7 Pediatric Otitis Media with Effusion

Amoxicillin versus placebo: Chance of becoming effusion-free

Jennifer J. Shin and Michael J. Cunningham

METHODS

A computerized Ovid search of MEDLINE 1966–January 2004 was performed. The terms “otitis media” and “antibiotics” were exploded and the resulting articles were cross-referenced, yielding 1947 trials. Given the known richness of the otitis media literature and the authority of higher levels of evidence, these articles were then limited to randomized controlled trials (RCTs), resulting in 302 articles. These articles were then reviewed to identify those that met the following inclusion criteria: 1) patient population <18 years of age with documented otitis media with effusion (OME), 2) intervention with amoxicillin therapy alone versus placebo control, 3) outcome measured in terms of presence or absence of middle ear effusion (MEE) with a statistical analysis. Articles comparing intervention with amoxicillin/clavulanate, cephalosporins, trimethoprim-sulfamethoxazole, and erythromycin with placebo were excluded here but are presented separately in this chapter. The bibliographies of articles that met these inclusion criteria were manually examined to determine if any further relevant articles could be identified. This process yielded four RCTs [1–4].

RESULTS

Outcome Measures. All four studies reported the percent of patients with resolution of effusion as the primary outcome measure. In addition, other studies also reported secondary outcomes of percent of patients developing acute otitis media (AOM), percent of time with MEE, percent of patients with recurrent MEE, and episodes of AOM, MEE, and OME per person year.

Potential Confounders. The specificity of the definitions of MEE, OME, and AOM are key, and these are outlined in as much detail as the primary papers allow. In addition, follow-up time, age, history of middle ear disease, duration of effusion at entry, season of the year, history of allergy or nasal obstruction, the status of the adenoid, the specific amoxicillin regimen, including the duration, may also affect results.

Study Designs. All four studies were RCTs. Each study focused on MEE, but there were well-delineated differences regarding the duration of effusions that were studied (ranging from any duration [2, 3] to a minimum of 2–3 months [1, 4]). In addition, there were differences in whether active AOM was present at the outset, with two studies excluding patients with symptoms or signs of AOM [2, 3] whereas one specified that AOM was acceptable in their inclusion criteria [4]. All four reports commented on the effectiveness of randomization in balancing confounders between the amoxicillin and control groups. Also, all were double-blind, placebo-controlled studies. The amoxicillin regimens ranged from 20 to 50 mg/kg/day, for a duration of 2 weeks to 1 year. Compliance was reported in three instances [2–4], as measured by the bottle method, caregiver diary, calendar method, and/or urine specimens. In those three instances, rates of compliance were high. No patients crossed over from one treatment group to another, and additional antimicrobial therapy necessary for the treatment of superimposed AOM were described in detail in three studies. A priori power calculations were noted in two studies [3, 4]; in both instances, the sample sizes were smaller than the estimate required for a 90% power to detect a 20% difference or a 50% reduction in MEE.

Highest Level of Evidence. Of the four RCTs, three showed that after 2 weeks of amoxicillin, there was a significantly higher percentage of effusion-free patients at 2 weeks to 2 months, as compared with placebo. In these three RCTs, rate differences (RD)1 ranged from 14.7% to 30.0%. These figures suggest numbers needed to treat (NNT)2 of 4–7, which means that 4–7 children must be treated with 2 weeks of amoxicillin therapy to result in 1 effusion-free child. At 1 year, however, one RCT showed no difference in the percent of patients with MEE after 1 year of amoxicillin or placebo treatment [4]. That same study, however, reported that the amoxicillin group experienced less time with MEE than the control group. In addition, it was reported that the amoxicillin group had a lower rate of new-onset MEE and OME. A

1RD is the absolute difference in successful outcomes between the study group and the control group. For example, in the Mandel, 1987 study, the RD is −14.7%, so that the NNT = 100/14.7 = 6.8. In this case, seven children would need to be treated so to obtain benefit for one child.
second outcome parameter, the percent of children developing subsequent AOM, was reported in three studies [2-4]. In two of these studies, there was no significant difference in the percent of patients developing AOM during the follow-up period [2, 3]. In the third study, however, the rate of AOM per person year was significantly lower in the amoxicillin group [4].

**Applicability.** These results are applicable to children 7 months to 12 years of age with MEE. Further specifics regarding the applicability of individual trials are tabulated for the reader under “Inclusion Criteria” and “Exclusion Criteria.”

**Morbidity.** Only minor adverse reactions were noted in either the amoxicillin or placebo groups and these are also tabulated for the reader. There is also potential morbidity in regard to development of antibiotic resistance.

**CLINICAL SIGNIFICANCE AND FUTURE RESEARCH**

There is level 1 evidence that demonstrates improved resolution of OME with amoxicillin, with NNT of 4–7 children. These data, along with those from other trials of antibiotics for OME, are also presented in a meta-analysis in this section. Results regarding the development of superimposed AOM in this patient population are varied.

Additional research may focus specifically on direct comparisons between amoxicillin and newer antibiotic regimens. In addition, the associated risk of sequelae of antibiotic resistance from amoxicillin use may be investigated.