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Overview of Reviews

The Cochrane Library and acute otitis media in children: an overview of reviews

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Background: Acute otitis media (AOM) is one of the most common clinical problems in childhood with peak incidence occurring in the first 2 years of life.

Objectives: To critically evaluate the available evidence in *The Cochrane Library* regarding the treatment of AOM.

Methods: The Cochrane Library was searched using the terms 'otitis media' and 'ear infection'. Reviews focusing on the treatment of AOM in children were included. Data on patient relevant outcomes (pain, treatment failure, AOM recurrence and adverse events) were extracted by two authors.

Main results: Six reviews were included in this overview. The first review compared antibiotics with placebo. Antibiotics reduced pain on days 2–7 [odds ratio (OR): 0.61; 95% confidence interval (CI): 0.49–0.75; Number needed to treat (NNT) = 14] but increased overall adverse events (OR: 2.35; 95% CI: 1.14–4.84; NNT = 7). Antibiotics also reduced the number of children with treatment failure (persistence of signs and symptoms at the end of therapy) (OR: 0.40; 95% CI: 0.27–0.60; NNT = 8), and this effect was larger in two recent randomized controlled trials which used stringent diagnostic criteria and were restricted to young children (OR: 0.24; 95% CI: 0.16–0.34; NNT = 4). The second review addressing the length of antibiotic treatment showed that shorter courses of oral antibiotics resulted in a slightly increased likelihood of treatment failure (OR: 1.34; 95% CI: 1.16, 1.55), although trial quality was limited. In the third review, no significant differences were noted between once- or twice-daily versus three times-daily administration of amoxicillin-based antibiotic treatment; however, the quality of the original data on which the review was based was less than optimal. The fourth review compared delayed antibiotics to immediate therapy or to no antibiotics for AOM, with no differences in pain between groups. In the fifth review, decongestants and/or antihistamines were compared with placebo. Decongestants and antihistamines provided no appreciable benefit and were associated with significant adverse events (OR: 3.74; 95% CI: 1.53, 9.16). In the sixth review, topical analgesic drops and placebo were compared. Use of analgesic drops was associated with a significant increase in pain reduction (OR: 3.07; 95% CI: 1.33, 7.05).

Authors' conclusions: Current evidence suggests that antibiotic treatment may be justified in young children with stringently diagnosed AOM.

Keywords: acute otitis media, Cochrane Library, meta-analysis, overview, systematic review

Plain language summary

Acute middle ear infection [acute otitis media (AOM)], or inflammation of the middle ear secondary to a bacterial or viral infection, is one of the most common diseases diagnosed in children. Accurate diagnosis is often difficult. Standard treatment involves antibiotics given for 7 days or longer, three or four times daily. Our overview of the literature showed that antibiotics appear to be effective in reducing ear pain in children less than two years old, with a properly diagnosed ear infection. Also, it appears that shortening the course of antibiotics treatment (to less than 7 days) results in more children who fail treatment (i.e., who still have symptoms like ear pain at the end of treatment). There is no evidence that once-daily administration of amoxicillin with or without clavulanate is better or worse than administration two or three times a day. Also,

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there was no difference in pain between children who were in a 'watch and see' (delayed treatment) group and those receiving immediate antibiotic treatment or no treatment at all. Ear drops with pain medications seem to be promising; the use of such drops resulted in significant pain relief. Decongestants and antihistamines are sometimes associated with serious side effects therefore they should not be used in children with acute otitis media.

Background

Description of the condition

Otitis media is a general term for middle-ear inflammation and may be classified clinically as either AOM or otitis media with effusion (OME). Accurate diagnosis of otitis media in infants and young children is often difficult. Symptoms frequently overlap with those of upper respiratory illness. The tympanic membrane (TM) may be obscured by cerumen, and subtle changes in the TM may be difficult to discern. OME is diagnosed if, on pneumatic otoscopy, there is evidence of middle-ear effusion but no signs of acute inflammation that would constitute evidence of middle-ear infection. When middle-ear fluid is present, the TM is discoloured and opaque and exhibits decreased mobility on pneumatic otoscopy. A diagnosis of AOM is justified when, in addition to evidence of middle-ear effusion, there is marked redness or bulging of the TM. Fever may or may not be present.

AOM remains one of the most common clinical problems in childhood. The peak incidence is in the first 2 years of life, particularly between 6 and 12 months of age. The increased susceptibility in infants may be explained, at least in part, by anatomic features (characteristics of the eustachian tube, such as short length, horizontal position and high compliance) and immunologic factors (limited response to antigens and lack of previous exposure to common bacterial and viral pathogens).

The antecedent event in the majority of cases of AOM is a viral upper respiratory tract infection, which causes inflammation of the mucosa of the nasopharynx and eustachian tube. Eustachian tube dysfunction impairs middle ear fluid drainage and establishes an environment that is conducive to bacterial growth (1). Bacteria are isolated from middle-ear fluid of approximately 70% of children with bulging TMs; only rarely (~6% of cases) do viral infections alone (in the absence of a bacterial superinfection) result in clinical features consistent with AOM (2).

Description of the interventions

The treatment of AOM remains controversial. The American Academy of Pediatrics recommends use of immediate antibiotics for all children younger than 6 months and for children 6 months to 2 years of age when the diagnosis of AOM is certain, otherwise advising an observation option depending on severity of symptoms (3). The Canadian Paediatric Society recommends a 'watchful waiting' approach for children older than 6 months with mild symptoms (4). In more severe cases, the use of antibiotics is recommended. The 'watch and see' approach is usually supported by oral or topical analgesic treatment. Although use of decongestants and/or antihistamines for AOM is not recommended, they are often administered as an adjunctive treatment.

How the interventions might work

Antibiotics eradicate bacteria from the middle ear space, and the more effective they are in this task, the better the clinical outcome (5). Because the inflammation in the nasopharynx and the consequent eustachian tube dysfunction are believed to play important roles in the pathophysiology of AOM, it has been postulated that decongestants and antihistamines could play a role in the treatment of AOM. Antihistamines work by modifying the systemic histamine-mediated allergic response, and decongestants work by constricting the blood vessels within the nasopharyngeal cavity. Because otalgia is the most prominent symptom of AOM, treatment of otalgia with analgesics is an important part of the management of this condition. Treatment consists of oral analgesic medications (e.g. acetaminophen, ibuprofen) or topical anaesthetic drops directly instilled into the ear canal.

Why it is important to do this overview

There are increasing concerns about antibiotic resistance and growing burden of antibacterial treatment. Antibiotic use is associated with increased antibiotic resistance among the pathogens causing AOM. Thus, it is of paramount importance to have evidence-based guidelines to justify their use. On the other hand, avoidance of inappropriate antibiotic use – for treatment of children with OME (misdiagnosed as having AOM) or for treatment of nonspecific upper respiratory tract symptoms – could go far toward preventing antimicrobial resistance. Decreasing the length of antibiotic therapy reduces the probability of occurrence of adverse events related to antibiotic consumption and may help to prevent the development of bacterial resistance. The effectiveness of antibiotics is also dependent on compliance with the recommended course of therapy. Reducing the frequency of dosing medications from three times to once or twice daily increases the chances of compliance; however, the question whether this approach influences the drug's efficacy remains unresolved. The use of decongestants and antihistamines, which are widely available through local pharmacies and are frequently used in the management of children with AOM, is controversial because their use has been associated with significant adverse events. In this overview, we examine the available evidence on the management of AOM in children.

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Objectives

The purpose of this overview is to critically evaluate the evidence currently available in the *Cochrane Database of Systematic Reviews* on the efficacy and safety of treatments of AOM in children.

Methods

Criteria for considering reviews for inclusion

All Cochrane reviews on the treatment of AOM in children between 0 and 18 years of age were considered for inclusion. Reviews on the prevention of AOM, complications of AOM or treatment of OME were excluded.

Search methods for the identification of reviews

The terms 'otitis media' and 'ear infection' were entered into the *Cochrane Database of Systematic Reviews* using the 'title, abstract or keywords' search field. The search was performed in August 2011. Two authors (RMF and NS) assessed the eligibility of reviews based on the inclusion criteria presented above.

We included all reviews regardless of date of completion (date assessed as up to date). When the date of completion was earlier than January 2009, we updated the reviews by rerunning the original search strategy used in the review in PubMed. Three authors (MO, NS and RMF) then screened these records for new trials. Two reviews (6, 7) were updated. Please refer to the Supporting information (Tables 1 and 2 in Appendix S1) for the detailed search strategies.

Types of outcome measures

We chose to focus on the following patient-relevant outcomes:

1. pain early in the course of therapy,
2. treatment failure (persistence of AOM signs and symptoms) at the end of therapy,
3. recurrence of AOM and
4. side effects of medications.

We did not focus on the complications of AOM because small to medium randomized controlled trials (RTCs) are inadequate to assess the incidence of rare complications. Other potentially relevant outcomes, such as compliance or costs, were also not evaluated.

Data collection and analysis

MO extracted the following data from the included reviews: population, intervention, comparison and outcomes (inclusion criteria), methodological quality of included trials and quantitative data. A second reviewer (RMF) independently verified the accuracy of numeric results.

Dichotomous data were summarized using odds ratios (OR); OR compare the odds of an event in the experimental group with the odds of an event in the control group. Meta-analyses are presented with related I^2 values, which represent the degree of statistical heterogeneity among trials. A value of 0% indicates no heterogeneity; larger values denote increasing heterogeneity with values higher than 50% representing substantial to considerable heterogeneity (8). Fixed- or random-effects models were employed according to the model used in the reviews. For the outcomes which were not included in the original reviews, the choice of model used was dependent on the degree of heterogeneity: for heterogeneity higher than 30%, we employed random-effects models. Review Manager 5 (9) was used to pool the data. Number needed to treat for an additional beneficial or harmful outcome (NNT) was calculated for statistically significant outcomes, based on ORs and using mean baseline risks from control groups of included trials. In some instances, NNTs calculated for this overview differ from NNTs presented in the corresponding reviews; the discrepancies are caused by a change of effect measures (OR vs. risk ratio) chosen for presentation in the meta-analyses. The GRADEpro program (10) was used to create the 'Summary of findings' tables (Tables 2–4).

In some instances, we felt that it would be useful to readers to present sensitivity analyses that were not included in the reviews. In particular, in the review comparing antibiotics to placebo, we assessed whether results were sensitive to the following:

1. Exclusion of trials in which either tympanocentesis or myringotomy was performed (which can alter the natural history of AOM (11)).
2. Exclusion of studies with nonstringent diagnostic criteria (defined as >25% of children having nonbulging TMs).

In the review examining the efficacy of decongestants (6), the primary outcome was treatment failure. However, in nine of the studies, the presence of middle-ear effusion (OME) was included in the definition of treatment failure. Because OME is generally asymptomatic and a usual consequence of AOM and because its presence in the month following AOM is unlikely to adversely affect future outcomes (12), we felt that excluding studies in which the definition of AOM persistence included the presence of OME would be informative.

Results

Description of included reviews

The search identified 35 potentially relevant records, 30 of which were excluded for the following reasons: 13 did not focus on AOM, eight focused on prevention, three were protocols and six discussed treatment of

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hearing loss associated with OME. The remaining five reviews were included (7, 13–16). In addition, one review that had been withdrawn due to lack of an update (6) was also included, resulting in a total of six reviews.

We performed updates of the searches of two reviews (6, 7). For the review comparing decongestants versus placebo (6) (last updated on May 2007), we found no new relevant trials. For the antibiotics versus placebo review (7) (last updated on November 2008), we found two new relevant trials (17, 18).

One review (16) did not pool the included studies because of concerns about varying risks of bias.

The six included reviews and two new trials comprised 92 trials (89 unique trials) which were considered in this overview. Characteristics of the six reviews are shown in Table 1.

Methodological quality of included trials

Multiple methods of methodological quality assessment of the included trials were used in the original reviews. One review (6) used the 5-point Jadad scale (19), one review (7) used the modified method proposed by Chalmers (20) and four reviews (13–16) used the Cochrane Collaboration's 'Risk of bias' tool (21). Detailed information on risk of bias for studies included in these reviews is presented in the Supporting information (Tables 1–3 in Appendix S2).

Effects of interventions

Antibiotics for AOM in children

One review (7) examined the efficacy of antibiotics versus placebo in reducing the severity and duration of pain in children with AOM. The studies included in the review were generally of high methodological quality and ranged in sample size from 83 to 980 children. Children 1 month to 15 years of age were included. The majority of the trials used amoxicillin as the active intervention.

The two new studies published after the review had been completed (17, 18) were both placebo-controlled randomized trials comparing twice-daily amoxicillin clavulanate with placebo in young children with stringently diagnosed AOM. Data extracted from

Table I. Characteristics of included reviews

Title of review	Date assessed as up to date	Population	Intervention	Comparison	Outcomes included in present overview
Antibiotics for acute otitis media in children (7)	November 2008	Children aged 1 month to 15 years	Antibiotics (immediate)	Placebo control or observational 'wait and see' approaches in which prescriptions may or may not be provided.	Treatment failure; pain; adverse events; late recurrences.
Short-course antibiotics for acute otitis media (14)	November 2009	Children aged 1 month to 18 years	Antibiotic therapy for less than 7 days (short course); included 'short-acting' (e.g. penicillin, amoxicillin), ceftriaxone and azithromycin	Antibiotic therapy for greater than or equal to 7 days (long course)	Treatment failure; adverse events.
Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media (16)	July 2010	Children aged 12 years or younger	Once- or twice-daily doses of amoxicillin, with or without clavulanate	Three or four times daily doses of amoxicillin, with or without clavulanate.	Treatment failure; adverse events
Decongestants and antihistamines for acute otitis media in children (6)	May 2007	Adults and children (trials with children only: 3 months to 18 years of age)	Decongestants, decongestants and antihistamines or antihistamines medications	No medication or placebo	Treatment failure; adverse events
Topical analgesia for acute otitis media (13)	February 2011	Children 3–19 years of age	Any otic preparation with an analgesic effect (excluding antibiotics)	Placebo or naturopathic ear drops.	Pain reduction
Delayed antibiotics for respiratory infections (15)	March 2009	Adults and children (AOM trials with children only: 6 months to 12 years of age)	Delayed use of antibiotics defined as the use of, or advice to use, antibiotics more than 48 hours after the initial consultation.	Immediate use of prescription of oral antibiotics given at the initial consultation or no prescription of antibiotics at the initial consultation	Pain

AOM, acute otitis media.

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these trials included the number of children who failed treatment at the end of therapy and total number of adverse events.

The results are summarized in Table 2. Pain at 24 hours was not statistically significantly different between groups [OR: 0.85; 95% confidence interval (CI): 0.67–1.07]. Pain on days 2–7 was seen in 16% versus 22% of children treated with antibiotics versus placebo, respectively (OR: 0.61; 95% CI: 0.49–0.75; NNT = 14). The results were comparable when excluding studies that used tympanocentesis (Figure 2 in Appendix S3; OR: 0.59; 95% CI: 0.48–0.74). There was no significant difference between antibiotics and placebo in the number of episodes of recurrent AOM in the month following the index episode (OR: 0.92; 95% CI: 0.74–1.14). Treatment failure was observed in 14% of children receiving antibiotics as compared to 26% children in the placebo group (OR: 0.40; 95% CI: 0.27–0.60; NNT = 8). There was substantial heterogeneity (Figure 3 in Appendix S3; $I^2 = 66\%$) among the studies with regard to this outcome. When we include only trials in which a bulging TM was observed in more than 75% of children at entry (for inclusion criteria, see Table 4 in Appendix S3), treatment failure was observed in 18% of children treated with antibiotics versus 47% of children in the placebo group (Figure 4 in Appendix S3; OR: 0.24; 95% CI: 0.16–0.34; NNT = 4).

Overall, adverse events were increased with antibiotic use (OR: 2.35; 95% CI: 1.14–4.84). Of note, there was a high degree of heterogeneity ($I^2 = 85\%$) in the latter analysis.

Short-course antibiotics for AOM

One review (14) compared short (<7 days) versus long (≥ 7 days) courses of antibiotics. The review included 49 studies, and the sample sizes of these studies ranged from 17 to 868. Nineteen studies examined short-acting oral antibiotics (e.g. penicillin, amoxicillin), 21 examined oral azithromycin and another nine examined intramuscular ceftriaxone. Tympanocentesis or myringotomy were performed in 20 of these trials. Forty-five trials reported treatment failure at 1 month or less. Gastrointestinal adverse effects were reported in 30 trials. Short-acting antibiotics (e.g. penicillin, amoxicillin) were analysed separately from ceftriaxone and azithromycin.

The findings are summarized in Table 3. Children who received a short course of oral antibiotics had a slightly higher likelihood of failing treatment than children who received a longer course (OR: 1.44; 95% CI: 1.21–1.71). This effect was larger when the analysis was limited to the studies in which both the patient and the investigator were blinded (Figure 5 in Appendix S3; OR: 2.18; 95% CI: 1.52–3.12). Comparisons between azithromycin or ceftriaxone versus other long-course antibiotics did not show any significant differences.

Compared to children receiving long-course treatment, children receiving short-course treatment had fewer gastrointestinal adverse events (OR: 0.72; 95% CI: 0.60–0.87). There was a high degree of heterogeneity ($I^2 = 58\%$) among trials. These findings were sensitive to risk of bias; there were no differences between groups when excluding studies with unclear or high risk of bias regarding blinding (Figure 6 in Appendix S3; OR: 1.36; 95% CI: 0.85–2.18).

Data on recurrence of AOM, which were not presented in the original review, showed no statistically significant differences between short and long courses of treatment (Figure 7 in Appendix S3; OR: 0.88; 95% CI: 0.71–1.09).

Table II. Summary of findings: antibiotics versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	I^2 (%)	Number of Participants (studies)	NNT (95% CI)
	Assumed risk Placebo	Corresponding risk Antibiotics				
Pain at 24 hours (all studies)	40 per 100	36 per 100 (31–41)	OR: 0.85 (0.67–1.07)	2	1229 (5)	
Pain at 24 hours (excluding studies with tympanocentesis)	41 per 100	36 per 100 (31–42)	OR: 0.82 (0.65–1.04)	0	1145 (4)	
Pain at 2–7 days (all studies)	22 per 100	15 per 100 (12–18)	OR: 0.61 (0.49–0.75)	0	2791 (10)	14 (10–22)
Pain at 2–7 days (excluding studies with tympanocentesis)	22 per 100	14 per 100 (12–17)	OR: 0.59 (0.48–0.74)	0	2619 (8)	13 (10–22)
Treatment failure† (excluding studies with tympanocentesis)	26 per 100	12 per 100 (8–17)	OR: 0.40 (0.27–0.60)	66	2803 (8)	8 (6–12)
Treatment failure† (excluding studies in which <75% of children had a bulging TM)	47 per 100	18 per 100 (13–23)	OR: 0.24 (0.16–0.34)	0	608 (2)	4 (3–5)
Late recurrence	21 per 100	19 per 100 (16–23)	OR: 0.92 (0.74–1.14)	0	2153 (6)	
Adverse events† (vomiting, diarrhoea or rash)	18 per 100	35 per 100 (25–52)	OR: 2.35 (1.14–4.84)	85	2011 (7)	7 (4–49)

CI, confidence interval; OR, odds ratio.

* Mean baseline risk in control group was used to calculate assumed risk. The corresponding risk (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).

† Meta-analysis includes new studies published after the review had been completed.

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Table III. Summary of findings: short- versus long-course antibiotics for AOM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	I^2 (%)	Number of participants (studies)	NNT (95% CI)
	Assumed risk Long-course antibiotics	Corresponding risk Short-course antibiotics				
Treatment failure (all studies)	17 per 100	22 per 100 (20–25)	OR: 1.34 (1.15–1.55)	28	5093 (16)	22 (14–48)
Treatment failure (excluding studies with tympanocentesis or myringotomy)	15 per 100	20 per 100 (17–23)	OR: 1.44 (1.21–1.71)	26	4065 (12)	20 (13–68)
Treatment failure (excluding studies with tympanocentesis or myringotomy and using only studies were both patients and investigator were blinded)	10 per 100	20 per 100 (15–27)	OR: 2.18 (1.52–3.12)	0	1038 (3)	11 (7–22)
Treatment failure (short course = single dose of azithromycin)	24 per 100	24 per 100 (18–31)	OR: 1.01 (0.69–1.47)	0	608 (2)	
Treatment failure (short course = 3–5 days of azithromycin)	19 per 100	19 per 100 (17–21)	OR: 1.02 (0.87–1.20)	31	4354 (19)	
Treatment failure (short course = 3–5 days of azithromycin; excluding studies with tympanocentesis or myringotomy)	31 per 100	26 per 100 (18–36)	OR: 0.79 (0.5–1.25)	N/A	362 (1)	
Treatment failure (short course = intramuscular ceftriaxone)	27 per 100	28 per 100 (23–33)	OR: 1.07 (0.85–1.33)	0	1709 (8)	
Treatment failure (short course = intramuscular ceftriaxone, excluding studies with tympanocentesis or myringotomy)	24 per 100	23 per 100 (18–28)	OR: 0.95 (0.71–1.27)	0	1038 (5)	
Gastrointestinal adverse effects	14 per 100	10 per 100 (9–12)	OR: 0.72 (0.60–0.87)	58	4918 (13)	29 (20–64)
Gastrointestinal adverse effects (oral antibiotics, excluding studies with tympanocentesis or myringotomy and using only studies were both patients and investigator were blinded)	12 per 100	16 per 100 (11–23)	OR: 1.36 (0.85–2.18)	0	610 (2)	
Recurrence of AOM (excluding studies with tympanocentesis or myringotomy)	13 per 100	12 per 100 (10–14)	OR: 0.88 (0.71–1.09)	0	3178 (9)	

* See comment under Table 2.

Reduced frequency of antibiotic administration for AOM

Five studies were included in the review that compared reduced frequency administration (once or twice daily) of amoxicillin with or without clavulanate with three times-daily administration for the treatment of AOM (16).

Due to moderate to high risk of bias in all included trials, review authors did not perform meta-analysis. None of the studies show statistically significant differences between the two compared regimens in the proportion of children categorized as having failed treatment at the end of therapy or in the number of adverse events reported. However, presented data are scarce and with heterogeneous quality which make any recommendation on this matter impossible.

Delayed antibiotics for AOM

Two reviews (7, 15), including five trials, evaluated the use of delayed antibiotics ('watchful waiting' or similar approach) compared to immediate therapy (four trials) or no antibiotics (one trial).

The findings are summarized in Table 4. There was no difference in pain at 3–7 days between groups of patients receiving immediate antibiotics and those randomized to 'watchful waiting' (Figure 8 in Appendix S3; OR: 0.67; 95% CI: 0.43–1.06). Adverse events were more frequent in patients randomized to immediate treatment (OR: 2.08; 95% CI: 1.42–3.06). The single trial comparing delayed versus no antibiotics found no difference between the two compared regimens (OR: 1.26; 95% CI: 0.68–2.33).

Decongestants and antihistamines for AOM in children

One review (6) compared the efficacy of either decongestants alone, decongestants combined with antihistamines, or antihistamines alone, to no medication or placebo, as adjunctive treatment in children with AOM.

The findings are summarized in Table 5. Children treated with decongestants with or without antihistamines showed a trend toward fewer treatment failures at 2 weeks, but the CI included 1.00 (OR: 0.8; 95% CI: 0.63–1.00). Similarly, there was no difference between treatment groups in the incidence of recurrent AOM (OR: 0.95; 95% CI: 0.57–1.57). Adverse events were more common with decongestant and/or antihistamine than with placebo (OR: 3.74; 95% CI: 1.53–9.16). Excluding studies in which

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Table IV. Summary of findings: immediate or no antibiotics versus delayed antibiotics

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Delayed antibiotics	Corresponding risk Immediate antibiotics	Relative effect (95% CI)	I^2 (%)	Number of participants (studies)	NNT (95% CI)
Pain at 3–7 days	36 per 100	27 per 100 (19–37)	OR: 0.67 (0.43–1.06)	45	959 (4)	
Adverse events (vomiting, diarrhoea or rash)	13 per 100	24 per 100 (18 to 32)	OR: 2.08 (1.42–3.06)	0	769 (3)	10 (6–22)
	Delayed antibiotics	No antibiotics				
Pain on day 3	25 per 100	29 per 100 (18 to 43)	OR: 1.26 (0.68–2.33)	N/A	206 (1)	

* See comment under Table 2.

the definition of treatment failure included the presence of OME showed similar results (Figure 9 in Appendix S3).

Topical analgesia for AOM

One review (13) compared the efficacy of topical analgesics with or without antibiotics to placebo in the treatment of pain associated with AOM. Because analgesic ear drops are given for immediate pain relief, we focused on pain reduction 10 minutes after administration of the drops.

The results are summarized in Table 6. Two trials compared the use of anaesthetic drops versus placebo. Anaesthetic drops were favoured using both 25% and 50% pain reduction outcomes (OR: 2.43; 95% CI: 1.15–5.15 and OR: 3.07; 95% CI: 1.33–7.05). Neither study described the occurrence of adverse events.

Discussion

Summary of main results

Effectiveness of antibiotics versus placebo for children with AOM

Compared to placebo, children treated with antibiotics had less pain on days 2–7. On the other hand, the use of antibiotics was associated with an increased incidence of vomiting, diarrhoea and rash. Thus, the review authors concluded that the use of antibiotics in the treatment of children with mild AOM, given their apparent marginal efficacy in pain reduction (NNT = 14) and their side effect profile (NNT = 7), was not prudent. An individual patient data analysis (22) included in the review found antibiotics to be most beneficial in children aged less than 2 years, children with bilateral AOM and children with AOM who have ruptured tympanic membranes.

Although this conclusion seems reasonable, its validity becomes questionable once the data are examined more closely. We identified the following threats to the validity of conclusions based on the data included in the original review:

1. It appears that most of the articles included in the original review used nonstringent criteria to diagnose AOM: all of these studies included many (>25%) children with nonbulging TMs. Because bulging of the TM – a finding crucial for the diagnosis of AOM – was not required, these trials may have permitted inclusion of children who did not actually have AOM but instead had OME in conjunction with some acute, unrelated, minor illness (23, 24). It thus seems possible that children with bona fide AOM were systematically underrepresented in these placebo-controlled studies, resulting in an underestimation of differences in efficacy between placebo and antibiotics.

Table V. Summary of findings: decongestants with or without antihistamines versus none

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Placebo	Corresponding risk Decongestants and/or antihistamines	Relative effect (95% CI)	I^2(%)	Number of participants (studies)	NNT (95% CI)
Treatment failure at 2 weeks (all studies)	23 per 100	19 per 100 (16–23)	OR: 0.8 (0.63–1)	21	2300 (12)	
Recurrent AOM (>2 weeks)	7 per 100	7 per 100 (4–10)	OR: 0.95 (0.57–1.57)	0	997 (5)	
Recurrent AOM (>2 weeks, excluding studies with tympanocentesis)	20 per 100	16 per 100 (9–26)	OR: 0.78 (0.41–1.45)	0	279 (2)	
Adverse events	0 per 100	2 per 100 (1–4)	OR: 3.74 (1.53–9.16)	0	983 (5)	82 (28–417)

* See comment under Table 2.

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Table VI. Summary of findings: topical analgesia versus placebo for AOM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	I^2(%)	Number of participants (studies)	NNT (95% CI)
	Assumed risk Placebo	Corresponding risk Topical analgesia				
Pain reduction of 25% after 10 minutes	42 per 100	64 per 100 (46–79)	OR: 2.43 (1.15–5.15)	56	117 (2)	5 (3–30)
Pain reduction of 50% after 10 minutes	20 per 100	44 per 100 (25–64)	OR: 3.07 (1.33–7.05)	0	117 (2)	5 (3–20)

* See comment under Table 2.

2. The original review focused on a single efficacy outcome: otalgia. Because otalgia is difficult to measure in preverbal children (25), many trials have not used otalgia as an outcome measure. Instead, the primary outcome in most trials has traditionally been 'treatment failure'. By reporting only data regarding otalgia (and not treatment failure), the conclusion of the original review are necessarily limited in their scope. A more comprehensive picture may be obtained by examining both otalgia and treatment failure.
3. In several of the studies included in the original review, tympanocentesis or myringotomy – aspiration or drainage of pus from the middle ear – was performed at the time of enrollment. These procedures can alter the natural history of AOM (11).
4. The methods by which pain was measured in the different studies varied considerably and had not been validated for this purpose. Thus, in some studies, the clinician decided whether the child was experiencing pain based on clinical information. In other studies, pain was recorded by parents in a diary or the authors reported data only for a composite outcome that included pain, for example pain and/or fever, or pain and/or otorrhoea (i.e. purulent discharge from the auditory canal). It is uncertain whether such methods of measuring outcomes are sensitive enough to detect differences between groups that might exist and whether these varied methods can simply be pooled into a single measure (e.g. pain at 2–7 days).

To be clear, we fully agree with the authors of the review that otalgia is the most relevant outcome in AOM trials. Nevertheless, because of the challenges of assessing otalgia in young children and because of the other limitations of the trials included in the review, we believe that including analysis on the surrogate outcome 'treatment failure' can indirectly aid in the assessment of the efficacy of antibiotics.

Indeed, when we conducted such an analysis on the trials included in the original review, we found much larger effect sizes that the ones presented in the review. In particular, when we pooled the results of the most recent randomized controlled trials (both had >90% of children with bulging TMs), the NNT was 4. Accordingly, it appears that the efficacy of antibiotics may be higher than what was reported the most recent Cochrane review.

Short-course antibiotics for AOM

In addition to the limitations discussed in the previous section, many of the trials included in this review were also limited by the lack of blinding. Overall, given the limitations of the trials and the relatively modest effect sizes, there is no compelling evidence to date to recommend one treatment length over the other. There is a large trial currently underway that will help provide more guidance regarding this important question (ClinicalTrials.gov identifier: NCT01511107).

Immediate versus delayed antibiotics

From the review, it appears that there is no difference in pain (at 3–7 days) between children receiving immediate antibiotics and delayed antibiotics. However, the four trials included suffered from many of the limitations mentioned above. For example, none of the trials used stringent diagnostic criteria (<75% had bulging TMs or these data were not reported). Again, we feel that the quality and quantity of data are lacking to make any firm conclusions with regards to risks and benefits of delayed antibiotics.

Use of decongestants and antihistamines for children with AOM

Only two studies (26, 27) examined the efficacy of antihistamines and/or decongestants on the acute signs or symptoms of AOM (and these studies found no significant differences between treatment groups). Although the data are very limited, the use of antihistamines and/or decongestants does not appear justified in the treatment of AOM given their side effect profile. Indeed, their use has been previously discouraged, and currently, it is not recommended in management of AOM.

Use of topical analgesia for children with AOM

Although the presented data suggest that analgesic drops may be somewhat effective in treating acute ear

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pain, the studies included only children over 5 years of age and adults. In addition, because of small number of patients, the CIs are wide. Finally, neither study described the occurrence of adverse events.

Limitations of the overview

The main limitation of this overview is in the quality of data and the reporting of the data in the original studies. Better standards of reporting of clinical trials (28) and use of standardized patient- or parent-reported outcome measures across trials may facilitate interpretation data from future studies (29).

Throughout the review, we performed sensitivity analyses using only those studies in which the diagnosis was established using stringent criteria. Although we acknowledge that the criteria used for diagnosis in these studies may be more stringent that is currently the case in many practices and that the results presented in these subgroup analyses may thus be less applicable to such practices, we believe that presenting these results is important for several reasons. First, we feel that clinicians should be aware of the efficacy of the various treatments evaluated in this overview for children meeting the more stringent diagnostic criteria. Second, that data may provide the necessary incentive for the development of educational programs that can help improve the diagnostic skills of general practitioners.

Authors' conclusions

Implications for practice

The literature to date suggests that antibiotic use in young children with stringently diagnosed AOM appears to be justified, although benefits must be balanced with risks, particularly adverse events and bacterial resistance, and with a role for parental preferences. Improving the accuracy of diagnosis (e.g. training programs for otoscopy and cerumen removal), is thus an important mechanism for reducing inappropriate antibiotic use. There is a need for development of unambiguous and more rigorous diagnostic criteria for AOM (30, 31). More data are needed regarding the optimal duration and frequency of antibiotic treatment, the use of topical analgesic drops and the role of delayed treatment.

Implications for research

There is a need for additional, well-designed, placebo-controlled trials comparing the efficacy of antibiotics with that of placebo in children >2 years of age with AOM. The efficacy of topical analgesic drops also deserves further examination.

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Contributions of authors

All authors of this overview contributed in its preparation. MO and RMF did the data extraction and analysis and wrote the Methods and Results sections. MO created the tables and figures and wrote the Abstract and Plain Language Summary sections. MO and NS wrote the Background section. NS wrote Discussion and Conclusion sections. DT commented on the various sections of the draft and coordinated the project. MO is the primary author of this overview. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

Declarations of interest

NS is an author of one of the trials included in this overview. No other declarations of interest are noted.

Supporting information

Additional Supporting information maybe found in the online version of this article:

APPENDIX S1. Search strategies used to update outdated reviews.

APPENDIX S2. Individual trials risk of bias assessment extracted from included reviews.

APPENDIX S3. Figures from Review Manager 5 where data were pooled and analysed differently in this overview than in the original Cochrane systematic reviews due to differing inclusion and exclusion criteria.

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References

1. Bluestone CD. Pathogenesis of otitis media: role of eustachian tube. *Pediatr Infect Dis J* 1996; **15**: 281–291.
2. Chonmaitree T, Owen MJ, Patel JA, Hedgpeth D, Horlick D, Howie VM. Effect of viral respiratory tract infection on outcome of acute otitis media. *J Pediatr* 1992; **120**: 856–862.
3. Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. *Pediatrics* 2004; **113**: 1451–1465.
4. Forgie S, Zhanel G, Robinson J. Management of acute otitis media. *Paediatr Child Health* 2009; **14**: 457–464.
5. Dagan R, Schneider S, Givon-Lavi N, Greenberg D, Leiberman A, Jacobs MR *et al*. Failure to achieve early bacterial eradication

DOI: 10.1002/ebch.1839

increases clinical failure rate in acute otitis media in young children. *Pediatr Infect Dis J* 2008; **27**: 200–206.
6. Coleman C, Moore M. WITHDRAWN: decongestants and antihistamines for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2011; Issue (3): Art. No.: CD001727.
7. Sanders S, Glasziou PP, Del-Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2004; Issue (1): Art. No.: CD00021.
8. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. 2009, version 5.0.2. pp276–282.
9. *Review Manager* (RevMan) [computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*; 2011.
10. Brozek J, Oxman A, Schunemann H. *GRADEpro* [computer program]. Version 3.6 for Windows. 2008.
11. Shaikh N, Wang EE, Arguedas A, Dagan R, Soley C, Song J, *et al*. Acute otitis media severity of symptom score in a tympanocentesis study. *Pediatr Infect Dis J* 2011; **30**: 253–255.
12. Paradise JL, Campbell TF, Dollaghan CA, Feldman HM, Bernard BS, Colborn DK, *et al*. Developmental outcomes after early or delayed insertion of tympanostomy tubes. *N Engl J Med* 2005; **353**: 576–586.
13. Foxlee R, Johansson A, Wejfalk J, Dawkins J, Dooley L, Del MC. Topical analgesia for acute otitis media. *Cochrane Database of Systematic Reviews* 2006; Issue (3): Art. No.: CD005657.
14. Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. *Cochrane Database of Systematic Reviews* 2010; Issue (9): Art. No.: CD001095.
15. Spurling GK, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. *Cochrane Database of Systematic Reviews* 2007; Issue (3): Art. No.: CD004417.
16. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database of Systematic Reviews* 2008; Issue (4): Art. No.: CD004975.
17. Hoberman A, Paradise JL, Rockette HE, Shaikh N, Wald ER, Kearney DH, *et al*. Treatment of acute otitis media in children under 2 years of age. *N Engl J Med* 2011; **364**: 105–115.
18. Tahtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med* 2011; **364**: 116–126.
19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
20. Chalmers I, Adams M, Dickersin K, Hetherington J, Tarnow-Mordi W, Meinert C, *et al*. A cohort study of summary reports of controlled trials. *JAMA* 1990; **263**: 1401–1405.
21. Higgins JPT, Douglas AG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Intervention*. Chichester, UK: Wiley-Blackwell; 2008; 187–241.
22. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, *et al*. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006; **368**: 1429–1435.
23. Pichichero ME, Casey JR. Comparison of study designs for acute otitis media trials. *Int J Pediatr Otorhinolaryngol* 2008; **72**: 737–750.
24. Shaikh N, Hoberman A, Kaleida PH, Rockette HE, Kurs-Lasky M, Hoover H, *et al*. Otoscopic signs of otitis media. *Pediatr Infect Dis J* 2011; **30**: 822–826.
25. Laine MK, Tahtinen PA, Ruuskanen O, Huovinen P, Ruohola A. Symptoms or symptom-based scores cannot predict acute otitis media at otitis-prone age. *Pediatrics* 2010; **125**: e1154–e1161.
26. Bain DJ. Can the clinical course of acute otitis media be modified by systemic decongestant or antihistamine treatment? *Br Med J (Clin Res Ed)* 1983; **287**: 654–656.
27. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH, *et al*. A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. *J Pediatr* 2003; **143**: 377–385.
28. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; **152**: 726–732.
29. Shaikh N, Hoberman A, Paradise JL, Wald ER, Switze GE, Kurs-Lasky M, *et al*. Development and preliminary evaluation of a parent-reported outcome instrument for clinical trials in acute otitis media. *Pediatr Infect Dis J* 2009; **28**: 5–8.
30. Hayden GF. Acute suppurative otitis media in children. Diversity of clinical diagnostic criteria. *Clin Pediatr (Phila)* 1981; **20**: 99–104.
31. Pichichero ME, Casey JR. Diagnostic inaccuracy and subject exclusions render placebo and observational studies of acute otitis media inconclusive. *Pediatr Infect Dis J* 2008; **27**: 958–962.

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