

# Antibiotics for acute otitis media: Which children are likely to benefit?

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## Clinical question

Does the use of antibiotics in children with acute otitis media lead to improved outcome, defined as an improvement in pain, fever or both after 3–7 days?

## Article chosen

Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;368:1429–35.

## Study objective

To identify subgroups of children with acute otitis media who are likely to benefit from antibiotic treatment. Benefit is defined by an improvement in pain (subjective parental perspective), fever (temperature > 38°C) or both after 3–7 days.

a high-risk bacterial etiology, as this impacts significantly the decision to prescribe antibiotics. Bacteria are the most common etiologic agent of AOM (50%–90% of isolates).<sup>1,6</sup> Viruses account for 5%–25% of cases, and 16%–25% of cases have no identifiable pathogen.<sup>3</sup> One study identified both bacteria and viruses in 66% of isolates.<sup>6</sup> Antibiotics are commonly used in the management of AOM, although the majority of cases of AOM resolve spontaneously, resulting in the unnecessary use of antibiotics and growing resistance.<sup>7</sup> Antibiotic use can also result in adverse effects such as diarrhea or vomiting (16%), and rash (2%).<sup>2</sup>

Many studies have been conducted to evaluate the effect of antibiotics on AOM outcomes. Meta-analyses of randomized controlled trials comparing antibiotics versus placebo in treating AOM have shown modest, if any, benefits for the clinically important outcomes of pain, fever and suppurative complications.<sup>6,8</sup> These studies found high aggregate rates of spontaneous resolution in the placebo arms, and only modest incremental benefits in the antibiotics arms.

## BACKGROUND

Acute otitis media (AOM) is the most common childhood illness for which antibiotics are prescribed.<sup>1,2</sup> Acute otitis media accounts for 13% of visits to the emergency department, and 30 million outpatient clinic visits annually, has a peak incidence between 6 and 18 months of age, and is the second most common cause (after upper respiratory infection) for clinic visits among patients under 15 years of age.<sup>3</sup> Risk factors for AOM include male sex, parental smoking, a family history of middle ear disease, and attendance at day care.<sup>2–4</sup> Breast feeding is thought to be protective.<sup>4</sup> The economic burden of AOM in the year 2000 was reported to exceed US\$5 billion. This cost is predominately due to drugs, visits, and procedures such as tympanostomies, mastoidectomies and adenoidectomies in children younger than 24 months.<sup>3,5</sup>

The management challenge in AOM for most clinicians is in determining which children are likely to have

## STUDY DESIGN

This meta-analysis collected individual patient data from randomized control trials in AOM. The authors screened studies for eligibility based on the following quality criteria: randomization, follow-up and multiple levels of blinding (e.g., patient, caregiver and outcome assessor). A systematic search of the literature identified 19 trials that investigated the effectiveness of antibiotics in children with AOM. However, the authors excluded 9 trials after screening that failed to meet eligibility criteria. Of the 10 eligible trials, 6 research groups provided individual patient data from their trials.

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## POPULATION INCLUDED AND STUDIED

This meta-analysis included individual patient data for 1643 children from 6 of the 10 eligible trials that randomly assigned patients (aged 6 mo to 12 yr) with AOM into intervention groups. The interventions compared antibiotic treatment with no treatment, and measured pain and fever as primary outcomes.

## OUTCOMES MEASURED

The primary outcome was an extended course of AOM, which was defined as a composite end point of pain, fever or both after 3–7 days. Pain was assessed by a subjective parental record in diary format. Fever was assessed objectively and defined as a temperature of 38°C or higher.

## RESULTS

The baseline characteristics of included children were identical in all predictor variable subgroups, as shown in Table 1. The clinical outcomes for included patients are summarized in Table 2. Details of included trials are shown in Table 3, including the diagnostic criteria for AOM used by each study.

## STUDY CONCLUSION

Predictor variables that showed significant benefit in the primary outcomes were patient age of less than 2 years and bilateral AOM. The number needed to treat (NNT) in a child under 2 years of age was 7 (95% confidence interval [CI] 4–14) and was 10 for children older than 2 (95% CI 6–17). A more significant difference was found in bilateral AOM with an NNT of 5

(95% CI 4–9), and unilateral AOM carried an NNT of 17 (95% CI 8–∞). Because the upper boundary of the 95% CI for the unilateral group approaches infinity, it is conceivable that there may be no meaningful benefit in this group. In contrast, when the 2 independent predictor variables are combined (children < 2 yr with bilateral AOM), the NNT is 4 and the CI is narrow (95% CI 3–7). Values, both significant and nonsignificant, for the other combinations are shown in Table 2.

## COMMENTARY

The results of this study indicate that there are specific subgroups of children with AOM who are more likely to benefit from antibiotic treatment. The most significant single predictor of benefit is the presence of bilateral AOM. Less powerful individual predictors are patient age of under 2 years and the presence of otorrhea. The presence of both age under 2 years and bilateral AOM strongly predicts benefit.

This study helps clinicians hone their approach to AOM by targeting those children who are most likely to respond to antibiotics, while helping to limit prescribing to avoid risks of side effects or possible contribution to local antibiotic resistance.

Other studies support the notion of delaying or withholding antibiotics for children with probable viral AOM. A Cochrane review by Glasziou and colleagues<sup>8</sup> pooled 8 trials (2287 children) and found that there was no benefit from treatment in pain reduction during the first 24 hours, and only a 7% pain reduction at 2 days with antibiotics (NNT = 15). They further found that

**Table 1. Baseline characteristics of patients in the 6 selected trials**

Predictor variable	No. (%) of patients		
	Antibiotics, n = 819	Controls, n = 824	Total, n = 1643
Age < 2 yr	280 (34.2)	287 (34.8)	567 (34.5)
Fever	282 (34.4)	287 (34.8)	569 (40.3)*
Bilateral AOM	236 (28.8)	220 (26.7)	456 (34.3)†
Otorrhea	51 (6.2)	65 (7.9)	116 (20.9)‡

AOM = acute otitis media.  
 \*n = 1411 because of missing data from some trials.  
 †n = 1328 because of missing data from some trials.  
 ‡n = 555 because of missing data from some trials.

**Table 2. Predictor variables and outcomes**

Predictor variable(s)	Primary outcome of interest (pain, fever or both after 3–7 days)	
	RR (95% CI)	NNT
Age < 2 yr	0.77 (0.68–0.89)	7
Age ≥ 2 yr	0.86 (0.80–0.93)	10
Bilateral AOM	0.72 (0.62–0.84)	5
Unilateral AOM	0.92 (0.85–1.00)	NS
Otorrhea present	0.52 (0.37–0.73)	3
Otorrhea absent	0.80 (0.70–0.92)	8
Age < 2 yr + bilateral AOM	0.64 (0.62–0.80)	4
Age < 2 yr + unilateral AOM	0.92 (0.76–1.11)	NS
Age ≥ 2 yr + bilateral AOM	0.84 (0.70–1.02)	NS
Age ≥ 2 yr + unilateral AOM	0.92 (0.85–1.01)	NS

AOM = acute otitis media; CI = confidence interval; NNT = number needed to treat; NS = not significant result/NNT not calculated; RR = relative risk.

**Table 3. Expanded characteristics of included randomized trials**

Study	No. of patients	Participant age	Intervention	Duration of intervention, d	Outcomes	Diagnostic criteria for AOM
Appelman et al. <sup>9</sup>	121	6 mo–12 yr	Amoxicillin (8.3 mg/kg) with clavulanate (2.08 mg/kg) v. placebo (weight-related dosing as per original paper)	7	<ul style="list-style-type: none"> <li>• Pain after 3 d</li> <li>• Fever after 3 d</li> <li>• Otorrhoea</li> <li>• Otoscopy and tympanometry after 1 mo</li> </ul>	<ul style="list-style-type: none"> <li>• Otagia</li> <li>• Otoscopic signs of middle ear infection</li> </ul>
Burke et al. <sup>10</sup>	232	3 mo–10 yr	Amoxicillin (125 mg tid) v. placebo	7	<ul style="list-style-type: none"> <li>• Symptoms noted by parents (including fever and ear pain)</li> <li>• Home visits by researcher after 24 h and 5–7 d</li> <li>• Otoscopy and tympanometry after 1 and 3 mo</li> </ul>	<ul style="list-style-type: none"> <li>• Ear pain</li> <li>• Abnormal ear drum</li> </ul>
Damoiseaux et al. <sup>11</sup>	240	6 mo–2 yr	Amoxicillin 40 mg/kg/d tid v. placebo	10	<ul style="list-style-type: none"> <li>• Symptoms at day 4 assessed by a GP (including fever and earpain)</li> <li>• Otoscopy and tympanometry after 6 wk and 3 mo</li> </ul>	<ul style="list-style-type: none"> <li>• Otoscopic signs of AOM</li> <li>OR</li> <li>• Otorrhea</li> <li>AND</li> <li>• one of: <ul style="list-style-type: none"> <li>- fever</li> <li>- recent earache</li> <li>- general malaise</li> <li>- recent irritability</li> </ul> </li> </ul>
Little et al. <sup>12</sup>	315	6 mo–10 yr	Immediate v. delayed treatment Amoxicillin 125 mg in 5 mL, tid, 100 mL in total	7	<ul style="list-style-type: none"> <li>• Symptoms noted by parents (including fever and ear pain)</li> <li>• Absence from school</li> <li>• Consumption of paracetamol</li> </ul>	<ul style="list-style-type: none"> <li>• Otagia</li> <li>• Otoscopic evidence of acute inflammation of the ear drum</li> </ul>
Le Saux et al. <sup>13</sup>	512	6 mo–5 yr	Amoxicillin (60 mg/kg daily) v. placebo	10	<ul style="list-style-type: none"> <li>• Telephone follow-up at day 1, 2, 3, and between 10 and 14 d (including fever)</li> <li>• Tympanometry at 1 and 3 mo</li> </ul>	<ul style="list-style-type: none"> <li>• Ear pain</li> <li>• Fever (&gt; 38°C)</li> </ul>
McCormick et al. <sup>14</sup>	223	6 mo–12 yr	Immediate v. delayed treatment Amoxicillin 90 mg/kg/d bid, max 1500 mg/d, for 10 d	10	<ul style="list-style-type: none"> <li>• Symptoms noted by parents (including fever and ear pain)</li> <li>• Nasopharyngeal carriage</li> <li>• Adverse events</li> <li>• Absence from school</li> <li>• Tympanometry after 12 and 30 d</li> </ul>	<ul style="list-style-type: none"> <li>• Symptoms of ear infection — pain, fever, irritability</li> <li>• Otoscopic evidence of AOM</li> </ul>

AOM = acute otitis media; bid = 2 times daily; GP = general practitioner; tid = 3 times daily.

80% of cases spontaneously resolved in this time frame with conservative care. However, the authors found benefits in pain and fever outcomes from days 3 to 7 with antibiotic treatment. This is consistent with observed benefits of treatment in the subject study, although there were no observations of outcomes at the 1–2 day point, as was analyzed in the review by Glasziou and colleagues. There was a significant increase in vomiting, diarrhea and rash in the treatment groups. The authors recommended that in developed countries, where the risk of mastoiditis is low, early antibiotic treatment is not warranted.<sup>8</sup>

This Cochrane review by Glasziou and coauthors included 4 studies that were excluded from the subject study, and all found benefits with antibiotic usage on days 3–7, but none on days 1–2. However, there were no subgroup analyses performed to look at the age group under 2 years old, although 3 of the 4 studies did enroll patients below this threshold. Also, no subgroups were analyzed on the basis of predictor variables included here (i.e., bilateral v. unilateral AOM, and the presence of otorrhea). This study also included new information from 2 trials that had not been published at the time of the Cochrane review; however, it did include the individual patient data that had been excluded from the Cochrane review as it was not a placebo-controlled trial and was therefore unsuitable for traditional meta-analysis models employed by the Cochrane Collaboration.

Studies such as those cited above suggest that a delayed approach to antibiotics usage in healthy children with AOM seems to have no adverse clinical consequences, with resolution rates similar to those for children who are treated conservatively with analgesics. This individual patient data meta-analysis helps clinicians identify those children under 2 years old with bilateral disease for whom the use of antibiotics will likely be of benefit. The choice to treat or not is influenced by many other factors including clinician and parent preference, but it is reasonable to educate parents with lower risk children on the benefits of a trial of conservative management. The pediatric guidelines in the United States advise a treatment duration of 10 days for children less than 2 years old or with severe disease, and 5–7 days for children older than 6 years and/or with mild to moderate disease (severity not clearly defined, strength of recommendations not stated).<sup>2</sup>

A number of published commentaries have examined the implications of this new work. Mattila<sup>15</sup> has commented that the results of this study have the potential

to reduce initial antibiotic prescribing by more than half on the first visit, with significant financial and public health benefits to follow. In another report, Matilla<sup>16</sup> noted that some of the original trials excluded children with severe symptoms or who were “too unwell.” Finally, Walling<sup>17</sup> also reinforced that these study results support the treatment of bilateral disease for all ages (NNT = 4 for < 2 yr; NNT = 9 for 2–12 yr) to reduce pain, fever or both at the 3–7 day point. It is evident from Table 3 that there is substantial clinical heterogeneity with respect to age groups studied, antibiotics chosen and dosing, as well as the treatment duration, all of which create challenges when trying to pool data and reach robust conclusions.

Another study by Rovers and colleagues<sup>18</sup> using the same data set, identified independent baseline predictors for what could develop into a prolonged course of AOM: 1) age (< 2 yr or ≥ 2 yr), 2) fever (yes or no) and 3) bilateral AOM. The authors did not comment on what diagnostic criteria were employed to establish a diagnosis of AOM, or whether this was consistently applied across the 6 included studies. As shown in Table 3, however, all studies incorporated otalgia and otoscopic findings for the diagnosis of AOM diagnosis, an approach that is likely congruent with the practice of most emergency physicians.

## CONCLUSION

This unique study identified a subgroup of children with a diagnosis of AOM for whom antibiotics are warranted, namely those with bilateral AOM (regardless of age), children under 2 years of age with either unilateral or bilateral AOM, and children with otorrhea. The use of individual patient data provided information that cannot be ascertained when traditional meta-analysis models are used to pool data at the study level, and the appropriate screening of children for specific predictor variables for treatment would benefit from further refinement.

**Competing interests:** None declared.

**Keywords:** antibiotics, acute otitis media, individual patient data meta-analysis

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