Antibiotics for acute otitis media in children (Review)

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Antibiotics for acute otitis media in children [Review]

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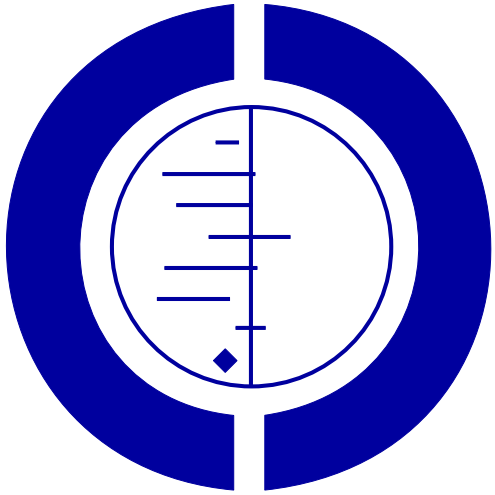

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ABSTRACT

Background
Acute otitis media is one of the most common diseases in early infancy and childhood. Antibiotic use for acute otitis media varies from 31% in the Netherlands to 98% in the USA and Australia.

Objectives
The objective of this review was to assess the effects of antibiotics for children with acute otitis media.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE, Index Medicus (pre 1965), Current Contents and reference lists of articles from 1958 to January 2000. The search was updated in 2003.

Selection criteria
Randomised trials comparing antimicrobial drugs with placebo in children with acute otitis media.

Data collection and analysis
Three reviewers independently assessed trial quality and extracted data.

Main results
Ten trials were eligible based on design, only eight of the trials, with a total of 2,287 children, included patient-relevant outcomes. The methodological quality of the included trials was generally high. All trials were from developed countries. The trials showed no reduction in pain at 24 hours, but a 30% relative reduction (95% confidence interval 19% to 40%) in pain at two to seven days. Since approximately 80% of patients will have settled spontaneously in this time, this means an absolute reduction of 7% or that about 15 children must be treated with antibiotics to prevent one child having some pain after two days. There was no effect of antibiotics on hearing problems of acute otitis media, as measured by subsequent tympanometry. However, audiometry was done in only two studies and incompletely reported. Nor did antibiotics influence other complications or recurrence. There were few serious complications seen in these trials: only one case of mastoiditis occurred in a penicillin treated group.

Authors' conclusions
Antibiotics provide a small benefit for acute otitis media in children. As most cases will resolve spontaneously, this benefit must be weighed against the possible adverse reactions. Antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is more common.

[This abstract has been prepared centrally.]

PLAIN LANGUAGE SUMMARY

Antibiotics are not very useful for most children with acute otitis media

Acute otitis media (infection in the middle ear space) is common in children and causes pain and deafness. The review found that antibiotics did not alter pain within the first day, (when most children were better), only slightly reduced it in the few days following and did not reduce the deafness (that can last several weeks). There was not enough information to know if antibiotics reduced rare complications. Antibiotics caused unwanted effects such as diarrhoea, stomach pain, and rash, (and may increase resistance to antibiotics in the community). It is difficult to balance the small benefits against the small harms of antibiotics for most children. However, they may be necessary in the very young or in severe or prolonged cases.

BACKGROUND

Acute otitis media is one of the most frequent diseases in early infancy and childhood. It has a high morbidity and low mortality (Stool 1989). Approximately 10% of children have an episode of acute otitis media by three months of age. The peak age-specific incidence is between six and 15 months (Klein 1989). Despite a large number of published clinical trials, there is no consensus on the therapy of acute otitis media; for example, the rates of use of antibiotics for acute otitis media varies from 31% in the Netherlands to 98% in the USA and Australia (Froom 1990). A meta analysis (Rosenfeld 1994) emphasises that for most children acute otitis media is a disease which resolves spontaneously. However, one semi-randomised trial in Sweden of 1,365 subjects in 1954 (Rudberg 1954) reported a rate of mastoiditis of 17% in the untreated group versus none in the penicillin treated groups.

OBJECTIVES

The aim of this review was to assess the usefulness of antibiotic treatment for acute otitis media in children.
We attempted to determine to what extent antibiotics therapy was more effective, and what, if any advantages it offered to children in terms of symptom relief, complications (such as mastoiditis), and longer term hearing problems from middle ear effusion (as measured by tympanometry or audiogram).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled clinical trials of antimicrobial drugs versus placebo control were identified. Where necessary and possible, intention-to-treat analyses were reconstructed from the available data (subjects failing to complete were considered to have the worse possible outcome).
All trials were assessed blind for three major quality criteria: proper randomisation; degree of follow-up; and blinding (Chalmers 1990). Details are given in the scoring sheet in the Methods of the review section.

Types of participants

Includes children of either gender without tympanostomy tubes, suffering from acute otitis media irrespective of the setting from which they were recruited.

Types of intervention

Antimicrobial drugs versus placebo control.

Types of outcome measures

We focused our data extraction on patient-relevant outcomes, that is, those symptoms or problems that are important to the patients sense of well-being. While other endpoints, such as microbiological cure may enhance medical understanding of the disease process, decisions about treatment should focus on helping the patient. For acute otitis media, we considered the most important outcomes for patients are severity and duration of pain; hearing problems (mid- to long-term)from the middle ear fluid; adverse effects; and recurrent attacks.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Acute Respiratory Infections Group methods used in reviews.

Computer-based and manual literature searches were used to compile all relevant published randomised controlled trials of antibiotic treatment of otitis media in children. The Cochrane Controlled Trials Register, MEDLINE and Current Contents were searched from 1966 to January 2000 by an expert librarian in conjunction with one researcher, using combinations of "OTITIS MEDIA" and a search strategy described by (Dickersin 1994) for optimally identifying controlled trials. In addition, titles in Index Medicus were checked from 1958 to 1965. The references of all relevant retrieved trials were checked to identify other articles.

The search was updated in March 2003. The Cochrane Central Register of Controlled Trials (CENTRAL) (issue 1, 2003); MEDLINE (January 2000 to March 2003); and EMBASE (January 1990 to March 2003) were searched. There were no language restrictions.

The following search strategy was run on MEDLINE and modified terms were used for the EMBASE database:

#1 explode 'Otitis-Media' / all subheadings in MIME, MJME
#2 'Otitis-Media-with-Effusion' / all subheadings in MIME, MJME
#3 'Otitis-Media-Suppurative' / all subheadings in MIME, MJME
#4 glue ear
#5 otitis media
#6 OME
#7 AOM
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 explode 'Antibiotics-' / all subheadings in MIME, MJME
#10 explode 'Drug-Therapy' / all subheadings in MIME, MJME
#11 explode 'Anti-Infective-Agents' / all subheadings in MIME, MJME
#12 antibiotic*
#13 #9 or #10 or #11 or #12
#14 #8 and #13
#15 #8 and #13 and (PY=2000-2003)

METHODS OF THE REVIEW

We used a modification of a published method to assess the methodological quality (Chalmers 1990). The items were assessed for the following four characteristics:

1. Method of treatment assignment
 a. Correct, blinded, randomisation method described OR
 randomised, double-blind stated AND group similarity documented
 b. Blinding and randomisation stated, but method not described OR
 suspect technique, e.g., envelope
 c. Randomisation claimed but not described, and investigator not blinded
 d. Randomisation not mentioned

2. Control of selection bias after treatment assignment
 a. Intention to treat analysis AND full follow-up
 b. Intention to treat analysis AND < 15% loss to follow-up
 c. Analysis by treatment received only OR no mention of withdrawals
 d. Analysis by treatment received AND no mention of withdrawals OR
 more than 15% withdrawals/loss-to-follow-up/post-randomisation exclusions

3. Blinding
 a. Blinding of (i) outcome assessor AND (ii) patient AND (iii) care giver
 b. Blinding of (i) outcome assessor OR (patient AND care giver)
 d. Blinding not done

4. Outcome assessment
 a. All patients had standardised assessment
 b. No standardised assessment OR not mentioned

The quality of all the study trials that met the inclusion criteria were assessed each reviewer. Assessment was done "blind", (i.e. without the knowledge of the study results, nor the names of the authors, institutions, journal of publication). The reviewers met after their study assessments in order to resolve any disagreements, still blinded to results.

Treatment differences are analysed as odds ratios with 95% confidence intervals calculated by the Peto method using a fixed-effects model. Results of the meta-analyses are reported as relative risk or relative risk reductions. Heterogeneity was assessed using the chi-squared heterogeneity test as well as visual inspection of the forest plots. When heterogeneity was present ($p<0.05$) the data were re-analysed using the random effects model. For the outcome of pain the magnitude of baseline risk and heterogeneity was explored using a L'Abbé plot (graph of the proportion of participants with an outcome by the proportion of participants without an outcome).

DESCRIPTION OF STUDIES

Ten trials were eligible for the review of antibiotics against placebo, though only eight included patient-relevant outcomes. One trial (vanBuchem 1981a) had a factorial design (myringotomy, antibiotics, both or neither): we used all arms of the trial (vanBuchem 1981b includes the myringotomy only and myringotomy plus antibiotic arms). One study (Howie 1972) did not report on patient-relevant outcomes such as symptoms or hearing problems; yet another study (Laxdal 1970) reported only recurrences. A recent trial (Little 2001) comparing immediate with delayed antibiotic therapy in which only 24% (36/150) of children in the delayed arm reported using antibiotics, has been included in a sensitivity analysis. Thus most analyses are based on at most eight studies.

METHODOLOGICAL QUALITY

The methodological quality of the ten eligible studies was generally high. Seven of the eight trials that reported patient-relevant outcomes used an adequately concealed allocation (blinded randomisation) and outcome assessment. Two studies failed to include all children in follow-up assessments, but exclusions were less than 10% (Halsted 1968; Howie 1972).

RESULTS

Pain : The combined results of the trials showed that by 24 hours from the start of treatment, two thirds of children had recovered whether or not they had placebo or antibiotics. At two to seven

days, approximately 80% of children had spontaneously recovered (pooled control groups). Antibiotics achieved a further 30% relative reduction in the risk of pain (95% CI: 19% to 40%). This means overall 7% fewer children had pain after two to seven days: about 15 (95%CI: 11 to 24) children needed to be treated to prevent one child experiencing pain after two to seven days (1/RRR*average risk). Results were similar when data from the trial (Little 2001) comparing immediate versus delayed antibiotics (only 24% of children in the delayed treatment arm used antibiotics) was included in a sensitivity analysis.

Hearing : There was no clinically or statistically significant difference in tympanometry results at one or three months after the acute episode, suggesting no effects on hearing. However, audiometry was done in only two studies and incompletely reported. The two studies that used audiograms were: (i) van Buchem, 1981, who reported that, "After one month, 31% of the patients showed an air/bone gap of more than 20 dB. After two months, this was still the case with 19% of the patients. Here again, there were no significant differences between the groups". (ii) Kaleida 1991, states that " Analysis of hearing acuity in children two years of age and older indicated that elevated hearing thresholds ... bore no apparent relationship ... to mode of treatment (amoxicillin vs placebo)."

Progression of symptoms : There appears to be reduced contralateral otitis media in the antibiotic group, though with the heterogeneous results, this was non-significant in the random effects model, but an increase in adverse effects, namely nausea, diarrhoea, and rash. This is largely based on the effects of amoxycillin seen in the Burke study, which was one of the few studies to report adverse effects. Relapse was common. Burke states "The mean number of recorded recurrences of otitis media or acute red ear was 0.70 (range 0-4) in the antibiotic group and 0.63 (range 0-7) in the placebo group and this difference was not significant (difference 0.06; 95% confidence interval -0.22 to 0.339)." Five other trials reported the proportions who relapsed; combined these give an odds ratio of 0.99, which is consistent with Burke's findings.

Complications : Few serious complications occurred in either the antibiotic treated group or the controls. In just over two thousand children studied, only one case of mastoiditis occurred (in a penicillin treated group - Mygind 1981). Hence the applicability of these findings to groups in whom mastoiditis is common is uncertain. One of the excluded studies (Rudberg 1954) did report high rates of mastoiditis. This was an open, semi-randomised study conducted in Sweden in 1954. Patients were randomised by case-sheet number, but a proportion (about 30 of 220) requested, and were granted, entry to the penicillin group. The rate of mastoiditis was 17% in the untreated group versus 1.5% in the sulphonamide group and 0% in the penicillin treated group. The biases of this study (semi-randomisation and unblinded outcome assessment) are unlikely to explain such a large difference.

DISCUSSION

This review shows that antibiotics have no early impact, and a modest overall impact on the clinical course of acute otitis media. However, in applying these results, there are a number of issues to consider, including the individual potential for serious complications and subgroups of children in whom there may be greater benefits.

What are the potential consequences of not using antibiotics? Besides the immediate pain of AOM, there are some more serious complications. Though none of the trials reported cases of mastoiditis occurring in the placebo group (one case occurred in a penicillin group), a semi-randomised trial in Sweden in 1954 (Rudberg 1954) reported a rate of 17% in the untreated group versus none in the penicillin treated groups. In populations or sub-populations where mastoiditis is still judged a frequent problem, such as in some developing countries (Berman 1995), antibiotic treatment would be strongly advised.

Does the effect vary in different clinical groups? Our NNT of 15 is for the "average" case, and may vary in subgroups. Age, fever, and the presence of vomiting may all have implications. Though generally the clinical predictors of a delayed resolution or unfavourable course have been little explored, Burke (Burke 1991) and Appelman (Appelman 1991) both found higher rates of failure of placebo treatment among the young (less than two years), and those with bilateral acute otitis media, but the differences were modest. The more recent trial (Damoiseaux 2000) in children under two confirms the longer duration, but same relative effect of antibiotics in this age group. A subgroup analysis of a trial by Little (Little 2001) suggested that most benefit was in the subgroup of children with high fevers or vomiting. Examination of the L'Abbé plot (Figure 01) for the presence of pain at 2-7 days suggests the absolute benefit of antibiotics increases with the severity of the disease (as measured by the control group event rate).

Does the impact vary by duration of antibiotics? Most trials use seven days of antibiotic treatment. A recent meta-analysis of five days of antibiotics compared with eight to ten days showed a further modest reduction, with an NNT of 44 at 20-30 days. However, it included signs of otitis as well as symptoms (Kozyrskyj 1998).

A previous meta-analysis had examined the question of whether antibiotics were indicated and concluded that the answer is a qualified "yes" (Rosenfeld 1994). It estimated a number needed to treat (NNT) of seven for "primary control", compared with our NNT of 15 for symptom relief. The difference may be the consequence of our focus on patient-oriented outcomes, such as pain, rather than clinical signs, such as eardrum appearance. This systematic review suggest that where mastoiditis is not a concern, primary medical carers could weigh the benefits against the risks of adverse effects from antibiotics with their patients. Children over 2 without high fever or vomiting could generally be treated with

analgesia, and if thought necessary, a "delayed prescription" for antibiotics.

Of note, is a recent paper has shown that doctors commonly over-diagnose acute otitis media (Rothman 2003). What effect might this have on the efficacy of antibiotics (or any treatment)? One effect will be to apparently blunt any treatment effect by dilution (from the cases of non-acute otitis media). On the other hand, if clinicians commonly use the same diagnostic methods (perhaps even less stringent), then the efficacy is a true reflection of actual clinical practice. However if new and more accurate diagnostic procedures are employed, then the estimate of efficacy will have to be reconsidered.

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotics shorten the course of acute otitis media. However in the West, most cases spontaneously remit with no complications, and the number-needed to treat is about 15. Therefore management should emphasize advice about adequate analgesia and the limited role for antibiotics. Cates has developed an appropriate handout and tested this together with an optional antibiotic prescription (Cates 1999). The handout is available at URL : http://www.cates.cwc.net/.

Implications for research

Further research is needed to identify which subgroups will have a prolonged or complicated course. Systematic reviews are needed on the role of different symptomatic treatments, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), and of preventive manoeuvres such as vaccines and xylitol.

FEEDBACK

Antibiotics for AOM

Summary

1. Types of interventions includes surgical procedures versus placebo which are not dealt with in this review and should therefore be deleted.

2. The authors included only six studies in the analysis but in 1994 another meta-analysis by Rosenfeld and colleagues to which the authors refer was published which included 33 randomized trials with 5400 children. Were any studies with a no-treatment control excluded and if so why?

3. The meta-analysis by Rosenfeld is only mentioned in the text; there is no reference to it. How many patients were included in the meta-analysis?

4. It is stated that trials analysed on an intention to treat basis were preferred. This indicates that other trials were excluded which does not seem reasonable?

5. The description of the factorial trial is unclear; I suppose the authors excluded all patients who were randomised to myringotomy?

6. In the trial by Laxdal the control group was more closely monitored. The trial therefore violates the principle that all other treatement etc. should be the same in the two randomised groups and it should therefore be excluded.

7. The strategy described by Dickersin lacks a publication year and it is not cited in the references.

8. The search was done in August 1994 and the Cochrane review was published in April 1997. The search should therefore have been updated before publication since Cochrane reviews are meant to be up-to-date.

9. There is no information whether the original authors and the pharmaceutical industry were contacted about additional data including unpublished trials and trials not registered in Medline. Useful trial data might be expected to be available in books published in connection with symposia arranged by the drug industry for example.

10. What is quality methodology?

11. The term blinded randomisation should be avoided since it may be confused with blinded treatments; the term concealed allocation should be used.

12. The elaborated quality assessment scale for the trials does not appear under Results and should therefore be deleted.

13. The authors refer to Rosenfeld's meta-analysis when they state that 80% of the children have recovered spontaneously after 24 hours. Since such a percentage refers to untreated patients it raises the question why the authors did not use their own data? If these data are used in a meta-analysis of the risk difference the NNT will be 23 not 12 as stated in the Cochrane review.

14. For several of the excluded studies the authors gave no reason for the exclusion.

15. There should be a cross-reference to the authors' nearly identical review in the BMJ (24 May 1997).

Author's reply

The changes made were:

1. We updated the search. (see Johansen criticism 7 & 8). No recent trials were found, but we recognised that the Appelman trial qualifies (originally we had thought this was only prevention of recurrent otitis, rather than treatment of acute otitis in children with a recurrent episode).

2. We have corrected and updated the Relative Risk Reduction and consequent Number-Needed-to-Treat (see Johansen criticism 13).

3. We have separate the four arms of the Van Buchem factorial trial, and treated this as "two" trials (i.e., two separate strata): (a) without myringotomy - antibiotics versus placebo (b) with myringotomy - antibiotics versus placebo. (see Johansen criticism 5)

4. As suggested by Andrew Herxheimer, we have added several references including (a) Chris Cates BMJ, and (b) Kozrskyj's meta-analysis of short versus long duration of antibiotics (rather than just the de Saintonge paper).

5. We have made small text changes in response to Johansen's criticisms 5 (description added), 7 (dropped), 10 (- methodological quality), 11 (- allocation concealment), 13 (corrected in text), 14 (exclusions explained), and 15 (reference added).

6. As we have pointed out to Johansen in the BMJ correspondence, and point out in the discussion here, the Rosenfeld meta-analysis is largely concerned with comparison between antiobiotics. (see Johansen criticism 2 & 3).

Contributors

Helle Krogh Johansen

Antibiotic versus placebo for acute otitis media

Summary

This excellent and important review was completed in 1996, and I hope it will soon be updated. It is especially worth noting and discussing the new study by Christopher Cates (BMJ 13 March 1999, p715-6), who has successfully tried a method in his general practice of substantially reducing the use of antibiotic in children with acute otitis media. This would considerably strengthen the 'implications for practice' in the conclusion.

I would like to suggest that in updating this review the objectives be amended and the trial by Chaput de Saintonge et al be added, because it contributes an important piece of evidence about the duration of amoxycillin therapy. The review concludes that some children will benefit from antibiotic treatment, and it would be valuable to say (as a result of the Chaput trial) that the evidence indicates that a 3-day course is no less effective than a 10-day course.

Author's reply

Chris and I have revised the acute otitis media review. We have made a number of modest changes, though none of these change the conclusions. However, because a new trial is included we've called it a "substantive update".

Contributors

Andrew Herxheimer

Antibiotic versus placebo for acute otitis media i

Summary

1. I am glad to see this has been updated, but the text does not explain what was updated, forcing the reader who wants to know to
compare the previous version with the new one. Is it the sentence referring to Cates 99 [in implics for practice] or other points as well?

2. There are embarrassingly many typos in the refs to excluded and additional studies: Chaput de SaintoNGE, amoxyciillin, author not in bold in the first few additional refs, below that several authors' names begin in lower case when they should all begin with a
capital.

3. It is implied that no comcrit was received before the final submission date for CL99 issue 3. Is this true? I think I sent one early this year.

CONFLICT OF INTEREST: None.

Author's reply

Excluded and additional references have been corrected and completed.

Contributors

Andrew Herxheimer

Incorrect NNT

Summary

I am a bit troubled by the way the conclusions of this review are written. By combining results of treatment at Days 2 to 7 in arriving at a NNT of 15 one is going to underestimate treatment benefit after 2 days. In your abstract though you say the ARR is 7% and NNT 15 for some pain after two days. This is simply not correct. If one carefully looks at trials that record pain at the end of day 2 the ARR is in fact 20% giving a NNT of 5. Clearly acute otitis media is an acute condition and the main benefit of antibiotics is pain control and symptom relief. If this is measured at the end of 2 days the benefits are greater than one would surmise just from reading the review. It would be absurd to do a review of pain relief for biliary colic treated with pethidine and measuring the outcome 7 days later. For acute conditions symptom control in the first few days should be the outcome of interest. NNT are meaningless unless giving a time period at which they apply. I think the review needs correcting. This is not just of academic interest but of direct relevance to parents and doctors faced with a child with AOM in pain. Unfortunately your review gets quoted uncritically and invariably the NNT of 15 is given for symptom control after 2 days. I am currently trying to correct a brochure produced here in New Zealand for GPs to give to parents of children with AOM and it uncritically repeats this misleading information. If you want

to comment on symptom control after Day 2 DO NOT pool it with data from Day 7 or later!

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Contributors

Paul Corwin

POTENTIAL CONFLICT OF INTEREST

None noted.

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We would like to thank Professor Charles Bridges-Webb for stimulating initial discussions and for constructive advice on the protocol for this review, and Professor Steve Berman for helpful comments on the draft review. We would also like to thank Bruce Arroll and Tom Fahey for peer refereeing the updated review.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

REFERENCES

References to studies included in this review

Appelman 1991 *{published data only}*

Appelman CL, Claessen JQ, Touw Otten FW, Hordijk GJ, de Melker RA. Co-amoxiclav in recurrent acute otitis media: placebo controlled study. *BMJ* 1991;**303**:1450–2.

Appelman CL, Claessen JQ, Touw Otten FW, Hordijk GJ, de Melker RA. Severity of inflammation of tympanic membrane as predictor of clinical course of recurrent acute otitis media. *BMJ* 1993;**306**:895.

Claessen JQ, Appelman CL, Touw Otten FW, de Melker RA, Hordijk GJ. Persistence of middle ear dysfunction after recurrent acute otitis media. *Clinical Otolaryngology* 1994;**19**:35–40.

Burke 1991 *{published data only}*

Burke P, Bain J, Robinson D, et al. Acute red ear in children: controlled trial of non-antibiotic treatment in general practice. *BMJ* 1991;**303**:558–62.

Damoiseaux 2000 *{published data only}*

Damoiseaux RAMJ, van Balen FAM, Hoes AW, Verheij TJM, de Melker RA. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. *BMJ* 2000;**320**:350–4.

Halsted 1968 *{published data only}*

Halsted C, Lepow ML, Balassanian N, Emmerich j, Wolinsky E. Otitis media: clinical observation, microbiology and evaluation of therapy. *American Journal of Diseases of Children* 1968;**115**(5):542–51.

Howie 1972 *{published data only}*

Howie VM, Ploussard JH. Efficacy of fixed combination antibiotics versus separate components in otitis media: effectiveness of erythromycin estolate, triple sulfonamide, ampicillin, erythromycin estolate-triple sulfonamide, and placebo in 280 patients with acute otitis media under two and one-half years of age. *Clinical Pediatrics* 1972;**11**(4):205–14.

Kaleida 1991 *{published data only}*

Kaleida PH, Casselhrant ML, Rockette HE, Paradise JL, Bluestone CD, Blatter MM, et al. Amoxicillin or myringotomy or both for acute otitis media: results of a randomized clinical trial. *Paediatrics* 1991;**87**(4):466–74.

Laxdal 1970 *{published data only}*

Laxdal OE, Merida J, Jones RHT. Treatment of acute otitis media: a controlled study of 142 children. *C.M.A Journal* 1970;**102**:263–8.

Mygind 1981 *{published data only}*

Mygind N, Meistrup-Larsen K-I, Thomsen J, Thomsen VF, Josefsson K, Sorensen H. Penicillin in acute otitis media: a double-blind placebo-controlled trial. *Clinical Otolaryngology* 1981;**6**:5–13.

Thomsen J, Meistrup-Larsen KI, Sorensen H, Larsen PK, Mygind N. Penicillin and acute otitis: short and long term results. *Annals of Otology, Rhinology and Laryngology, Supplement* 1980;**89**:271–4.

Thalin 1985 *{published data only}*

Thalin A, Densert 0, Larsson A, Lyden E, Ripa T. Is penicillin necessary in the treatment of acute otitis media?. Proceedings of the International Conference on Acute and Secretory Otitis Media, Jerusalem. Amsterdam: Kugler Publications, 1985:441–6.

vanBuchem 1981a *{published data only}*

van Buchem FL, Dunk JHM, van't Hof MA. Therapy of acute otitis media: myringotomy, antibiotics or neither? A double-blind study in children. *The Lancet* 1981;**2**:883–7.

vanBuchem 1981b *{published data only}*

van Buchem FL, Dunk JHM, van't Hof MA. Therapy of acute otitis media: myringotomy, antibiotics or neither? A double-blind study in children. *The Lancet* 1981;**2**:883–7.

References to studies excluded from this review

Chaput 1982

Chaput de Saintonge DM, Levine DF, Temple Savage IT, Burgess GW, Sharp J, Mayhew SR, et al. Trial of three-day and ten-day courses of amoxycillin in otitis media. *BMJ Clinical Research Edition* 1982; **284**(6322):1078–81.

Engelhard 1994

Engelhard D, Strauss N, Jorczak-Sarni L, Cohen D, Sacjs TG, Shapiro, M. Randomised study of myringotomy, amoxycillin/clavulanate, or both for acute otitis media in infants. *The Lancet* 1989;**2** (8655):141–3.

Little 2001

Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;**322**:336–42.

Ostfeld 1987

Ostfeld E, Segal J, Kaufstein M, Gelernter I. Management of acute otitis media without primary administration of systemic antimicrobial agents. Recent advances in otitis media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1987:235–9.

Rudberg 1954

Rudberg, RD. Acute otitis media: comparative therapeutic results of sulphonamide and penicillin administered in various forms. *Acta Otolaryngology* 1954;**113**(Suppl):1–79.

Ruohola 2003

Ruohola A, Heikkinen T, Meurman O, Puhakka T, Lindblad N, Ruuskanen O. Antibiotic treatment of acute otorrhea through tympanostomy tube: Randomized double-blind placebo-controlled study with daily follow-up. *Pediatrics* 2003;**111**(5):1061–7.

vanBuchem 1985

van Buchem F, Peeters M, Van' t Hof M. Acute otitis media: a new treatment strategy. *BMJ* 1985;**290**:1033–7.

Additional references

Berman 1995

Berman S. Otitis media in developing countries. *Pediatrics* 1995;**96**: 126–31.

Cates 1999

Cates C. An evidence based approach to reducing antibiotic use in children with acute otitis media: controlled before and after the study. *BMJ* 1999;**318**:715–6.

Chalmers 1990

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**(10):1401–5.

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286–91.

Froom 1990

Froom J, Culpepper L, Grob P, Bartelds A, Bowers P, Bridge-Webb C, et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. *BMJ* 1990;**300**: 582–6.

Klein 1989

Klein JO. Epidemiology of oitis media. *Pediatic Infectious Disease Journal* 1989;**8**(Suppl 1):89.

Kozyrskyj 1998

Kozyrskyj AL, Hildes-Ripstein GE, Longstaffe SEA, Wincott JL, Sitar DS, Klassen TP, et al. Treatment of acute otitis media with a Shortened Course of Antibiotics. *JAMA* 1998;**279**:1736–42.

Rosenfeld 1994

Rosenfeld RM, Vertrees JE, Carr J, Cipolle RJ, Uden DL, Giebink GS, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from thirty-three randomized trials. *Journal of Pediatrics* 1994;**124**:355–67.

Rothman 2003

Rothman R, Owens T, Simel D. Does this child have acute otitis media?. *JAMA* 2003;**290**(12):1633–1640.

Stool 1989

Stool SE, Field MJ. The impact of otitis media. *Pediatic Infectious Disease Journal* 1989;**8**(1 Suppl):11–4.

TABLES

Characteristics of included studies

Study	Appelman 1991
Methods	R= computer generated list place in sealed envelopes - allocated by otolaryngologist. Double blind (GP and patient blind). Baseline comparability documented.
Participants	Netherlands. 121 children in a general practice aged 6 months to 12 years with acute otitis media and a previous episode of otitis media within 1 to 12 months.
Interventions	Rx: Amoxycillin/clavulanate (weight tailored dose) Control: matching placebo. Duration: 7 days All children were also given paracetomol and oxymetazoline nose drops.
Outcomes	Assessment by (blinded) GP at (i) 3 days of fever (>38^C) and otalgia, and (ii) 14 days or otorrhoea, and (iii) 1 month otoscopy and tympanometry.
Notes	"failure" = either otalgia or fever > 38 or both at 3 days.
Allocation concealment	A

Study	Burke 1991
Methods	R=identical number bottles; sealed randomisation code double blind Intention to treat analysis
Participants	United Kingdom Children aged between 3 and 10 years Acute earache and at least one abnormal eardrum.
Interventions	Rx: Amoxycillin 250mg tds Control: matching placebo tds Duration: 7 days.
Outcomes	Symptom diary kept by parents Home visits by researcher: 24hrs, 5-7 days.
Notes	1. Fig 2 appears to show that, at baseline (0 hours), fewer children were crying in the amoxycillin arm, suggesting a failure of randomisation. 2. It is not clear whether the "discharging ears" in Table I should be included as perforations.
Allocation concealment	A

Study	Damoiseaux 2000
Methods	R= computerised two block randomisation
Participants	Netherlands. 240 children between 6 mths and 2 years attending general practice. Diagnosis according to Dutch guidelines.
Interventions	Rx: Amoxicillin suspension 40mg/kg/day in three divided doses for 10 days of placebo suspension
Outcomes	Persistent symptoms at day 4 assessed by GP. Defined as persistent earache, fever (>38'C), crying or irritability.
Notes	
Allocation concealment	A

Study	**Halsted 1968**
Methods	R=randomisation by predetermined code, unknown to physician Blinded using placebo
Participants	USA clinical diagnosis of acute otitis media, excluded if rupture or recent antibiotics
Interventions	Rx: ampicillin 100mg/kg/day or phenethicillin 30mg/kg/day plus sulfisoxazole 150mg/kg/day Control: placebo
Outcomes	Culture results and clinical improvement = decrease symptoms and defervescence.
Notes	
Allocation concealment	B

Study	**Howie 1972**
Methods	R= randomisation controlled by pharmacist Placebo controlled - all medications given 4 times daily
Participants	USA age 2.5 years or less clinical diagnosis of acute otitis media
Interventions	Rx: One of erythromycin, ampicillin, or triple sulphonamide plus erythromycin Control: placebo
Outcomes	culture and randomisation compared with culture at 2-5 days. No patient-relevant outcomes.
Notes	
Allocation concealment	A

Study	**Kaleida 1991**
Methods	R=stratified randomisation, method not stated. Baseline comparability documented. double blind Intention to treat analysis
Participants	USA Children aged between 7 months and 12 years Acute otitis media: otoscopic middle ear effusion plus general symptoms or signs
Interventions	Rx: Amoxycillin 40mg/kg/day in 3 doses Control: Placebo in 3 divided doses Duration: 14 days.
Outcomes	"treatment failure" = high otalgia score or high fever
Notes	
Allocation concealment	A

Study	**Laxdal 1970**
Methods	R=randomisation claimed but no method stated Not blinded
Participants	Canada Children Clinical diagnosis of acute otitis media for at least one ear; excluded if rupture had occured.
Interventions	Rx: Penicillin 250mg/sq.m./day qid or ampicillin 250mg/sq.m./day qid

Characteristics of included studies (*Continued*)

	Control: symptomatic therapy only
Outcomes	Poorly defined - "failure" was either deterioration or no improvement on 7th day based on middle ear inflammation.
Notes	Unblinded assessment, and surveillance bias - control was more closely monitored.
Allocation concealment	C

Study	**Mygind 1981**
Methods	R=coded bottles; documented baseline comparability double blind dropouts excluded (9 of 165)
Participants	Denmark Children between the ages of one and ten years, Acute otitis media, who had had earache for I-24 hours.
Interventions	Rx: Penicillin-V 55mg/kg/day in three doses Control: placebo Duration: 7 days
Outcomes	Parents completed score cards for pain and fever each evening. Otoscopy at follow-up. Tympanometry classifed blind.
Notes	
Allocation concealment	A

Study	**Thalin 1985**
Methods	R=block randomization controlled by hospital pharmacy double blind
Participants	Sweden Children aged 2 to 15 years Acute otitis media = clinical diagnosis
Interventions	Rx: Penicillin 50mg/kg/day in 3 doses Control: matching placebo duration: 7 days
Outcomes	Examined on days 0, 3-4, 8-10, 30. audiogram at days 30 (repeat at 2 months if abnormal)
Notes	
Allocation concealment	A

Study	**vanBuchem 1981a**
Methods	R=identical bottles; baseline comparability documented double blind not intention to treat (31 of 202 patients excluded)
Participants	Netherlands Children aged 2-12 years acute otitis media - clinical diagnosis
Interventions	Rxs: Amoxycillin 250mg tds; (2x2 factorial design) Control: Matching placebo; sham myringotomy Duration: 7 days
Outcomes	Parent report of pain

Characteristics of included studies (*Continued*)

	Clinical assessment: day 2, 7, 14, 28, 56. Audiogram at > 2 weeks assessed blind
Notes	(a) is the two arms without myringotomy
Allocation concealment	A

Study	**vanBuchem 1981b**
Methods	R=identical bottles; baseline comparability documented
Participants	Netherlands Children aged 2-12 years acute otitis
Interventions	Rxs: Amoxycillin 250mg tds and myringotomy; (2x2 factorial design) Control: Matching placebo; myringotomy Duration: 7 days
Outcomes	Parent report of pain Clinical assessment: day 2, 7, 14, 28, 56. Audiogram at > 2 weeks assessed blind
Notes	(b) is the two arms with myringotomy
Allocation concealment	A

Characteristics of excluded studies

Chaput 1982	short versus long course of therapy
Engelhard 1994	No comparison of antibiotic to placebo; the 3 arms were: augmentin, myringotomy, or both.
Little 2001	No placebo control. Immediate versus delayed therapy.
Ostfeld 1987	Non-randomisaed study.
Rudberg 1954	Non-randomised study: assigned "randomly" based on case-number but then allowed to change groups.
Ruohola 2003	Conducted in children with tympanostomy tubes.
vanBuchem 1985	Non-randomised study.

ANALYSES

Comparison 01. Antibiotic versus Placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain			Peto Odds Ratio 95% CI	Subtotals only
02 Abnormal Tympanometry			Peto Odds Ratio 95% CI	Subtotals only
03 Perforation	2	381	Peto Odds Ratio 95% CI	0.51 [0.20, 1.26]
04 Vomiting, diarrhoea, or rash	4	938	Peto Odds Ratio 95% CI	1.94 [1.28, 2.94]
05 Contralateral Otitis (in unilateral cases)	3	666	Odds Ratio (Random) 95% CI	0.45 [0.16, 1.23]
06 Late Recurrences	5	1669	Peto Odds Ratio 95% CI	1.00 [0.78, 1.26]

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Age Factors; Anti-Bacterial Agents [*therapeutic use]; Otitis Media [*drug therapy]; Randomized Controlled Trials

MeSH check words

Child; Humans

COVER SHEET

Title	Antibiotics for acute otitis media in children
Authors	Glasziou PP, Del Mar CB, Sanders SL, Hayem M
Contribution of author(s)	CDM, PG and MH prepared the original version of the review. SLS has checked and updated the review. PG and CDM reviewed and contributed to the review by re-extracting data and by providing expert interpretation of the findings.
Issue protocol first published	1996/1
Review first published	1997/1
Date of most recent amendment	17 February 2005
Date of most recent SUBSTANTIVE amendment	26 November 2003
What's New	The search was updated in March 2003. Two new trials were identified (Little01) (Ruohola03) but excluded from the review. One of the trials (Little01) did not include a placebo group and the other (Ruohola03) was conducted in children with tympanostomy tubes. In the Little (Little01) trial, immediate antibiotics were compared with delayed administration. As only 24% of children in the delayed arm actually received antibiotics, the results of the trial were included in a sensitivity analysis. For the out come pain at 24 hours and 2-7 days, inclusion of this trial did not alter the overall conclusions of the primary analysis. A L'Abbé plot (graph of the proportion of participants with an outcome by the proportion of participants without an outcome) for pain at 2-7 days is now included. We have corrected some minor data abstraction errors. This results in small changes. The reduction in pain at 24 hours, (none), remains unchanged, but at 2-7 days it has fallen from 28% to 30% reduction in pain in the groups treated with antibiotics (and a consequent NNT of 15 rather than 17). There was no change in the absence of significant effect for hearing problems.
Date new studies sought but none found	01 March 2003
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	05 February 2000
Date authors' conclusions section amended	05 February 2000
Contact address	Prof Paul Glasziou Department of Primary Health Care University of Oxford, Institute of Health Sciences Old Road Headington Oxford OX3 7LF UK E-mail: paul.glasziou@public-health.oxford.ac.uk

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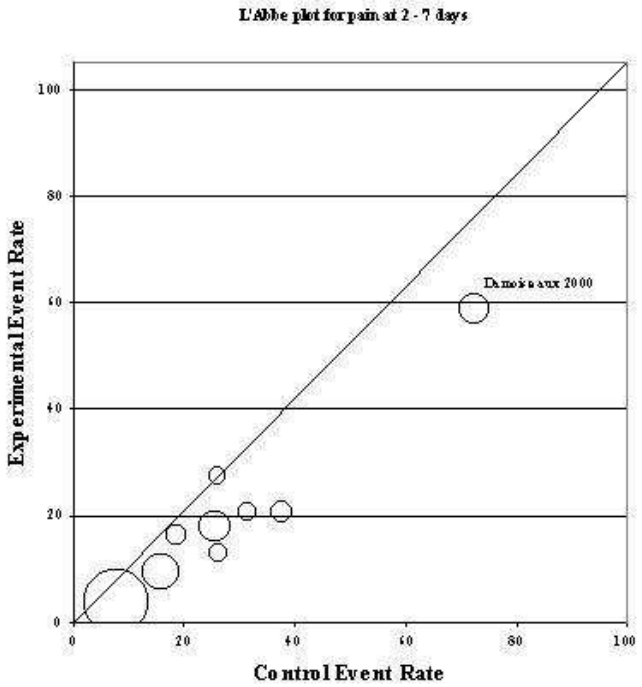
GRAPHS AND OTHER TABLES

Figure 01.

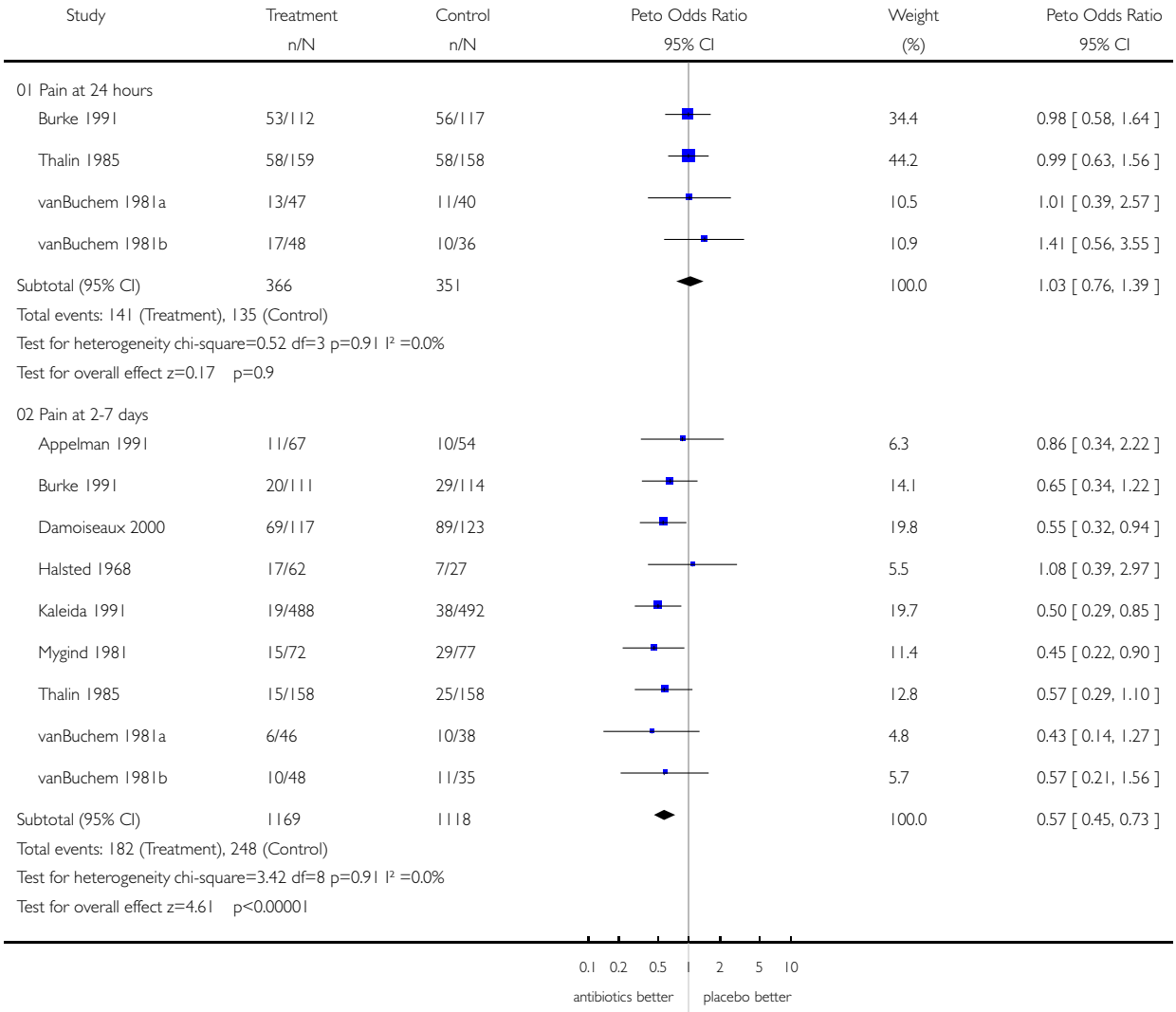


Analysis 01.01. Comparison 01 Antibiotic versus Placebo, Outcome 01 Pain

Review: Antibiotics for acute otitis media in children

Comparison: 01 Antibiotic versus Placebo

Outcome: 01 Pain



Analysis 01.02. Comparison 01 Antibiotic versus Placebo, Outcome 02 Abnormal Tympanometry

Review: Antibiotics for acute otitis media in children

Comparison: 01 Antibiotic versus Placebo

Outcome: 02 Abnormal Tympanometry

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 1 Month					
Appelman 1991	21/51	25/45		22.0	0.57 [0.25, 1.26]
Burke 1991	41/111	41/116		48.1	1.07 [0.62, 1.84]
Mygind 1981	23/72	25/77		29.9	0.98 [0.49, 1.94]
Subtotal (95% CI)	234	238		100.0	0.91 [0.62, 1.32]
Total events: 85 (Treatment), 91 (Control)					
Test for heterogeneity chi-square=1.75 df=2 p=0.42 I^2 =0.0%					
Test for overall effect z=0.52 p=0.6					
02 3 months					
Burke 1991	20/110	31/111		58.9	0.58 [0.31, 1.08]
Mygind 1981	18/72	18/77		41.1	1.09 [0.52, 2.31]
Subtotal (95% CI)	182	188		100.0	0.75 [0.47, 1.21]
Total events: 38 (Treatment), 49 (Control)					
Test for heterogeneity chi-square=1.63 df=1 p=0.20 I^2 =38.6%					
Test for overall effect z=1.17 p=0.2					

Analysis 01.03. Comparison 01 Antibiotic versus Placebo, Outcome 03 Perforation

Review: Antibiotics for acute otitis media in children

Comparison: 01 Antibiotic versus Placebo

Outcome: 03 Perforation

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Burke 1991	0/114	2/118		10.7	0.14 [0.01, 2.23]
Mygind 1981	7/72	12/77		89.3	0.59 [0.23, 1.55]
Total (95% CI)	186	195		100.0	0.51 [0.20, 1.26]

Total events: 7 (Treatment), 14 (Control)

Test for heterogeneity chi-square=0.94 df=1 p=0.33 I^2 =0.0%

Test for overall effect z=1.46 p=0.1

Analysis 01.04. Comparison 01 Antibiotic versus Placebo, Outcome 04 Vomiting, diarrhoea, or rash

Review: Antibiotics for acute otitis media in children

Comparison: 01 Antibiotic versus Placebo

Outcome: 04 Vomiting, diarrhoea, or rash

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Burke 1991	53/114	36/118		62.0	1.96 [1.16, 3.32]
Damoiseaux 2000	20/117	12/123		31.3	1.88 [0.90, 3.96]
Mygind 1981	3/72	1/77		4.4	2.98 [0.41, 21.58]
Thalin 1985	1/159	1/158		2.2	0.99 [0.06, 15.96]
Total (95% CI)	462	476		100.0	1.94 [1.28, 2.94]
Total events: 77 (Treatment), 50 (Control)					
Test for heterogeneity chi-square=0.41 df=3 p=0.94 I^2 =0.0%					
Test for overall effect z=3.13 p=0.002					

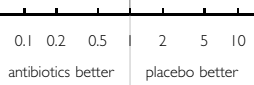
Analysis 01.05. Comparison 01 Antibiotic versus Placebo, Outcome 05 Contralateral Otitis (in unilateral cases)

Review: Antibiotics for acute otitis media in children

Comparison: 01 Antibiotic versus Placebo

Outcome: 05 Contralateral Otitis (in unilateral cases)

Study	Treatment n/N	Control n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
Burke 1991	29/98	33/102		45.3	0.88 [0.48, 1.60]
Mygind 1981	2/72	6/77		22.2	0.34 [0.07, 1.73]
Thalin 1985	4/159	17/158		32.5	0.21 [0.07, 0.65]
Total (95% CI)	329	337		100.0	0.45 [0.16, 1.23]
Total events: 35 (Treatment), 56 (Control)					
Test for heterogeneity chi-square=5.38 df=2 p=0.07 I^2 =62.8%					
Test for overall effect z=1.56 p=0.1					



Analysis 01.06. Comparison 01 Antibiotic versus Placebo, Outcome 06 Late Recurrences

Review: Antibiotics for acute otitis media in children

Comparison: 01 Antibiotic versus Placebo

Outcome: 06 Late Recurrences

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Kaleida 1991	125/448	124/446		67.2	1.00 [0.75, 1.35]
Laxdal 1970	24/94	10/48		8.7	1.29 [0.57, 2.91]
Mygind 1981	19/72	21/77		11.0	0.96 [0.46, 1.97]
Thalin 1985	9/159	7/158		5.7	1.29 [0.47, 3.53]
vanBuchem 1981a	10/92	13/75		7.4	0.58 [0.24, 1.41]
Total (95% CI)	865	804		100.0	1.00 [0.78, 1.26]

Total events: 187 (Treatment), 175 (Control)

Test for heterogeneity chi-square=2.09 df=4 p=0.72 I^2 =0.0%

Test for overall effect z=0.04 p=1