

EDITORIAL

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“...the present and future major challenge for all the specialists involved in the epidemiology and treatment of acute otitis media will be the identification of those children who will benefit most from the antibiotic treatment.”

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Antibiotic treatment of acute otitis media in children: to wait or not to wait?

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Acute otitis media, the most common bacterial infection in early childhood, is caused in the majority of cases by four bacterial pathogens: *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis* and group A *Streptococcus* [1,2]. The pendulum on the controversial topic of treating acute otitis media with antibiotics has swung back and forth during the last 50–60 years. The use of antibiotics in the treatment of this condition seems logical, because the role of these agents is to eradicate the causative organisms from the middle ear fluid of infants and children with acute otitis media and, indeed, recent studies showed that failure to eradicate the bacteria early during treatment increases the clinical failure rates in children younger than 2 years of age [3,4]. Of course, in general, the efficacy of the antibiotic therapy is measurable, and may be reported by assessing the improvement in acute otitis media symptoms in children treated with antibiotics and by showing that the percentage of patients with a clinical cure is higher at a certain time point in treated patients when compared with placebo [4,5].

However, a spontaneous cure is common in patients with acute otitis media and previous studies showed that between seven and 20 children must be treated with antibiotics in order for one to derive benefit from the treatment [6,7]. Since broad and sometimes unskilled antibiotic therapy is responsible for the selection of increasingly resistant bacteria, the observation option (‘watchful waiting’) in the treatment of acute otitis media, a strategy already used in Holland, the UK and other European countries since the beginning of 1980s, was reconsidered during the last years [8,9]. The diagnostic keys essential for the management of acute otitis media via the observation method are the certainty of the examining physician on the diagnosis of acute otitis media, patient age and severity of illness. An additional and crucial factor is represented by the ability of the treating physician to see and recheck the patients during the next 24–48 h in order to decide if they are improving or deteriorating and if there is need for initiating the antibiotic treatment during a second visit. The American Academy of Pediatrics recommends the observation option in children older than 6 months of age who do not present with severe illness or in whom the diagnosis is uncertain, and in patients older than 2 years of age without severe illness [10]. In contrast, immediate antibiotic therapy is recommended for children younger than 6 months of age and for all those with a severe form of the disease, due to the association with increased risk of failure when using the ‘watchful waiting’ policy. The broad implementation of the ‘watchful waiting’ policy is still controversial, and the evidence presented in many studies supporting the broad use of this method in the treatment of acute otitis media in children is problematic,

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taking into consideration a lack of stringent diagnostic criteria for acute otitis media in the enrollment of many patients in such studies. In addition, in the majority of the 'watchful waiting' studies, insufficient numbers of patients were enrolled in order to drive significant conclusions and the age limits of the patients were broad, including considerable numbers of patients older than 2 years. The enrollment of patients with severe acute otitis media symptoms was avoided due to concern on the outcome of the observation-alone method and bacteriologic studies were not performed in order to determine the microbiology of the disease [11,12].

Today, for children with acute otitis media, the circumstances in which immediate antimicrobial treatment is the preferred strategy have remained unclear. In an effort to address the controversy related to acute otitis media treatment in children, two groups of researchers from the USA and Finland completed and published, in parallel, in *The New England Journal of Medicine*, two prospective, randomized, blinded trials comparing the efficacy of amoxicillin-clavulanate versus placebo in infants and children diagnosed with acute otitis media [13,14]. The group of researchers from the USA enrolled 291 children aged 6–23 months who met three major criteria for a diagnosis of acute otitis media (in addition to symptom onset within 48 h):

- Parent rating of three or higher on a well-established score scaling the severity of symptoms [15]
- Presence of middle-ear effusion
- Moderate or marked bulging of the tympanic membrane or, alternatively, slight bulging accompanied by otalgia or marked erythema [13].

The children were randomized to a 10-day course of high-dose amoxicillin-clavulanate or matching placebo, in addition to acetaminophen for symptom relief. The main end points were the symptomatic responses (by parental daily scoring) and the clinical failures (by recording lack of substantial improvement or worsening of symptoms during treatment and also failure to achieve complete/nearly complete resolution of symptoms and otoscopic signs by end of therapy). The authors found that 35% of the antibiotic-treated patients had initial symptom resolution by day 2, 61% by day 4, and 80% by day 7, while the corresponding figures for the observation group were 28, 54 and 74% ($p = 0.14$). Rates of sustained symptom resolution (based on measurement of time to the second of two successive parental recordings of improvement) on the same days were 20, 41 and 67% with amoxicillin-clavulanate versus 14, 36 and 53% with observation ($p = 0.04$). Mean symptom

scores over the first 7 days also were significantly lower in the antibiotic arm ($p = 0.02$). Clinical failure rates before the day 4–5 were 4% with antibiotics and 23% with placebo, increasing to 16 versus 51% by day 10–12 ($p < 0.001$ for both comparisons). Diarrhea and diaper rash occurred in significantly more patients in the antibiotic group compared with the placebo group [13].

The Finnish study enrolled 319 children aged 6–35 months, with a diagnosis of acute otitis media by standardized criteria that included clinical, otoscopic and tympanometric examinations. The patients were randomized to a 7-day course of low-dose amoxicillin-clavulanate (appropriate for the low pneumococcal-resistance rates reported in Finland) or placebo. The primary end point was time to treatment failure (established by six components defining failure on day 3 of treatment or deterioration in patient's overall condition including adverse events and otoscopic signs of acute otitis media during the time period till the end-of-therapy visit on day 8) while the second outcome end point was related to time to initiation of rescue treatment and the development of contralateral acute otitis media. Treatment failure occurred in significantly less patients treated with antibiotics compared with the placebo group (18.6 vs 44.9%; $p < 0.001$). The difference had become apparent at the first follow-up on day 3, when treatment failure had occurred in 13.7% of the antibiotic group versus 25.3% in the placebo group. Treatment with amoxicillin-clavulanate reduced the progression to treatment failure by 62% and the need for rescue treatment by 81%. As per authors' calculations, the number needed to treat for one child to benefit from the antimicrobial therapy was 3.8, much lower than reported on previous meta-analyses. As in the US study, diarrhea occurred significantly more often in the antibiotic arm (47.8 vs 26.6%; $p < 0.001$), as did rash (8.7 vs 3.2%; $p = 0.04$) [14].

Both studies have convincingly demonstrated, in very thoroughly performed prospective, randomized, placebo-controlled studies, a significant benefit when treating children with acute otitis media with antibiotics (specifically with amoxicillin-clavulanate) as compared with placebo. The investigators in the USA and Finland demonstrated that more young children with a certain diagnosis of acute otitis media recover more quickly when they are treated with an appropriate antimicrobial agent compared with patients treated symptomatically only. The major elements contributing to these impressive findings, most likely, reside in the use of stringent diagnostic criteria of acute otitis media (leading to maximal diagnostic accuracy) for the enrolled patients, enrollment of younger children (as appropriate to the true epidemiology of the disease), inclusion of patients with severe and recurrent acute otitis media and use of

an effective antimicrobial agent. Indeed, only children with a certain diagnosis of acute otitis media, made by validated otoscopists on the basis of the presence of acute clinical symptoms with emphasis on a full or bulging tympanic membrane as the main otoscopic finding, were enrolled. It is well known that the clinical diagnosis of acute otitis media is difficult and cannot be based on signs and symptoms which may overlap with other respiratory infections or on parental description [16]. Furthermore, an accurate diagnosis relies on appropriate cleaning of the external ear canal, good visualization of the eardrum, cooperation from children and parents and, extremely important, good training of the practicing physicians, minimizing the discrepancies in diagnosis described between otolaryngologists, pediatricians and general practitioners [17].

Today, in the era of antibiotic resistance, only very few drugs were proved to be able to eradicate the acute otitis media pathogens and, in fact, only two drug regimens (high-dose amoxicillin-clavulanate and intramuscular ceftriaxone) reached appropriate bacteriological and clinical results [4,10,18]. The high-dose regimen showed a total percentage of bacteriological success of 96% and had better results in the eradication of *H. influenzae* compared with the low-dose regimen. High-dose amoxicillin-clavulanate is today the recommended antibiotic choice in the American Academy of Pediatrics guidelines as the first-line treatment of patients with severe acute otitis media and in the second-line treatment of the disease [10].

What are the practical implications of the results of these two studies for the practicing physician? Do they mean that we have to reconsider (again) our approach and start treating every patient diagnosed with acute

otitis media with antibiotics? First, the presented studies underscore the need to restrict treatment to children whose illness is diagnosed only with the use of stringent criteria. Second, while these two studies indicate clearly that children with acute otitis media benefit from immediate antimicrobial treatment as compared with placebo, 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. Third, it is clear that a substantial proportion of bacterial acute otitis media cases in children will resolve without use of antimicrobial drugs. Therefore, the present and future major challenge for all the specialists involved in the epidemiology and treatment of acute otitis media will be the identification of those children who will benefit most from the antibiotic treatment. Meanwhile, recent studies have clearly demonstrated that children younger than 2-years old diagnosed with bilateral disease (which is frequent and may represent more than 50% of all cases diagnosed with acute otitis media) and children presenting with otorrhea derived the most beneficial effect from immediate antibiotic treatment [19,20].

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