Trials Give Nod to Antibiotics for Certain AOM

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Children with a certain diagnosis of acute otitis media who were treated with amoxicillin-clavulanate recovered more quickly, compared with those who received placebo, results from two large, separate studies demonstrated.

The findings, conducted by researchers at the University of Pittsburgh and at the University of Turku, Finland, provide the strongest evidence to date supporting a regimen of antimicrobial therapy in children with a certain diagnosis of acute otitis media (AOM).

"A study with an appropriate design was needed to resolve the controversy regarding antimicrobial therapy versus observation in children with certain diagnoses of acute otitis media," Dr. Jerome O. Klein of the department of pediatrics at Boston University, wrote in an editorial about the studies (N. Engl. J. Med. 2011;364:168-9). "The investigators in both Pittsburgh and Turku have provided such a study. They performed randomized, blinded trials of the use of amoxicillin-clavulanate as compared with placebo in the age group at greatest risk."

In 2004, the American Academy of Pediatrics and the American Academy of Family Physicians issued a clinical practice guideline that endorsed initial observation as an option in children aged 6-23 months with mild otalgia and a temperature of less than 39° C in the last 24 hours, and in whom the diagnosis of AOM is uncertain (Pediatrics 2004;113:1451-65).

However, those recommendations were based on previous clinical trials that contained "substantial limitations,"

VIEW ON THE NEWS

Trials Are Well Designed

Prior clinical studies have compared the outcome of AOM treated with antibiotics to that with placebo and have in general reported a more rapid resolution of signs and/or symptoms of AOM in the antibiotic-treated cohort. What is new?

First, both studies employed stringent criteria for entry ensuring that most, if not all, had AOM. Second, the choice and dose of amoxicillin-clavulanate provided coverage based on pharmacokinetic-pharmacodynamic principles for the majority of pneumococcal and *Haemophilus* isolates in each community. Thirdly, the study protocol provided for a sufficient frequency of follow-up to address the primary outcome (time to resolution in Pittsburgh and time to treatment failure in Turku). The results, a high rate of treatment failure in the placebo groups in both studies, distinguish these trials from several recent clinical trials and detail the potential advantages of effective antimicrobial therapy on the resolution of signs and symptoms.

Will these results change our approach to young children with AOM? As most episodes are currently treated with antibiotics, presumably these results will reinforce that approach. But these results also should challenge clinicians to further develop their diagnostic approach to AOM with greater emphasis on physical exam and to emphasize close follow-up for children who are initially managed with symptomatic care only.

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according to researchers from one of the studies, who were led by Dr. Alejandro Hoberman of the department of pediatrics at the University of Pittsburgh (N. Engl. J. Med. 2011;364:105-15).

These include "the lack of stringent diagnostic criteria, the inclusion of very young children, and the use of an antimicrobial drug that had limited efficacy or that was administered in suboptimal doses. Moreover, rates of spontaneous improvement similar to the rates seen in those studies among children receiving placebo have not been found uniformly. Therefore, for children with acute otitis media, the circumstances in which immediate antimicrobial treatment is the preferred strategy have remained unclear," they said.

Dr. Hoberman, who is also vice chair of clinical research at Children's Hospital of Pittsburgh, and his associates randomized 291 children aged 6-23 months who were diagnosed with AOM to receive amoxicillin-clavulanate or placebo for 10 days. To meet eligibility for the trial, the children were required to have received at least two doses of pneumococcal conjugate vaccine and to have AOM that was diagnosed based on one of three criteria: onset of symptoms within 48 hours that parents rated with a score of at least 3 on the Acute Otitis Media Severity of Symptoms (AOM-SOS) scale; the presence of middle-ear effusion; and moderate or marked bulging of the tympanic membrane or slight bulging accompanied by either otalgia or marked erythema of the membrane.

A significantly higher proportion of children who received amoxicillin-clavulanate had initial clearance within 7 days, compared with their counterparts in the placebo group (35% vs. 28%, respectively by day 2; 61% vs. 54% by day 4; and 80% vs. 74% by day 7). A similar relationship was seen in terms of sustained resolution of symptoms (20% vs. 14% by day 2; 41% vs. 36% by day 4; and 67% vs. 53% by day 7).

The rate of clinical failure, which was defined as the persistence of signs of acute infection on otoscopic evaluation, was less likely in the children who received amoxicillin-clavulanate, compared with those who received placebo (4% vs. 23%, respectively, at or before the visit on day 4 or 5; and 16% vs. 51% at or before the visit on days 10-12).

Dr. Hoberman and his associates concluded that treatment with amoxicillin-

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clavulanate for 10 days in children aged 6-23 months with AOM "affords a measurable short-term benefit, irrespective of the apparent severity of the illness. The benefit must be weighed against concern not only about the side effects of the medication but also about the contribution of antimicrobial treatment to the emergence of bacterial resistance. These considerations underscore the need to restrict treatment to children whose illness is diagnosed with the use of stringent criteria."

Researchers from Finland reported similar findings. With equally strict eligibility criteria, Dr. Paula Tähtinen and her associates at Turku University Hospital randomized 319 children aged 6-35 months who were diagnosed with AOM to receive amoxicillin-clavulanate or placebo for 7 days (N. Engl. J. Med. 2011;364:116-26).

The main outcome of the study was time to treatment failure from the first dose until the end-of-treatment visit on day 8. Treatment failure was a composite outcome consisting of six components: no improvement in overall condition by the first scheduled visit (day 3); a worsening of the child's condition at any time; no improvement in otoscopic signs by day 8; perforation of the tympanic membrane at any time; severe infection that required systemic open-label antimicrobial treatment at any time; or any other reason for discontinuing the study drug.

Dr. Tähtinen and her associates reported that a significantly lower rate of treatment failures occurred in children who received amoxicillin-clavulanate, compared with those who received placebo (18.6% vs. 44.9%, respectively). The difference in treatment failures was already apparent on day 3 in 13.7% of children who received amoxicillin-clavulanate, compared with 25.3% of those who received placebo. They also reported that overall, amoxicillin-clavulanate reduced the progression to treatment failure by 62% (hazard ratio 0.38) and the need for rescue treatment by 81% (HR 0.19).

In terms of side effects, the prevalence of diarrhea and eczema in the amoxicillin-clavulanate group was 47.8% and 8.7%, respectively, which was statistically higher than the rates in the placebo group (26.6% vs. 3.2%).

Going forward, they hypothesized, the identification of prognostic markers, "together with the use of stringent diagnostic criteria, could reduce the use of antimicrobial agents in the treatment of acute otitis media. Reduced use of antimicrobial agents may limit the development of resistant bacteria and increase the chances that the subsequent use of antimicrobial agents, when truly indicated, would be beneficial."

Dr. Klein noted in his editorial that since physicians "cannot determine at the onset of the illness which child is likely to benefit from antimicrobial therapy, we need to consider these data as applicable to all young children in whom a certain diagnosis of acute otitis media has been made. Is acute otitis media a treatable disease? The investigators in Pittsburgh and Turku have provided the best data yet to answer the question, and the answer is yes; more young children with a certain diagnosis of acute otitis media recover more quickly with an appropriate antimicrobial agent."

Dr. Hoberman disclosed that he has received honoraria and travel expense reimbursement from GlaxoSmithKline. One of the other study authors, Dr. Ellen R. Wald, disclosed that she has received grant support from Merck and GlaxoSmithKline. Dr. Jack Paradise disclosed that he received a consulting fee from University of Pittsburgh Medical Center. The study was supported by a grant from the National Institute of Allergy and Infectious Diseases.

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Dr. Klein disclosed that he received honoraria from Innovia Medical from 2005 to 2008. ■