

# Antibiotic treatment of acute otitis media in children under two years of age: evidence based?

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## SUMMARY

**Background.** Appropriate use of antibiotics is one of the major issues in medicine today. In most countries, acute otitis media in children is treated with antibiotics; however, the efficacy of antibiotic use in every acute otitis media is a controversial issue. It may be worthwhile looking for special risk groups that benefit more from antibiotic treatment for acute otitis media. Children under two years of age with acute otitis media are at risk of poor outcome.

**Aim.** To assess whether the current high prescription rates of antibiotics for acute otitis media in children under two years of age (being a risk group for poor outcome) are based on an established increased efficacy.

**Method.** Systematic literature review and a quantitative analysis with an assessment of the methodological quality of published trials, comparing antibiotic treatment with non-antibiotic treatment in acute otitis media in children aged under two years.

**Results.** Six trials were included. Trials from before 1981 had a poor methodological quality. Four were suitable for the quantitative analysis. Only two of them were truly placebo-controlled. Of these two, one included only recurrent acute otitis media and the other included only non-severe episodes. With these restricted data, no statistically significant difference was found between antibiotic-treated children and controls under two years of age with acute otitis media, judged on the basis of clinical improvement within seven days (common odds ratio = 1.31; 95% CI = 0.83–2.08).

**Conclusion.** The current high prescription rates of antibiotics among children under two years of age with acute otitis media are not sufficiently supported by evidence from published trials. New randomized placebo-controlled trials using reliable methodology are needed in this young age group.

**Keywords:** antibiotics; infants; acute otitis media; prescription rates.

## Introduction

ALTHOUGH most children with acute otitis media (AOM) may need only symptomatic treatment, up to 86% of all episodes of the infection are treated with antibiotics.<sup>1-2</sup> Two

recent meta-analyses on the effect of antibiotic treatment for AOM showed only a modest effect.<sup>3,4</sup> Rosenfeld *et al* included 33 studies of children aged four weeks to 18 years, and the outcome of AOM was improved in only one in seven children treated with antibiotics.<sup>3</sup> Del Mar *et al* included six studies of children aged seven months to 15 years and they found that 17 children needed to be treated to prevent pain in one child at 2–7 days after presentation.<sup>4</sup> Currently, no studies have identified subcategories of patients with AOM in whom antibiotic treatment is more effective. Howie introduced the ‘otitis prone’ condition for children suffering six or more episodes of otitis media before the age of six.<sup>5</sup> Of his ‘otitis prone’ patients, 91% had their first AOM episode during the first year of life. Appelman found, in his study of children with recurrent AOM, that those under two years of age were more likely to follow an abnormal course of illness, defined as pain and/or fever after three days.<sup>6</sup> Other authors report a higher recurrence rate and a higher rate of persistent middle ear effusion (MEE) in this age group.<sup>7-10</sup> This is probably the reason why antibiotic therapy is prescribed more often in children under two years with AOM than in older children.<sup>2</sup> Whether this strategy is justified by an established increased efficacy is not known.

We systematically reviewed the available literature to determine the efficacy of antibiotic treatment for AOM in children under two years of age.

## Method

We carried out a computer search using MEDLINE on articles published between 1966 and January 1997, and using EMBASE from 1974 until January 1997, using the following keywords: otitis media, child, clinical trial, and placebo. In addition, the reference sections of these articles, and of several major review articles, were checked for missing trials meeting the inclusion criteria. Furthermore, an extensive hand search for clinical trials of therapy for AOM in patients of all ages, performed by our group in 1991, was used.<sup>11</sup> An article was included when the following criteria were met:

- Random allocation to the different treatment groups
- Comparison of antibiotic treatment with non-antibiotic treatment in AOM (not comparison of different antibiotics or different durations of treatment)
- Inclusion of children aged under two years, with separate presentation of the results for these young children.

The quality of the studies was assessed using the scoring system proposed by Chalmers *et al*.<sup>12</sup> The items included in this method are divided in four main categories (Box 1):

1. study protocol,
2. blinding procedures,
3. testing procedures, and
4. statistical analysis.

The items ‘blinding of physicians and patients as to ongoing results’ and ‘multiple looks considered’ were not considered in our analysis because no interim analyses were performed in the relatively short-term AOM trials. Because ‘retrospective analysis’ may be viewed as both a positive and a negative aspect of a

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<p><b>STUDY PROTOCOL (15 points)</b></p> <ul style="list-style-type: none"> <li>• selection description</li> <li>• reject log</li> <li>• withdrawals</li> <li>• therapeutic regimens definition</li> <li>• control regimen (placebo)</li> </ul> <p><b>BLINDING PROCEDURES (30 points)</b></p> <ul style="list-style-type: none"> <li>• randomization</li> <li>• blinding of patients</li> <li>• blinding of physicians as to therapy received</li> <li>• blinding of physicians and patients as to ongoing results</li> </ul> <p><b>TESTING PROCEDURES (15 points)</b></p> <ul style="list-style-type: none"> <li>• prior estimate of numbers</li> <li>• testing randomization</li> <li>• testing blinding</li> <li>• testing compliance</li> </ul> <p><b>STATISTICAL ANALYSIS (30 points)</b></p> <ul style="list-style-type: none"> <li>• on major endpoints</li> <li>• posterior <i>b</i> estimate of observed difference for negative trials</li> <li>• statistical inference</li> <li>• appropriate statistical analysis</li> <li>• handling of withdrawals</li> <li>• side effects, statistical discussion</li> <li>• retrospective analysis</li> <li>• blinding of statistician</li> <li>• multiple looks considered</li> </ul>
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**Box 1.** Items for assessing the methodological quality of a trial proposed by Chalmers *et al*.

study, we did not include this item. Finally, the item 'blinding of statistician' was not mentioned in any study and thus not included in our assessment.

The maximum score was 79 points. All studies were scored independently by the four authors. The papers were blinded by removing all identifying information prior to distribution to the four reviewers. A consensus meeting was held to discuss any disagreements on assessment after the individual scoring, with differences resolved by discussion.

Where possible, data were extracted for a quantitative analysis. As an endpoint, symptomatic clinical improvement within seven days after start of treatment was used: the outcome measure presented most often in the trial reports. Otitic appearance, middle ear effusion, or bacteriological results were not considered as endpoints because they were presented infrequently in the available studies. An estimate of the common odds ratio (with approximate 95% confidence intervals) was computed according to the Mantel-Haenszel approach.<sup>13</sup>

## Results

In total, 115 articles were identified after the computer search on MEDLINE and EMBASE. Based on the abstracts, only five articles met the inclusion criteria.<sup>6,14-17</sup> In the reference sections, one additional trial was found that met all the criteria.<sup>18</sup> Most papers (53) were excluded because they studied the efficacy of additional therapy compared with a placebo in antibiotic-treated AOM. Other reasons for exclusion were that prevention of recurrent AOM (18), otitis media with effusion (14), or different duration of antibiotic treatment (9) were studied. Three trials were excluded because data of children younger than two years of age were missing.<sup>1,19,20</sup> In the reference sections, one additional trial had to be excluded for the same reason.<sup>21</sup> The remaining papers (13) were review articles or duplicate publications.

The characteristics of the six studies included in our analysis are shown in Table 1. The diagnosis of AOM was based on otoscopic appearance of the tympanic membrane and clinical signs of acute infection in three studies,<sup>6,16,17</sup> and on otoscopy alone in two studies.<sup>14,18</sup> One study did not mention the diagnostic criteria.<sup>15</sup> Appelman included only recurrent AOM, and Kaleida compared antibiotic treatment with placebo in children under two years of age only in non-severe episodes. Severity in this study was assessed by temperature and otalgia score. Two studies presented only separate data of children under three years of age.<sup>14,18</sup> In the study by Halsted *et al*, 80% of this group aged under three years were below two years of age.

A methodological quality assessment was carried out for all six studies. The methodological quality of the six studies ranged from 27% to 73% of the maximum score. The studies published after 1981 scored better (range 60–73%) than those published earlier (range 27–43%).

## Efficacy

The results of the individual studies are mentioned in Table 1. Four individual studies reported, at short-term, a statistically significant reduction in clinical failure, persistent effusion at two weeks, persistent bacterial growth (at 2–7 days), or otoscopic signs of AOM in favour of antibiotic treatment.<sup>15-18</sup> Long-term results were mentioned in three studies, and no differences were seen between antibiotic therapy and placebo.<sup>6,14,17</sup>

We were able to extract data for quantitative analysis from four studies.<sup>6,14,16,17</sup> One study was excluded because the absolute number of children in the young age group was not reported.<sup>18</sup> Another was excluded because no data on clinical improvement were reported.<sup>15</sup> Clinical improvement in the four studies included in the quantitative analysis was assessed after a period lasting from 24 hours to six days after the start of treatment. The common odds ratio of clinical improvement in patients treated with antibiotics, compared with the reference group, was 1.31 (95% CI = 0.83–2.08) (Table 2).

Restricting the quantitative analysis to studies with a methodological quality of 60% or more did not change the results (OR = 1.42; 95% CI = 0.85–2.39).<sup>6,16,17</sup> Exclusion of the study from Kaleida, in which only non-severe episodes were included, yielded an odds ratio of 1.10 (95% CI = 0.56–2.15). Exclusion of the study of Appelman *et al*, which reported rather strong positive results, yielded an odds ratio of 1.20 (95% CI = 0.74–1.94).

## Discussion

To assess the methodological quality of the trials, we used the method introduced by Chalmers *et al*.<sup>12</sup> Although many other methods have been proposed, most use similar items.

The paradigm for studies assessing drug efficacy is the double-blind, randomized, placebo-controlled trial, and the reporting of these trials requires high standards.<sup>22</sup> Trials before 1981 score moderately or poorly when judged by present standards. Conducting and reporting of a trial in that time did not require the same standards, but in order to assess the current value of their results judgement according to the present standard seems reasonable. On the other hand, requirements could have been met by the earlier studies but not mentioned in their reports because it was not required at that time.<sup>12</sup> This could result in an underestimation of the quality of the earlier trials.

The conclusion of our pooled analysis should be judged with caution. Only four studies were involved and only two were truly placebo-controlled (Table 1). Furthermore, diagnostic certainty of AOM in this young age group is lowest compared with that of all ages, and this makes satisfactory comparisons of different

**Table 1.** Characteristics and methodological quality score of six trials.

Trial	Treatment	Controls	Sample size (aged <2 years)	Follow-up/outcome measures	Methodological quality	Results in young age group
Halsted (1968)	Ampicillin/Penicillin-sulfa(+myringotomy) <sup>a</sup>	Placebo (+ myringotomy) <sup>a</sup>	106 (80)	3–9 months/ clinical improvement, bacterial cure, recurrent attacks	43%	ND
Laxdal (1970)	Ampicillin/Penicillin	Symptomatic	142 (±70)	21 days/ clinical failure	27%	AS (clinical failure)
Howie (1972)	Erythromycin/Ampicillin/Sulfonamide (+myringotomy) <sup>a</sup>	Placebo (+ myringotomy) <sup>a</sup>	280 (±280)	7 days/ persistent effusion, bacterial cure	33%	AS (persistent effusion, bacterial cure)
Engelhard (1989)	Amoxy/clav (+myringotomy) <sup>b</sup>	Placebo (+ myringotomy) <sup>b</sup>	105 (105)	11 days/ clinical improvement, otoscopy	61%	AS (otoscopy)
Appelman (1991)	Amoxy/clav	Placebo	121 (27)	1 year/irregular course (3 days) recurrent attacks	73%	ND
Kaleida (1991)	Amoxycillin	Placebo	536 (270)	1 year/initial treatment failure persistent effusion	60%	AS (persistent effusion at two weeks)

<sup>a</sup>Myringotomy for bacterial culture only; <sup>b</sup>myringotomy as part of treatment (only in half of the antibiotic group); ND denotes no statistically significant difference in efficacy between antibiotic and control group; AS denotes antibiotic therapy superior to control treatment (endpoint for which antibiotic superior), the methodological quality, expressed as a percentage of the maximum score.

**Table 2.** Clinical improvement within seven days following antibiotic treatment for AOM in children less than two years of age. Results of four randomized trials.

Trial	Basic data from trials patients improved/total no.patients evaluated (%)			
	Antibiotic therapy	Control treatment	Odds ratio	95% CI
Halsted	45/62 (73%)	20/27 (74%)	0.93	(0.29-2.87)
Engelhard	42/62 (68%)	23/32 (72%)	0.82	(0.29-2.3)
Appelman	11/15 (73%)	5/12 (42%)	3.85	(0.59-27.73)
Kaleida <sup>a</sup>	259/277 (94%)	229/254(90%)	1.57	(0.8-3.09)
Total	357/416 (86%)	277/325 (85%)	–	–

Weighted odds ratio (Mantel-Haenszel) = 1.31 (95% confidence interval = 0.83–2.08); <sup>a</sup>numbers from this study are based on evaluated episodes of AOM, not patients.

studies when addressing treatment efficacy in AOM in this age group even more hazardous.<sup>2</sup> In addition, one study included only recurrent AOM and another looked only at non-severe episodes.<sup>6,17</sup> Of the four studies, the study by Appelman *et al* reported rather strong positive results compared with the other studies, suggesting heterogeneity of the trial's results. These results, however, were based on 27 patients only and, therefore, the 95% confidence interval was very wide. Importantly, exclusion of this trial did not materially change the results of our quantitative analysis.

The choice of the treatment endpoint is also important in interpreting treatment efficacy. To allow for pooling, we chose a broad endpoint. Rosenfeld *et al* did the same in their meta-analysis, and mentioned that specific benefits of antibiotic therapy on the time course of individual symptom resolution could have been missed.<sup>3</sup> The endpoints for which antibiotic therapy was superior, compared with placebo in the individual studies, were bacterial cure, resolution of middle ear effusion within two weeks, and otoscopic appearance. These endpoints seemed not to be related to symptomatic clinical improvement.<sup>3,15-17</sup> To assess

the effect of antibiotic therapy on outcome of AOM, the use of symptomatic clinical improvement seems most valuable, notably in view of the known relationship between the severity of symptomatology and medical use.<sup>23</sup>

Our results are compatible with either a two-fold increase of clinical improvement, or a lower rate of symptomatic clinical improvement within seven days for antibiotic therapy in AOM in children under two years of age. The estimation of the odds ratio (1.31; 95% CI = 0.83–2.08) for this young age group is lower than the estimation of the odds ratio (2.9; 95% CI = 1.76–4.88) that Rosenfeld *et al* found for all children. But if the event rate of an abnormal course with AOM in the young age group is high, even a small relative risk reduction will have a potentially important impact on clinical practice.<sup>24</sup>

We conclude that the current high prescription rates of antibiotics among children aged under two years with AOM, being a risk group with regard to poor outcome, are not sufficiently supported by evidence from the published trials. New randomized placebo-controlled trials using a reliable methodology are needed to assess the effect of antibiotics for AOM in this age group.

**Keypoints**

- Acute otitis media is a common childhood disease, and most episodes are treated with antibiotics.
- The need to treat every episode of acute otitis media is a controversial issue, and it may be worthwhile to look at special risk groups that may benefit more from antibiotic treatment.
- Children aged under two years with acute otitis media are at risk for poor outcome.
- The current high prescription rates of antibiotics among children aged under two years with acute otitis media are not sufficiently supported by evidence from published trials.
- New randomized placebo-controlled trials assessing the efficacy of antibiotic treatment for acute otitis media in children aged under two years are needed.

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