptoms of fever (49% versus 63%)</p>
Interventions	<p>All children received single-dose antibiotic intramuscular injections of ceftriaxone (50 mg/kg) and were randomised to either:</p> <p>Intervention: corticosteroid (prednisolone) 2 mg/kg per day in 3 divided doses for 5 days (N = 89), or</p> <p>Comparison: matching placebo for 5 days (N = 90)</p> <p>Due to the factorial design, the corticosteroid group was a combination of a corticosteroid-only group (prednisolone 2 mg/kg per day in 3 divided doses; N = 45) and corticosteroid plus antihistamine group (prednisolone plus chlorpheniramine maleate; N = 44). The placebo group was a combination of an antihistamine group (chlorpheniramine maleate; N = 44) and a double placebo group (N = 46). We therefore analysed the outcomes of prednisolone versus placebo</p>
Outcomes	<p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Treatment failure defined as persistent clinical symptoms (i.e. fever > 38 °C rectally, ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, watery eyes) with inflamed tympanic membrane at either visit 2 (Day 5) or

	<p>visit 3 (Day 14) that required additional antibiotic treatment</p> <ol style="list-style-type: none"> 2. Duration of middle ear effusion 3. AOM recurrence during the first 6 months <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Reduction of symptom severity scores: fever > 38 °C rectally, ear pain, irritability, poor feeding, rhinorrhoea, nasal stuffiness, cough, sneezing, watery eyes with the range of zero (none) to 2 (severe) and sign severity scores. The sign severity scores were characterised by: position (0 = normal to 2 = bulging), colour/transparency (0 = shiny to 2 = red/yellow), and mobility (0 = normal to 2 = non-mobile) with 6 as the maximum otoscopic score. 2. Presence of middle ear effusion measured using tympanometry 3. Side effects
Notes	<ol style="list-style-type: none"> 1. Information on the randomisation and concealment of allocation was not provided in the published paper, therefore we contacted the trial author to retrieve this information 2. Data of sign and symptom severity scores and side effects from each group at various time points were not provided in the published paper. The trial author was not able to provide this information 3. Out of 198 randomised children, 19 were not analysed (9.6%). However, the allocation of these children to their treatment group was evenly distributed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated based on additional information obtained from the trial author
Allocation concealment (selection bias)	Unclear risk	There was no clear description of how the allocation was concealed. We contacted the trial author, who merely reported that only the statistician who generated the randomisation schedule knew the code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "colored syrups similar to the drugs in taste and color were used as the placebos"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Based on additional information obtained from the trial author, the clinicians as the outcome assessors were not aware of the codes or the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 children (9.6%) were excluded from the analysis due to their non-adherence to the treatment drug and the follow-up visits and have not been analysed. However, their dis-

Chonmaitree 2003 (Continued)

		tribution into each treatment group was generally even
Selective reporting (reporting bias)	Unclear risk	We could not retrieve the trial protocol. Despite this study being registered in the clinical trial registry, the primary or secondary outcomes were not clearly described
Other bias	Low risk	No other bias detected. We contacted the trial author, who declared that there was no scientific or financial contribution from the pharmaceutical industry

McCormick 2003

Methods	<p>Randomised: yes, it was computer-generated with block randomisation (RCT)</p> <p>Concealment of allocation: yes, the list of randomisation was in codes and only the statistician who had generated the randomisation was aware of the code</p> <p>Double-blind: syrups similar to prednisolone in taste and colour were used as placebo</p> <p>Intention-to-treat: not an ITT analysis. Analysis was done on children who had more than 70% adherence. Adherence to treatment was assessed by diary and medication bottle weight (available-case analysis)</p> <p>Loss to follow-up: unclear</p> <p>Design: 2 x 2 factorial design</p>
Participants	<p>N: 80 children (N = 73 children included in analysis)</p> <p>Age: 3 months to 6 years</p> <p>Setting: the paediatric outpatient clinic of the University of Texas Medical Branch at Galveston, USA</p> <p>Inclusion criteria: acute otitis media was diagnosed based on: (1) acute symptoms (i.e. fever, irritability, ear pain, lack of appetite, or lack of sleep); (2) signs of acute inflammation of the tympanic membrane (i.e. red, yellow, or bulged tympanic membrane); and (3) the presence of middle ear effusion identified with tympanocentesis procedure</p> <p>Exclusion criteria: children who had: (1) received treatment for AOM in the preceding 30 days; (2) received antibiotic treatment within 1 week; (3) allergy to treatment medication; (4) other concurrent medication; (5) perforation of the tympanic membrane or with tympanostomy tube(s); (6) a major medical condition or immunologic disorders; (7) anatomic or physiologic defect of the ear or nasopharynx; (8) been exposed to chickenpox during the past 3 weeks</p> <p>Baseline characteristics: most of the baseline characteristics were balanced except day-care attendance and passive smoking. There were fewer numbers of children in the corticosteroid group compared to placebo group who had attended a day-care centre (30% versus 45%), and there were more children in the corticosteroid group compared to the placebo group who had been exposed to smoking (50% versus 35%)</p>
Interventions	<p>All children received single-dose antibiotic intramuscular injection of ceftriaxone (50 mg/kg) and were randomised to either:</p> <p>Intervention: corticosteroid (prednisolone) 2 mg/kg per day in 3 divided doses for 5</p>

	<p>days (N = 37), or</p> <p>Comparison: matching placebo for 5 days (N = 36).</p> <p>Due to the factorial design, the corticosteroid group was a combination of a corticosteroid-alone group (prednisolone 2 mg/kg per day in 3 divided doses; N = 18) and corticosteroid plus antihistamine group (prednisolone plus chlorpheniramine maleate; N = 19). The placebo group was a combination of an antihistamine group (chlorpheniramine maleate; N = 18) and a double placebo group (N = 18). We therefore analysed the outcomes of prednisolone versus placebo</p>	
Outcomes	<p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Total outcome defined as clinical outcomes at visit 2 (Day 4 to Day 6) and visit 3 (Day 14) and bacterial outcome at visit 2 2. The changes in histamine and leukotriene B4 (LTB4) in the middle ear fluid taken by tympanocentesis at the baseline and visit 2 (Day 4 to Day 6) <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. The duration of the middle ear effusion 2. AOM recurrence during the first 4 months following the baseline visit 	
Notes	<ol style="list-style-type: none"> 1. Information on the randomisation and concealment of allocation was not provided in the published paper, therefore we contacted the trial author to retrieve this information 2. Data on clinical outcomes at visit 2 and visit 3 were not provided in the published paper. The trial author was not able to provide this information 3. Out of 80 randomised children, 7 children were not analysed (8.7%). However, the allocation of these children to their treatment group was evenly distributed 	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was computer-generated based on additional information obtained from the trial author
Allocation concealment (selection bias)	Unclear risk	There was no clear description of how the allocation was concealed. We contacted the trial author, who merely reported that only the statistician who generated the randomisation schedule knew the code and that neither the parent nor the examining physician was informed of the type of treatment given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A light straw-colored solution similar to the drug was used as the placebo"

McCormick 2003 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Neither the parent nor the examining physician was informed of the type of treatment given”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “Seven cases were lost to follow-up after the enrolment visit” 7 children (8.7%) who were lost to follow-up after randomisation were excluded from the analysis. However, their distribution into each treatment group was generally even
Selective reporting (reporting bias)	High risk	The authors did not report the clinical outcome at visit 2 (Day 4 to Day 6) and visit 3 (Day 14). This information was crucial to determine the total outcome. We also could not retrieve the trial protocol, and neither the primary nor secondary outcomes were clearly described in the clinical trial registry
Other bias	Low risk	We detected no other bias. We contacted the trial author, who declared that there was no scientific or financial contribution from the pharmaceutical industry

AOM: acute otitis media

ITT: intention-to-treat

RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Albernaz 2001	STUDY DESIGN Study was a literature review (non-English language article)
Arusgamov 1966	PARTICIPANTS Adults only (non-English language article)
Cajfinger 1967	INTERVENTIONS Trial using topical or ear drop corticosteroid instead of systemic corticosteroid (non-English language article)
Califano 2014	PARTICIPANTS Trial including non-acute otitis media effusion

(Continued)

Capella 1984	STUDY DESIGN Study was a retrospective observation using medical records (non-English language article)
Carvalho 1984	STUDY DESIGN Study was a literature review (non-English language article)
Chinski 2003	PARTICIPANTS Trial including non-acute otitis media effusion (more than 2 months)
Chirileanu 1978	INTERVENTIONS Trial using an invasive intervention method by opening Eustachian tube ostium employing a probe and not using a systemic corticosteroid (non-English language article)
Choung 2008	PARTICIPANTS Trial excluding children with acute otitis media
Crysdale 1984	STUDY DESIGN Study was a literature review.
Daly 1991	OTHERS Children eligible to receive corticosteroid treatment were those whose otitis media effusion did not improve after 2 weeks of antibiotic treatment
Endo 1997	PARTICIPANTS Trial including children with persistent middle ear effusion for more than 3 months (non-English article)
Fradis 1983	STUDY DESIGN Study was a letter to the Editor
Han 2009	COMPARATORS Study was a quasi-randomised controlled trial and did not use placebo as a comparator (non-English language article)
Hearey 1990	PARTICIPANTS Trial including children with longstanding effusion for more than 10 weeks
Hussein 2017	PARTICIPANTS Trial including children with chronic middle ear effusion
Martin 1975	INTERVENTIONS Trial using topical or ear drop corticosteroid instead of systemic corticosteroid (non-English article)
Matsubara 2007	STUDY DESIGN Study was a literature review (non-English article)
Oppenheimer 1968	ALLOCATION Trial was a non-randomised study and did not include a placebo

(Continued)

Persico 1978	ALLOCATION Trial was a non-randomised study and did not include a placebo
Puhakka 1985	PARTICIPANTS Trial excluding children who had an acute otitis media episode during the preceding 3 months
Pulkki 2006	STUDY DESIGN Study was a retrospective observation using medical records
Rosenfeld 1992	STUDY DESIGN Study was a literature review
Roydhouse 1978	STUDY DESIGN Study was a literature review
Ruohola 1999	PARTICIPANTS Trial including children with tympanostomy tubes
Saffar 2001	PARTICIPANTS Trial including children with otitis media with effusion for more than 3 months
Schwartz 1979	PARTICIPANTS Trial including children with persistent otitis media effusion for 3 weeks or more
Schwartz 1981	PARTICIPANTS Trial including children with persistent otitis media effusion for 3 weeks or more
Seehusen 2012	STUDY DESIGN Study was a clinical scenario
Sergienko 1975	ALLOCATION Study was a non-randomised controlled trial (pre- and post study)
Terjung 1967	INTERVENTIONS Trial using topical or ear drop corticosteroid instead of systemic corticosteroid (non-English article)
Wang 2007	COMPARATORS Study did not use placebo as a comparator (non-English article)
Woodhead 1986	PARTICIPANTS Trial including children without inflammation signs of the tympanic membrane

Several articles did not provide abstracts or provided an unclear definition of otitis media effusion in their abstracts. We therefore had to retrieve the full text, and they were not included in our eligibility criteria (e.g. literature reviews, non-acute otitis media studies).

DATA AND ANALYSES

Comparison 1. Systemic corticosteroids versus placebo for children with acute otitis media

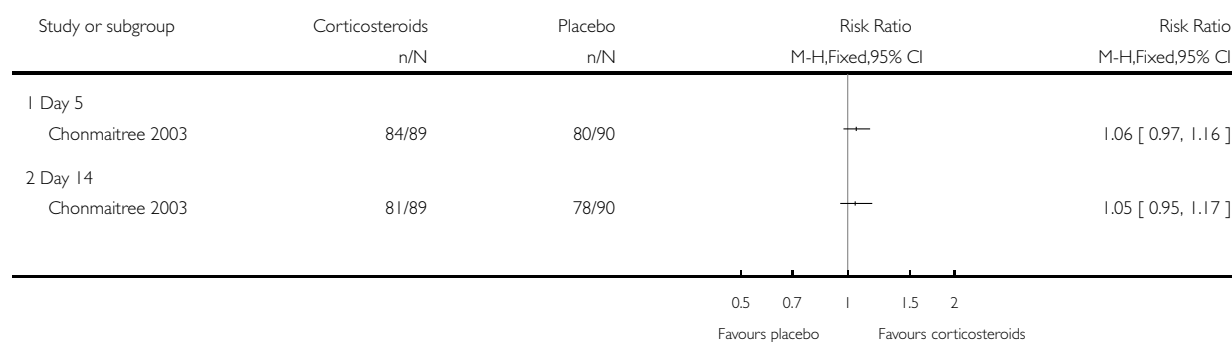
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of overall or specific symptoms at various time points	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 5	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Changes in tympanometry measurement at various time points	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Month 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Month 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Month 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 AOM recurrence at various time points	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Month 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Month 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Month 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 During Month 4 to Month 6	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Systemic corticosteroids versus placebo for children with acute otitis media, Outcome 1 Reduction of overall or specific symptoms at various time points.

Review: Systemic corticosteroids for acute otitis media in children

Comparison: 1 Systemic corticosteroids versus placebo for children with acute otitis media

Outcome: 1 Reduction of overall or specific symptoms at various time points

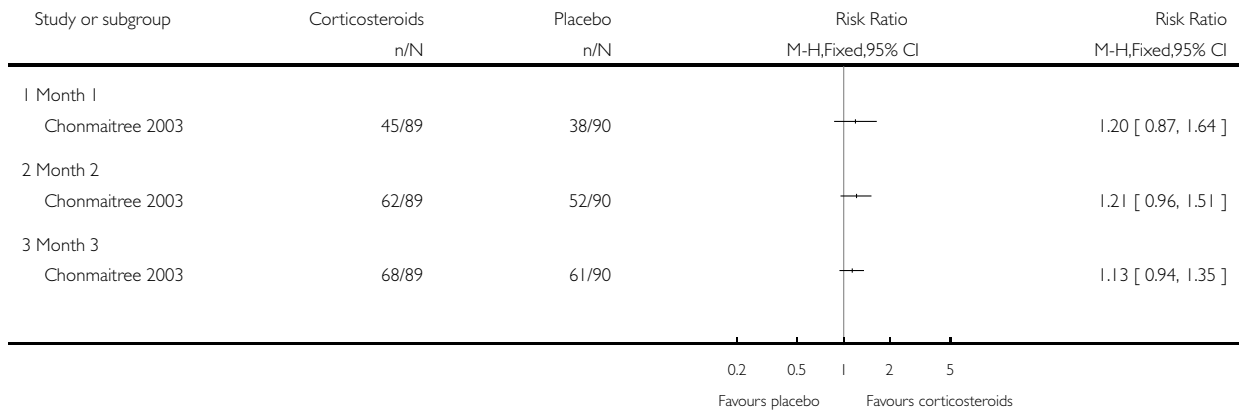


Analysis 1.2. Comparison 1 Systemic corticosteroids versus placebo for children with acute otitis media, Outcome 2 Changes in tympanometry measurement at various time points.

Review: Systemic corticosteroids for acute otitis media in children

Comparison: 1 Systemic corticosteroids versus placebo for children with acute otitis media

Outcome: 2 Changes in tympanometry measurement at various time points

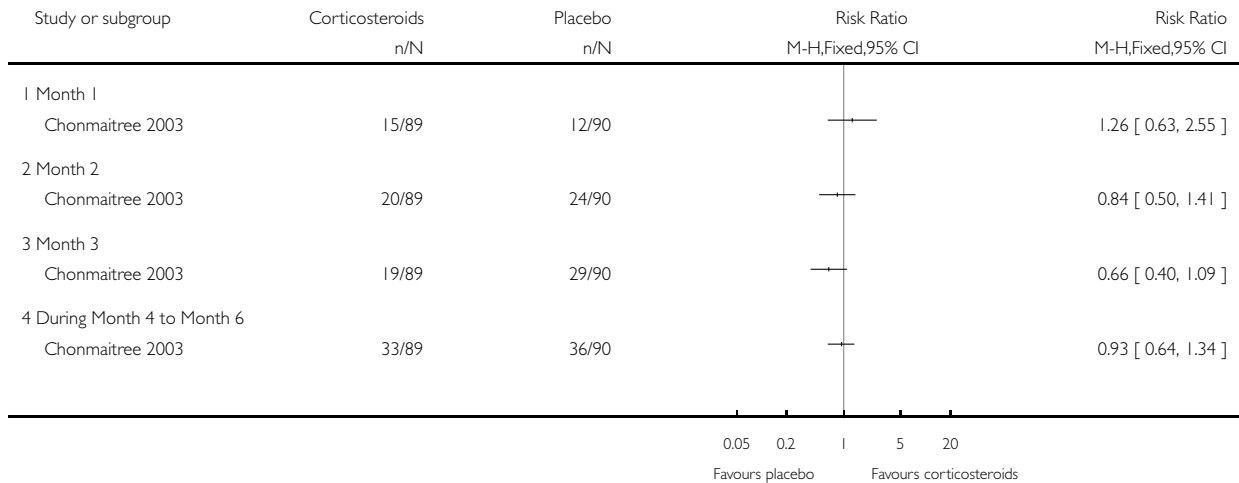


Analysis 1.3. Comparison 1 Systemic corticosteroids versus placebo for children with acute otitis media, Outcome 3 AOM recurrence at various time points.

Review: Systemic corticosteroids for acute otitis media in children

Comparison: 1 Systemic corticosteroids versus placebo for children with acute otitis media

Outcome: 3 AOM recurrence at various time points



APPENDICES

Appendix I. CENTRAL (Cochrane Library)

#1MeSH descriptor: [Otitis Media] explode all trees

#2otitis media:ti,ab,kw (Word variations have been searched)

#3“middle ear” near/5 (infect* or inflam* or effusion):ti,ab,kw (Word variations have been searched)

#4ome or aom:ti,ab,kw (Word variations have been searched)

#5#1 or #2 or #3 or #4

#6MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#7adrenal cortex hormone*:ti,ab,kw (Word variations have been searched)

#8corticosteroid* or corticoid* or steroid* or glucocorticoid*:ti,ab,kw (Word variations have been searched)

#9MeSH descriptor: [Pregnenediones] explode all trees

#10pregnenedione* or pregnenolone* or hydrocortisone* or hydroxypregnenolone* or tetrahydrocortisol* or cortodoxone* or cortone acetate or cortisone or corticosterone:ti,ab,kw (Word variations have been searched)

#11aristocort or triamcinolone:ti,ab,kw (Word variations have been searched)

#12deltasonone or prednisone or prednicot:ti,ab,kw (Word variations have been searched)

#13prednisolone or bubbli-pred or cotolone or prelone or pediaped or pms-prednisolone:ti,ab,kw (Word variations have been searched)

#14paramethasone or methylprednisolone or baycadron or dexamethasone or decadron:ti,ab,kw (Word variations have been searched)

#15clobetasol or beclomethasone or betamethasone or budesonide:ti,ab,kw (Word variations have been searched)

Systemic corticosteroids for acute otitis media in children (Review)

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#16fcortisol or hydrocortone or solu-cortef or cortef or A-Hydrocort:ti,ab,kw (Word variations have been searched)
 #17betnelan or betnesol or celestone:ti,ab,kw (Word variations have been searched)
 #18deflazacort or calcort:ti,ab,kw (Word variations have been searched)
 #19medrone or medrol or solu-medrone or depo-medrone or methylpred-DP:ti,ab,kw (Word variations have been searched)
 #20kenalog or novolizer or pulmicort or symbicort or entocort EC:ti,ab,kw (Word variations have been searched)
 #21beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte:ti,ab,kw (Word variations have been searched)
 #22cortisol:ti,ab,kw (Word variations have been searched)
 #23MeSH descriptor: [Mineralocorticoids] explode all trees
 #24mineralocorticoid* or mineralcorticoid*:ti,ab,kw (Word variations have been searched)
 #25MeSH descriptor: [Aldosterone] explode all trees
 #26aldosterone or florinef acetate or fludrocortisone:ti,ab,kw (Word variations have been searched)
 #27#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
 #28#5 and #27 in Trials

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Otitis Media/
 2 otitis media.tw.
 3 (middle ear adj5 (infect* or inflam* or effus*)).tw.
 4 (ome or aom).tw.
 5 or/1-4
 6 exp Adrenal Cortex Hormones/
 7 adrenal cortex hormone*.tw,nm.
 8 corticosteroid*.tw,nm.
 9 corticoid*.tw,nm.
 10 steroid*.tw,nm.
 11 glucocorticoid*.tw,nm.
 12 exp Pregnenediones/
 13 pregnenedione*.tw,nm.
 14 pregnenolone*.tw,nm.
 15 hydrocortisone.tw,nm.
 16 hydroxypregnenolone.tw,nm.
 17 tetrahydrocortisol.tw,nm.
 18 cortodoxone.tw,nm.
 19 (cortone acetate or cortisone).tw,nm.
 20 corticosterone.tw,nm.
 21 (aristocort or triamcinolone).tw,nm.
 22 (deltasone or prednisone or prednicot).tw,nm.
 23 (prednisolone or bubbli-pred or cotelone or prelone or pediaped or pms-prednisolone).tw,nm.
 24 paramethasone.tw,nm.
 25 methylprednisolone.tw,nm.
 26 (baycadron or dexamethasone or decadron).tw,nm.
 27 clobetasol.tw,nm.
 28 beclomethasone.tw,nm.
 29 betamethasone.tw,nm.
 30 budesonide.tw,nm.
 31 (efcortisol or hydrocortone or solu-cortef or cortef or A-Hydrocort).tw,nm.
 32 (betnelan or betnesol or celestone).tw,nm.
 33 (deflazacort or calcort).tw,nm.
 34 (medrone or medrol or solu-medrone or depo-medrone or methylpred-DP).tw,nm.

- 35 kenalog.tw,nm.
 36 (novolizer or pulmicort or symbicort or entocort EC).tw,nm.
 37 (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm.
 38 cortisol.tw,nm.
 39 exp Mineralocorticoids/
 40 mineralocorticoid*.tw. or mineralcorticoid*.tw,nm.
 41 Aldosterone/
 42 aldosterone.tw,nm.
 43 (florinef acetate or fludrocortisone).tw,nm.
 44 or/6-43
 45 5 and 44

Appendix 3. Embase (Elsevier) search strategy

#31	#27 AND #30	
#30	#28 OR #29	
#29	random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR factorial:ab,ti OR volunteer*:ab,ti OR allocat*:ab,ti OR assign*:ab,ti OR ((singl* OR doubl*) NEAR/2 blind*):ab,ti AND [embase]/lim	
#28	'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/exp OR 'randomized controlled trial'/de	
#27	#5 AND #26	
#26	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	
#25	aldosterone:ab,ti OR 'florinef acetate':ab,ti OR fludrocortisone:ab,ti AND [embase]/lim	
#24	'aldosterone'/de AND [embase]/lim	
#23	mineralcorticoid*:ab,ti OR mineralocorticoid*:ab,ti AND [embase]/lim	
#22	'mineralocorticoid'/exp AND [embase]/lim	
#21	cortisol:ab,ti AND [embase]/lim	
#20	beclometasone:ab,ti OR aerobec:ab,ti OR asmabec:ab,ti OR beclazone:ab,ti OR becodisks:ab,ti OR becotide:ab,ti OR 'clenil modulite':ab,ti OR qvar:ab,ti OR becloforte:ab,ti AND [embase]/lim	

(Continued)

#19	novolizer :ab,ti OR pulmicort :ab,ti OR symbicort :ab,ti OR 'entocort ec' :ab,ti AND [embase]/lim
#18	kenalog :ab,ti AND [embase]/lim
#17	medrone :ab,ti OR medrol :ab,ti OR 'solu-medrone' :ab,ti OR 'depo-medrone' :ab,ti OR 'methylpred-dp' :ab,ti AND [embase]/lim
#16	deflazacort :ab,ti OR calcort :ab,ti AND [embase]/lim
#15	betnelan :ab,ti OR betnesol :ab,ti OR celestone :ab,ti AND [embase]/lim
#14	clobetasol :ab,ti OR beclomethasone :ab,ti OR betamethasone :ab,ti OR budesonide :ab,ti OR efcortisol :ab,ti OR hydrocortone :ab,ti OR 'solu-cortef' :ab,ti OR cortef :ab,ti OR 'a-hydrocort' :ab,ti AND [embase]/lim
#13	paramethasone :ab,ti OR methylprednisolone :ab,ti OR baycadron :ab,ti OR dexamethasone :ab,ti OR decadron :ab,ti AND [embase]/lim
#12	prednisolone :ab,ti OR 'bubli-pred' :ab,ti OR cotolone :ab,ti OR prelone :ab,ti OR pediapred :ab,ti OR 'pms-prednisolone' :ab,ti AND [embase]/lim
#11	pregnenedione *:ab,ti OR pregnenolone *:ab,ti OR hydrocortisone :ab,ti OR hydroxypregnenolone :ab,ti OR tetrahydrocortisol :ab,ti OR cortodoxone :ab,ti OR 'cortone acetate' :ab,ti OR cortisone :ab,ti OR corticosterone :ab,ti OR aristocort :ab,ti OR triamcinolone :ab,ti OR deltasone :ab,ti OR prednisone :ab,ti OR prednicot :ab,ti AND [embase]/lim
#10	'pregnane derivative' /de AND [embase]/lim
#9	corticoid *:ab,ti OR steroid *:ab,ti OR glucocorticoid *:ab,ti AND [embase]/lim
#8	corticosteroid *:ab,ti AND [embase]/lim
#7	'adrenal cortex hormone' :ab,ti OR 'adrenal cortex hormones' :ab,ti AND [embase]/lim
#6	'corticosteroid' /exp AND [embase]/lim
#5	#1 OR #2 OR #3 OR #4

(Continued)

#4	ome:ab,ti OR aom:ab,ti AND [embase]/lim
#3	('middle ear' NEAR/5 (infect* OR inflam* OR effusion)); ab,ti AND [embase]/lim
#2	'otitis media':ab,ti AND [embase]/lim
#1	'otitis media'/exp AND [embase]/lim

Appendix 4. CINAHL (EBSCO) search strategy

S1	(MH "Otitis Media+")
S2	TI otitis media OR AB otitis media
S3	TI (middle ear N5 (infect* or inflam* or effusion)) OR AB (middle ear N5 (infect* or inflam* or effusion))
S4	TI (ome or aom) OR AB (ome or aom)
S5	S1 OR S2 OR S3 OR S4
S6	(MH "Adrenal Cortex Hormones+")
S7	TI adrenal cortex hormone* OR AB adrenal cortex hormone
S8	TI (corticosteroid* or corticoid* or steroid* or glucocorticoid*) OR AB (corticosteroid* or corticoid* or steroid* or glucocorticoid*)
S9	TI (pregnenedione* or pregnenolone* or hydrocortisone* or hydroxypregnenolone* or tetrahydrocortisol* or cortodoxone*) OR AB (pregnenedione* or pregnenolone* or hydrocortisone* or hydroxypregnenolone* or tetrahydrocortisol* or cortodoxone*)
S10	TI (aristocort or triamcinolone) OR AB (aristocort or triamcinolone)
S11	TI (prednisolone or bubbli-pred or cotolone or prelone or pediaped or pms-prednisolone) OR AB (prednisolone or bubbli-pred or cotolone or prelone or pediaped or pms-prednisolone)
S12	TI (paramethasone or methylprednisolone) OR AB (paramethasone or methylprednisolone)
S13	TI (baycadron or dexamethasone or decadron) OR AB (baycadron or dexamethasone or decadron)
S14	TI (clobetasol or beclomethasone or betamethasone or budesonide) OR AB (clobetasol or beclomethasone or betamethasone or budesonide)

(Continued)

S15	TI (efcortisol or hydrocortone or solu-cortef or cortef or A-Hydrocort) OR AB (efcortisol or hydrocortone or solu-cortef or cortef or A-Hydrocort)
S16	TI (betnelan or betnesol or celestone) OR AB (betnelan or betnesol or celestone)
S17	TI (deflazacort or calcort) OR AB (deflazacort or calcort)
S18	TI (medrone or medrol or solu-medrone or depo-medrone or methylpred-DP) OR AB (medrone or medrol or solu-medrone or depo-medrone or methylpred-DP)
S19	TI kenalog OR AB kenalog
S20	TI (novolizer or pulmicort or symbicort or entocort EC) OR AB (novolizer or pulmicort or symbicort or entocort EC)
S21	TI (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte) OR AB (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte)
S22	TI cortisol OR AB cortisol
S23	(MH "Mineralocorticoids+")
S24	TI (mineralcorticoid* or mineralocorticoid*) OR AB (mineralcorticoid* or mineralocorticoid*)
S25	(MH "Aldosterone")
S26	TI aldosterone OR AB aldosterone
S27	TI (florinef acetate or fludrocortisone) OR AB (florinef acetate or fludrocortisone)
S28	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
S29	S5 AND S28
S30	(MH "Clinical Trials+")
S31	PT clinical trial
S32	TI clinic* N1 trial* OR AB clinic* N1 trial*
S33	TI ((singl* or doubl* or tripl* or trebl*) N1 (mask* or blind*)) OR AB ((singl* or doubl* or tripl* or trebl*) N1 (mask* or blind*))
S34	(MH "Random Assignment")
S35	TI random* OR AB random*
S36	(MH "Placebos")

(Continued)

S37	TI placebo* OR AB placebo*
S38	S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S39	S29 AND S38

Appendix 5. Web of Science (Thomson Reuters) search strategy

<p>#4 AND #3 Refined by: PUBLICATION YEARS: (2016 OR 2017) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years</p>
<p>#4 AND #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years</p>
<p>TOPIC: (random* or placebo* or crossover* or “cross over” or allocat* or ((singl* or doubl*) NEAR/1 blind*)) OR TITLE: (trial) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years</p>
<p>#2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years</p> <p>TOPIC: (“adrenal cortex hormone*” or corticosteroid* or corticoid* or steroid* or glucocorticoid*) OR TOPIC: (pregnenedione* or pregnenolone* or hydrocortisone or hydroxypregnenolone or tetrahydrocortisol or cortodoxone or “cortone acetate” or cortisone or corticosterone or aristocort or triamcinolone or deltasone or prednisone or prednicot or prednisolone) OR TOPIC: (“bubpli-pred” or cotolone or prelone or pediaped or “pms-prednisolone” or paramethasone or methylprednisolone or baycadron or dexamethasone or decadron or clobetasol or beclomethasone or betamethasone or budesonide or efcortisol or hydrocortone or solu-cortef or cortef or A-Hydrocort or betnelan) OR TOPIC: (betnesol or celestone or deflazacort or calcort or medrone or medrol or solu-medrone or depo-medrone or methylpred-DP or kenalog or novolizer or pulmicort or symbicort or entocort or beclometasone or aerobec or asmabec or beclazone or becodisks or becotide) OR TOPIC: (“clenil modulite” or qvar or becloforte or cortisol or mineralcorticoid* or aldosterone or “florinef acetate” or fludrocortisone) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years</p>
<p>TOPIC: (“otitis media”) OR TOPIC: (“middle ear” NEAR/5 (infect* or inflam* or effus*)) OR TOPIC: (ome or aom) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan= All years</p>

Appendix 6. LILACS (BIREME) search strategy

tw:((mh:"Otitis Media" OR "Otitis Media" OR "Otitis Média" OR mh:c09.218.705.663* OR "middle ear infection" OR "middle ear inflammation" OR "middle ear effusion" OR "serous otitis media" OR "OME" OR "AOM") AND (mh:"Adrenal cortex hormones" OR "Adrenal Cortex Hormones" OR corticoesteroides OR corticosteroides OR corticoides OR corticosteroides OR "Hormonas de la Corteza Suprarrenal" OR corticoid* OR corticoesteroides OR "Hormônios do Córtex Suprarrenal" OR mh:d06.472.040* OR corticosteroid* OR corticoid* OR steroid* OR glucocorticoid* OR esteroid* OR corticoid* OR mineralocorticoid* OR mh:pregnenediones OR pregnenodionas OR mh:d04.808.745.745.654* OR dicetopregnenos OR pregnenedionas OR pregnenedione* OR pregnenolone OR hydrocortisone OR hydroxypregnenolone OR tetrahydrocortisol OR cortodoxone OR "cortone acetate" OR cortisone OR corticosterone OR aristocort OR triamcinolone OR daltasone OR prednisone OR prednicot OR prednisolone OR "bubpli-pred" OR cotolone OR prelone OR pediaped OR "pms-prednisolone" OR paramethasone OR methylprednisolone OR baycadron OR dexamethasone OR decadron OR clobetasol OR beclomethasone OR betamethasone OR budesonide OR efcoresol OR hydrocortone OR "solu-cortef" OR cortef OR "A-Hydrocort" OR betnelan OR betnesol OR celestone OR deflazacort OR calcort OR medrone OR medrol OR "solu-medrone" OR "depo-medrone" OR "methylpred-DP" OR kenalog OR novolizer OR pulmicort OR symbicort OR "entocort EC" OR beclometasone OR aerobec OR asmabec OR beclazone OR becodisks OR becotide OR "clenil modulate" OR qvar OR becloforte OR cortisol OR mh:mineralocorticoids OR mineralocorticoid* OR mineralcorticoid* OR mh:aldosterone OR aldosterone OR aldosterona OR "florinef acetate" OR fludrocortisone)) AND (instance:"regional") AND (db:("LILACS"))

CONTRIBUTIONS OF AUTHORS

Respati W Ranakusuma (RR) drafted the protocol and contributed as a primary review author, selected studies for inclusion, extracted data, assessed the risk of bias, entered data into Review Manager 5, and carried out and interpreted the analysis.

Yupitri Pitoyo (YP) selected studies for inclusion, extracted data, and assessed the risk of bias.

Eka Dian Safitri (EDS) selected studies for inclusion, extracted data, and assessed the risk of bias.

Sarah Thorning (ST) developed and ran the search strategy, and obtained copies of studies.

Elaine M Beller (EMB) carried out and interpreted the analysis, contributed as the fourth review author for disagreements on methodological/statistical issues, and checked the correct use of grammar.

Sudigdo Sastroasmoro (SS) drafted the protocol, contributed to drafting the final review, and checked the correct use of grammar.

Chris B Del Mar (CDM) drafted the protocol and contributed as the fifth review author for disagreements on clinical issues (if needed), drafted the final review, and checked the correct use of grammar.

DECLARATIONS OF INTEREST

Respati W Ranakusuma: none known

Yupitri Pitoyo: none known

Eka Dian Safitri: none known

Sarah Thorning: none known

Elaine M Beller: her work on this review was supported by a grant from the National Health and Medical Research Council, Australia, to the Centre for Research in Evidence-Based Practice, Bond University

Sudigdo Sastroasmoro: none known

Chris B Del Mar: none known

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adrenal Cortex Hormones [*therapeutic use]; Anti-Bacterial Agents [therapeutic use]; Ceftriaxone [therapeutic use]; Histamine Antagonists [therapeutic use]; Otitis Media [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Child, Preschool; Humans; Infant