

Antibiotics for Acute Otitis Media in Young Children

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Purpose

In *AFP Journal Club*, three presenters review an interesting journal article in a conversational manner. These articles involve “hot topics” that affect family physicians or “bust” commonly held medical myths. The presenters give their opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

Articles

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(2):105-115.

Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med.* 2011;364(2):116-126.

Should antibiotics be used to treat acute otitis media in young children?

Andrea: Acute otitis media (AOM) in children represents a significant burden to the U.S. economic and health care systems, including the direct costs of care (e.g., office visits), indirect costs of care (e.g., development of antibiotic resistance), and social costs (e.g., loss of time from work). Data from 1995 estimated direct costs of \$1.96 billion and indirect costs of \$1.02 billion.¹ One can reasonably surmise that these costs have increased in the intervening 16 years.

In 2004, the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) attempted to clarify which patients should be treated with antibiotics during an AOM episode and which could confidently be treated with a watchful-waiting approach and pain control.¹ The two articles we review here aim to clarify the appropriate use of antibiotic treatment in the youngest children with AOM—those six months to two years of age for whom current guidelines suggest the need for antibiotic therapy in all cases of certain diagnosis.

What do these articles say?

Andrea: In both studies, young children with a certain diagnosis of AOM were randomized to either amoxicillin/

clavulanate (Augmentin) or placebo for seven to 10 days. Hoberman, et al., randomized 291 children six to 23 months of age to high-dose amoxicillin/clavulanate (90 mg per kg of amoxicillin) or placebo, and Tähtinen, et al., randomized 319 patients six to 35 months of age to standard-dose amoxicillin/clavulanate (40 mg per kg of amoxicillin) or placebo. Both studies were appropriately powered to evaluate primary outcomes: time to resolution of symptoms (Hoberman, et al.) and time to treatment failure (Tähtinen, et al.), which was a composite outcome of no improvement in clinical conditions by physician or parental assessment, no improvement in otoscopic signs, tympanic membrane perforation, severe infection requiring change to an alternative antibiotic, or any other reason for stopping or not adhering to the study drug.

Both sets of authors reported that antibiotics improved outcomes compared with placebo. Hoberman, et al., reported that children receiving antibiotic treatment were less likely to have evidence of clinical failure at or before the four- to five-day visit (4 versus 23 percent; absolute risk reduction [ARR] = 19 percent; 95% confidence interval [CI], 12 to 27; $P < .001$) or at or before the 10- to 12-day visit (16 versus 51 percent; ARR = 35 percent; 95% CI, 25 to 45; $P < .001$). Based on these data, the number needed to treat (NNT) to prevent one clinical failure is six at four to five days and three at 10 to 12 days. Tähtinen, et al., reported an NNT of four to prevent one treatment failure (as a composite outcome). However, when broken down into individual outcomes, the NNT increases significantly (i.e., NNT to prevent one child from not improving at day 3 was 16; NNT to prevent worsening of overall condition as reported by the parent or physician was 10). Additionally, in the Tähtinen, et al., study, the number needed to harm for any adverse event was six. The most common adverse events were diarrhea and eczema.

Should we believe these studies?

Andrea: I don't think these studies clarified the use of antibiotics in these patients at all. I'm not sure that many physicians in the real world can compete with dedicated “otoscopists” in the ability to be absolutely certain of an

AOM diagnosis in these small (and wriggly) patients. *Because of this, there is significant selection bias in these studies toward patients who have “real” disease.* Even though the AAP/AAFP guidelines and these articles use strict criteria for the diagnosis of AOM, in real practice, it is often difficult to get a good view of the tympanic membrane. Diagnostic criteria for AOM include rapid onset of signs and symptoms of middle ear effusion and inflammation; documentation of the presence of middle ear effusion (includes any of the following: bulging tympanic membrane, decreased mobility of the tympanic membrane, air-fluid level behind the tympanic membrane, otorrhea); and documentation of middle ear inflammation (tympanic membrane erythema or distinct otalgia that limits normal daily activities or interrupts sleep).¹

We make a clinical judgment based on a quick peek at the ear, so the effectiveness of antibiotic treatment will necessarily be less in our practices because we treat many children who would not meet the strict definition of AOM. This will also lead to an increase in the adverse effect/effectiveness ratio; proportionally more patients will have adverse effects compared with those who benefit because many of our patients may not have “real” AOM.

Mark: Also, only 498 of 1,385 patients screened by Hoberman, et al., were included in the final study. In our practices, we have to include everyone. The same is true of the Tähtinen, et al., study; fewer than 50 percent of screened patients were included in the final study. One of the reasons for exclusion was that the patients did not have certain AOM; yet, some of these patients will undoubtedly be diagnosed with AOM in practice.

Bob: The accuracy of clinical diagnosis of AOM isn't very good. Pediatricians get it right only 50 percent of the time, and ears, nose, and throat specialists 73 percent of the time (based on tympanocentesis, which none of us routinely perform).² And many of these patients have both viral and bacterial components.³ It is likely that the viral component leads to prolonged otitis media, which cannot be treated with antibiotics.⁴

Mark: Let's talk about the outcomes. In the Hoberman, et al., study, the only clinically significant outcome was likelihood of treatment failure; yet, this was defined as the presence of any symptom of AOM *and* persistent otoscopic signs of AOM on day 10 to 12. *Treatment did not fail in any children based on symptoms alone—all treatment failures were defined by persistent inflammation on examination. The treatment failed even if the patient was symptomatically better.* Most of these asymptomatic children likely would never have presented for follow-up in routine practice. And, only four to six children had to be treated to cause diarrhea, rash, or diaper dermatitis. In fact, in the Hoberman, et al., study, six children in the amoxicillin/clavulanate group developed *Clostridium difficile* colitis,

compared with one child in the placebo group. Although this is not statistically significant in this study, the risk multiplies when this aggressive antibiotic treatment is extended to patients at all of our clinical practices.

Andrea: I'd like to propose an alternative view of the results for this generally self-limited illness. Instead of looking at NNT, let's look at the number of young children who improved regardless of the use of antibiotics and see if that changes how we view antibiotic treatment in these children. Using that paradigm, two out of three children did not benefit from treatment in the Hoberman, et al., study, and three out of four children did not benefit from treatment in the Tähtinen, et al., study. To take that even further, 15 children had to be unnecessarily treated for one child to feel better on day 3 of the latter study. I'm not saying *don't* use antibiotics, but we really need to look at the risk/benefit ratio, as well as alternatives for symptom-based management.

What should the family physician do?

Bob: These studies support having a discussion with parents about the option of watchful waiting in the treatment of AOM in young children. I'm reassured by these data—children get better even when we *don't* treat them with antibiotics, and the risk of bad outcomes because of lack of antibiotic treatment is quite low. The most concerning outcome, mastoiditis, is uncommon (1.2 per 10,000 child-years); in a recent retrospective study, it did not typically coincide with the diagnosis of AOM (i.e., mastoiditis may not be a preventable complication of AOM because nearly two-thirds of mastoiditis cases occur without a recent diagnosis of AOM).⁵

Andrea: I agree that these studies make me more confident in the watchful-waiting approach, particularly because AOM diagnosis is less likely to be certain in these younger children. If you do opt to treat with antibiotics, consider recommendations from a recent Agency for Healthcare Research and Quality (AHRQ) report on AOM, which documented a change in pathogens from *Streptococcus pneumoniae* to *Haemophilus influenzae*. With this pathogenic shift, amoxicillin and amoxicillin/clavulanate (40 mg per kg of amoxicillin) are more appropriate choices for treatment than azithromycin (Zithromax) because of in vitro and clinical resistance patterns. You can expect more diarrhea with amoxicillin/clavulanate and cephalosporins than with amoxicillin alone (or watchful waiting).⁶

Of note, the AHRQ found that immediate treatment of uncomplicated AOM had modest benefit compared with placebo or delayed treatment with antibiotics. It also confirmed a higher risk of diarrhea and diaper rash with antibiotic treatment, and physicians are cautioned to discuss risks and benefits of antibiotic treatment with

parents. Based on the AHRQ's analysis of 100 average-risk children with AOM, approximately 80 can be expected to get better in approximately 10 days without antibiotic treatment. If all the children are immediately treated with ampicillin or amoxicillin, an additional 12 can be expected to improve; however three to 10 will develop rash and five to 10 will develop diarrhea.⁶

Mark: We have other options for managing the pain associated with otitis media in these young children. Make sure to review appropriate analgesic dosing with parents and empower them to treat their children. Topical analgesics, such as benzocaine, can also provide relief. Prescribe generic antipyrine/benzocaine otic drops and avoid Auralgan, which has been reformulated and is more expensive. Remember to avoid over-the-counter cold medications in these children because of lack of effectiveness and safety concerns.

Main Points

- Be strict in your diagnosis of AOM. If you interpret the data to suggest that there is benefit to antibiotic treatment, then you need to be accurate in your diagnosis. The less accurate we are, the less patients benefit from the treatment.
- Amoxicillin and amoxicillin/clavulanate remain first-line treatment options if you choose to treat uncomplicated AOM with antibiotics. In the postpneumococcal vaccination era, *H. influenzae* is the most common bacterial pathogen. Some areas have higher *H. influenzae* resistance to amoxicillin than others, so be sure to check your local susceptibility data. Amoxicillin/clavulanate outperforms azithromycin because of resistance patterns.
- Provide parents with options for both oral and topical analgesia. In this self-limited illness, symptom management is most important.

EBM Points

- When looking at NNT outcomes for studies, make sure to look at the specific clinical outcomes you care about (e.g., no improvement in overall condition) rather than composite end points, which will make any clinical effect appear more significant than it really is. In these studies, composite end points, including disease-oriented outcomes such as persistent otoscopic signs of inflammation, made the overall benefit look better than it really was.
- Consider changing how you think about NNT in a low-risk clinical situation. How many patients do you need to treat to provide them with no benefit? In these studies, anywhere from 66 to 75 percent of children did not benefit from treatment.
- Selection bias can make a treatment look better than it is in actual practice. In these studies, only patients with "real" AOM were included. The diagnostic regimen is not as strict in our practices.

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