

Randomised controlled trial

Amoxicillin-clavulanate improves symptoms, reduces treatment failure in select children with acute otitis media and increases risk of diarrhoea

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Commentary on: **Tähtinen PA**, Laine MK, Huovinen P, *et al.* A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med* 2011;**364**:116–26.

Commentary on: **Hoberman A**, Paradise JL, Rockette HE, *et al.* Treatment of acute otitis media in children under 2 years of age. *N Engl J Med* 2011;**364**:105–15.

Context

The debate about whether to treat acute otitis media (AOM) with antibiotics affects nearly all practicing paediatricians. In 2004, the American Academy of Pediatrics (AAP) recommended watchful waiting, long practiced in European countries, as an option in children 6–23 months old with ‘non-severe’ illness and an ‘uncertain’ diagnosis.¹ This recommendation was based on clinical trials showing high rates of spontaneous resolution of symptoms, so that an estimated 7–17 children would need to be treated with antibiotics to improve one child’s clinical outcomes. However, limitations of previous trials, including variability in diagnostic criteria, participants’ ages and antimicrobial and supportive treatments used, have kept the debate alive.^{2–4} Two recent randomised trials by Hoberman and colleagues and Tähtinen and colleagues have addressed the benefit of antibiotics in young children with AOM diagnosed by strict criteria.

Methods

Both studies were randomised, double-blind trials that compared amoxicillin-clavulanate (amox/clav) with a

taste-matched placebo in children with carefully diagnosed AOM. Participants, inclusion criteria and main outcomes were similar (table 1). Both studies had high completion rates (96% and 98%). The trials differed mainly in the dose and duration of antibiotic used, and how outcomes were measured.

Findings

Both studies showed a statistically significant benefit of antibiotics on primary outcomes and some secondary outcomes (table 2). The benefit appeared to be larger in the study by Tähtinen and colleagues.

Commentary

Both trials were of high quality and showed statistically significant improvement in clinical and otoscopic outcomes in children with strictly diagnosed AOM treated with a strong antibiotic. The benefits of antibiotics were greater than those shown in previous trials, probably because the rate of spontaneous resolution in the placebo group was lower. To systematically consider how to

Table 1 Methodologic features

	Hoberman and colleagues	Tähtinen and colleagues
Time period	November 2006 to March 2009	March 2006 to December 2008
Study question	Does antimicrobial treatment hasten the resolution of symptoms and signs of AOM, among children 6–23 months of age, diagnosed by strict criteria and irrespective of severity?	Does antimicrobial treatment reduce the risk of treatment failure for AOM among children 6–35 months of age, diagnosed by strict criteria?
Study population	AOM diagnosed per protocol, ≥2 doses pneumococcal conjugate vaccine Excluded: other illness, allergy to amoxicillin, recent antibiotics, TM perforation 144 treatment, 147 placebo	AOM diagnosed per protocol Exclusions: similar 161 treatment, 158 placebo
Diagnosis of otitis media	Acute symptoms (≥3 on AOM-SOS Scale*) Otoscope diagnosis by validated otoscopists, strict criteria	Similar
Intervention	10-day course of amox/clav (90 mg/kg amox//6.4 mg/kg clav per day)	7-day course of amox/clav (40 mg/kg amox//5.7 mg/kg clav per day)
Primary outcome	Time to resolution of symptoms (AOM-SOS score ≤1) Symptom burden (daily mean score, 7-day mean) F/U visits on day 4, 10, 21	Time to treatment failure (by one of six clinical or otoscopic components) F/U visits on day 3, 8

*AOM-SOS Scale: seven clinical items, rated by parents as 0, 1 or 2 (none, a little or a lot).

AOM, acute otitis media; AOM-SOS, AOM-Severity of Symptoms; amox/clav, amoxicillin-clavulanate; TM = tympanic membrane.

Table 2 Outcomes

	Hoberman and colleagues	Tahtinen and colleagues
Primary outcomes	Faster sustained symptom resolution ($p=0.04$) Day 4: 41% vs 36%, (NNT=20) Day 7: 67% vs 53% (NNT=7) Reduced symptom scores Absolute difference (AD) at 10 days = 0.87 (95% CI 0.29 to 1.45) AD over 7 days = 0.63 (95% CI 0.15 to 1.10)	Reduced risk of treatment failure: 18.6% vs 44.9% (NNT=4) Decreased time to treatment failure by 62% HR 0.38 (95% CI 0.25 to 0.59)
Adverse events	Increased diarrhoea: NNH=3 Mastoiditis in one child in placebo (day 5)	Increased diarrhoea: NNH=5 No cases of mastoiditis
Authors' conclusions	"Treatment with amoxicillin-clavulanate among children 6–23 months with definite acute OM affords measurable short-term benefit, regardless of severity of illness"	"In children 6–35 months of age, treatment of acute otitis media with an antimicrobial agent that gives adequate coverage. . . reduces the risk of treatment failure by improving both overall condition and otoscopic signs"

NNH, number needed to harm; NNT, number needed to treat.

apply the results of these studies to clinical practice, we can look at how the participants, the intervention and the outcomes differ from those we might see, use or find most relevant clinically.

Participants

The age group of participants in both trials is certainly the age group of interest for the question being debated, as well as an age in which AOM is common. Both trials appropriately excluded children for whom the treatment protocol would be inappropriate and for whom different criteria for diagnosis or treatment might apply.

In both studies, AOM was diagnosed by clinical and otoscopic criteria, by trained otoscopists. We agree with the authors' suggestion that the strict criteria for AOM and the careful training of the otoscopists in these trials probably account for the low resolution rate in the placebo group (and hence greater benefit observed) compared with previous trials: a higher proportion of the participants really had AOM. However, the strict inclusion criteria also mean that the magnitude of benefit to be expected in patients or settings where there is more diagnostic uncertainty (which includes most settings and many patients) is likely to be less.

Clinicians also consider clinical severity when deciding whether to treat with antibiotics; those with more severe illnesses have the most to gain from treatment. Hoberman and colleagues presented results consistent with this consideration: the absolute difference in resolution of symptoms by day 10 was 42% in those with severe illness but only 29% in those with non-severe illness.

Intervention

Both trials used amox/clav, which is not the first-line recommended treatment for uncomplicated AOM in the USA.¹ Tahtinen and colleagues used a 40 mg/kg dose of amoxicillin, whereas Hoberman and colleagues used 90 mg/kg. Tahtinen and colleagues state in the supplement that, in Finland, the majority of *Streptococcus pneumoniae* is not resistant to penicillin, which is why they used the lower dose.

Of note, both studies showed a substantial increase in diarrhoea in the treatment group. The number needed

to harm for diarrhoea^{3–5} is similar to the number needed to treat for benefit in both trials (ie, about one additional child gets diarrhoea for each one with faster resolution of AOM).

Could children treated with 90 mg/kg/day of amoxicillin only, according the current AAP guideline, be expected to experience the same benefit shown in these trials, perhaps with less diarrhoea? Neither trial was designed to address a comparison of the two antibiotics. However, both benefit and harm is likely to be smaller because of resistance from β -lactamase producing organisms and a lower rate of diarrhoea.

Outcomes

Most clinicians would agree that clinical symptom resolution is the most important benefit of antibiotics. Resolution of symptoms was accelerated by treatment in both studies. However, in both trials, even though the children included had a more definitive diagnosis, most children in the placebo groups recovered: 53% were symptom free at 7 days (Hoberman and colleagues), and 65% did not require rescue treatment (Tahtinen and colleagues).

Is the symptomatic benefit clinically significant? Perhaps a more relevant measure would be the difference in time to reach a level of symptom relief that would allow parents rest and children to go back to day care. For example, in the Hoberman and colleagues trial, the placebo group reached an AOM-SOS score of ≤ 3 by day 4, whereas the treatment group reached that score at day 2.5. This is a 1.5-day benefit of antibiotics in getting to a symptom score low enough that a child (and parent) can eat, sleep and function.

One non-symptomatic outcome of interest is the persistence of middle ear effusion, which is associated with recurrent AOM and hearing loss. The Tahtinen and colleagues trial showed a 33% difference in effusion rates at 7 days versus 13% in the Hoberman and colleagues trial (at 10 days). However, neither trial followed the children long enough to document more clinically relevant, longer term reductions in middle ear effusions.

What about the possibility of waiting 48 h to identify children less likely to resolve spontaneously? Although the results of these studies support initial treatment with

antibiotics, they also support the option of watchful waiting in some patients. The less severe the disease and the more uncertain the diagnosis, the less likely it is that the expected benefits of antibiotics will justify the side effects and costs of antibiotics.

Finally, neither study adequately addressed symptom control. Both studies recommended that parents use symptomatic treatment but did not standardise the agent or dose. In both studies, use of symptomatic treatment did not significantly differ between groups, suggesting that the symptoms that most concern parents and bother children are due to the underlying viral infection and less likely to respond to antibiotics. It seems likely that the observed benefit of antibiotics in reducing symptoms would be smaller if both groups used more effective symptom control, such as ibuprofen.

Conclusions

Most readers will probably not be surprised that a big-gun antibiotic provides a non-zero benefit in children with a bacterial infection. Thus, the fact that the benefit of treatment was statistically significant in both studies may seem like old news. However, it is a mistake simply to dichotomise clinical trials into 'positive' and 'negative'.⁵ The contribution of these well-conducted studies is to help us more precisely estimate the actual magnitude of the benefit in patients we are likely to see.

Thus, the news is that, even in these large, rigorous studies designed to show benefit in carefully selected patients, the magnitude of benefit is modest, and the treatment has the same chance of causing diarrhoea as it does of improving the signs/symptoms of AOM. These studies

likely overestimate the benefit that would be expected in children with less severe AOM or uncertain diagnosis, or in those treated with amoxicillin alone.

We believe that the current AAP recommendation for this age group, which is to treat (with 80–90 mg/kg/day of amoxicillin) those children who are sicker and have a more certain diagnosis, remains reasonable. These trials do not persuade us to treat children in this age group with less severe or uncertain AOM. In fact, these trials provide a helpful upper limit of the benefit that might be expected in such children, and make us more convinced that they do not need amox/clav. Even in those with more severe symptoms and a more certain diagnosis, the magnitude of the net benefit does not exclude the possibility that a watch-and-wait strategy could be used in these children as well.

Competing interests None.

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