Treating Acute Otitis Media In Young Children: What Constitutes Success?

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Researchers embarking on clinical trials of antimicrobial treatment for acute otitis media (AOM) must make several key decisions beforehand. They must choose a study age group, stipulate study eligibility, specify criteria for the diagnosis of AOM, decide on the antimicrobial drug to be used and on its dosage, specify analgesic use, and settle on 1 or more endpoints or outcome measures. If more than 1 outcome is to be measured, convention calls preferentially for only 1 of them to be designated as primary. Each of these decisions potentially bears on what the eventual study findings will be, on how they may be interpreted and on the treatment recommendations that logically flow from them.

THE PITTSBURGH STUDY

We recently completed a double-blind, randomized, placebo-controlled clinical trial designed to address uncertainty concerning the relative merits of prompt antimicrobial treatment in young children with AOM, when compared with expectant management in which antimicrobial treatment is reserved for those children deemed not to be responding satisfactorily.1 Certain of the needed advance decisions regarding trial design were easy and straightforward. We limited enrollment to otherwise healthy children younger than 2 years because it is in that age group that AOM occurs most commonly and also is most resistant to treatment. We used stringent criteria for the diagnosis of AOM, requiring the presence of middle-ear effusion and bulging of the tympanic membrane (TM), because any effects of treatment would best be demonstrated in children whose diagnosis of AOM initially had been quite certain. We chose high-dose amoxicillin-clavulanate, administered for 10 days, as our active drug because in previous studies in children with AOM it had proven the most effective and demonstrated in children whose diagnosis of AOM initially had been quite certain. We chose high-dose amoxicillin-clavulanate, administered for 10 days, as our active drug because in previous studies in children with AOM it had proven the most effective.

PROTOCOL-DEFINED OUTCOMES

Resolution of Infection

We categorized children as having experienced clinical failure at the day 4–5 visit if otoscopic signs of infection had worsened, and at the day 10–12 visit if otoscopic evidence of infection (ie, TM bulging) persisted.

Abatement of Symptoms

To rate symptoms, we used the Acute Otitis Media Severity of Symptoms (AOM-SOS) scale,1,4 comprising 7 discrete, parent-reported symptoms: ear tugging or rubbing, crying, irritability, difficulty sleeping, diminished activity, diminished appetite and fever. Parents were to rate each of these symptoms at specified intervals, in comparison with the child’s usual state, as “none,” “a little” or “a lot,” with corresponding scores of 0, 1 and 2. Summing the scores thus gave an AOM-SOS score at each evaluation within a range of 0 to 14. We considered that symptom abatement comprised 2 main components: time to resolution of symptoms and symptom burden over time, and we measured each of these components in 2 ways, giving a total of 4 discrete measures.

CHOICE OF PRIMARY OUTCOME

Our original predilection was to designate resolution of infection as our primary outcome, reflecting our belief that the assessment of TM status by a validated otoscopist better reflects middle-ear status than do symptoms, which, in infants and young children with AOM, are mostly nonspecific, variable and not infrequently absent.5 Nonetheless, to conform with a Food and Drug Administration recommendation at the time,6 we designated abatement of symptoms as our primary trial outcome and resolution of infection as 1 of several secondary outcomes.
Other commenters, on the other hand, were unapproving. Their criticisms centered mainly on what they considered the unimpressive magnitude of the differences we had found favoring the amoxicillin-clavulanate group over the placebo group in symptomatic response, and they questioned whether that advantage outweighed the side effects of antibiotic treatment—in this case, mainly diarrhea and diaper dermatitis—and the risk that the treatment imposed of promoting bacterial resistance. The criticisms either ignored the larger between-group difference we had found in the persistence of otoscopic signs of infection or disparaged that difference as of dubious clinical importance.

WHICH OUTCOME MATTERS MOST?

What then constitutes a successful treatment outcome? To address this question, it is instructive to look to our study’s data set and consider the differing conclusions concerning the efficacy of amoxicillin-clavulanate that would result from applying to the data an array of different hypothetical criteria for defining clinical failure, each arguably plausible. Results of this exercise are summarized in Table 1 and bring to light the following relationships:

- The between-group difference was largest when a conclusion of clinical failure was based simply on persistence of TM bulging of any degree, whether or not any symptoms as reflected in children’s AOM-SOS scores persisted (set 1).
- Criteria for clinical failure that incorporated persistence of TM bulging as well as of symptoms (set 2), compared with criteria based only on comparable persistence of symptoms (set 3), resulted in smaller proportions of children in each treatment group meeting failure criteria. However, between-group differences in sets 2 and 3, respectively, were of generally similar magnitude.
- As criteria for clinical failure that included TM bulging were increased in stringency and accordingly were met by fewer children (sets 1 and 2), between-group differences in the rate of treatment failure tended to narrow progressively; this tendency, however, was not apparent when the criteria for clinical failure concerned only symptoms (set 3).

<table>
<thead>
<tr>
<th>Criteria Sets Used for Defining Clinical Failure at or Before Days 10–12*</th>
<th>Number of Children With Clinical Failure According to Specified Criteria for Failure‡</th>
<th>Between-group Difference (95% CI)</th>
<th>P</th>
<th>Number Needed to Treat10 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Set 1</strong></td>
<td>Any degree of TM bulging; AOM-SOS score ≥0</td>
<td>23 (17)</td>
<td>71 (51)</td>
<td>35% (23%, 45%)</td>
</tr>
<tr>
<td>Any degree of TM bulging; AOM-SOS score ≥1</td>
<td>17 (12)</td>
<td>51 (37)</td>
<td>24% (15%, 34%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any degree of TM bulging; AOM-SOS score ≥2</td>
<td>16 (12)</td>
<td>43 (31)</td>
<td>19% (10%, 29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any degree of TM bulging; AOM-SOS score ≥3</td>
<td>15 (11)</td>
<td>37 (27)</td>
<td>16% (7%, 25%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Set 2</strong></td>
<td>Moderate or marked TM bulging; AOM-SOS score ≥0</td>
<td>18 (13)</td>
<td>63 (45)</td>
<td>32% (22%, 42%)</td>
</tr>
<tr>
<td>Moderate or marked TM bulging; AOM-SOS score ≥1</td>
<td>14 (10)</td>
<td>45 (32)</td>
<td>22% (13%, 31%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate or marked TM bulging; AOM-SOS score ≥2</td>
<td>13 (9)</td>
<td>38 (27)</td>
<td>18% (9%, 27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate or marked TM bulging; AOM-SOS score ≥3</td>
<td>12 (9)</td>
<td>32 (23)</td>
<td>14% (6%, 23%)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Set 3</strong></td>
<td>AOM-SOS score ≥1 without regard to TM bulging</td>
<td>70 (50)</td>
<td>87 (63)</td>
<td>12% (±1%, 23%)</td>
</tr>
<tr>
<td>AOM-SOS score ≥2 without regard to TM bulging</td>
<td>44 (32)</td>
<td>63 (45)</td>
<td>14% (2%, 25%)</td>
<td>0.03</td>
</tr>
<tr>
<td>AOM-SOS score ≥3 without regard to TM bulging</td>
<td>28 (20)</td>
<td>50 (36)</td>
<td>16% (5%, 26%)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Set 4</strong></td>
<td>Ear tugging or rubbing and/or fever, without regard to TM bulging</td>
<td>19 (14)</td>
<td>45 (32)</td>
<td>19% (9%, 28%)</td>
</tr>
<tr>
<td>Ear tugging or rubbing and/or fever, with any degree of TM bulging</td>
<td>12 (9)</td>
<td>37 (27)</td>
<td>18% (9%, 27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ear tugging or rubbing, without regard to TM bulging</td>
<td>10 (7)</td>
<td>30 (22)</td>
<td>14% (6%, 23%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ear tugging or rubbing, with any degree of TM bulging</td>
<td>9 (6)</td>
<td>30 (22)</td>
<td>15% (7%, 23%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*For the 5 children receiving amoxicillin-clavulanate and the 36 children receiving placebo who met the study’s criteria for clinical failure before the scheduled follow-up visit at days 10–12, the AOM-SOS score is the score recorded at the time of failure.

†Data for 1 child in the amoxicillin-clavulanate group and 2 children in the placebo group were incomplete and are not included in the table.

‡Percentage values may not be exact because of rounding.

¶As indicated in the parental AOM-SOS recordings.

CI indicates confidence interval.

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but who are substantially free of symptoms, benefit sufficiently to warrant additional (or newly instituted) antimicrobial treatment.

TOWARD ANSWERING THE QUESTION

Conceptually, the design of a study to address the question seems quite simple. Enrollment would be limited to children younger than 2 or 3 years who have unequivocal otoscopic evidence of middle-ear infection but who are substantially asymptomatic. The children would be randomly assigned to receive a course of either an antimicrobial or placebo and would then be monitored over an extended period to ascertain the extent to which they experience recurrent symptoms, new AOM episodes and persistent middle-ear effusion. Eligible children could comprise not only those completing a course of antimicrobial treatment for AOM but also those in whom an episode of AOM was purposely not treated or in whom the presence of AOM is discovered incidentally in the course of routine well-child care.

Practically, however, mounting and effectively conducting such a study will likely not be so simple. The appearance of potentially eligible children will not be an everyday occurrence in most clinical settings, so that a sustained, multicenter effort will likely be required to enroll sufficient numbers of subjects to enable reaching definitive conclusions. Potentially interested researchers should nonetheless not be deterred; until such a study is successfully carried out, the symptoms-versus-signs debate will almost certainly go on, and decisions about antimicrobial treatment for many young children with AOM will continue to be based on opinion rather than on relevant evidence.

REFERENCES