Published in final edited form as:
Pediatr Infect Dis J. 2013 July ; 32(7): 745–747. doi:10.1097/INF.0b013e31828e1417.

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

Jack L. Paradise, MD[*,†], **Alejandro Hoberman, MD**[*,†], **Howard E. Rockette, PhD**[‡], and **Nader Shaikh, MD, MPH**[*,†]

[*]Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA

[†]Department of Pediatrics, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, PA

[‡]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

Keywords

acute otitis media; antimicrobial treatment; clinical trials; outcome measures

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 one or more endpoints or outcome measures. If more than one outcome is to be measured, convention calls preferentially for only one 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, as 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 under 2 years of age 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 as well as 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 of the available orally-administered antimicrobials.[2] We advised all parents to administer acetaminophen as needed for relief of symptoms.

Corresponding Author: Jack L. Paradise, MD, Division of General Academic Pediatrics, Children's Hospital of Pittsburgh of UPMC, Children's Hospital Office Bldg., 3rd Fl., 4401 Penn Ave., Pittsburgh, PA 15224., Phone: 617-489-0877., FAX: 617-489-0877 (must telephone first)., jpar@pitt.edu.

Conflicts of Interest
No conflicts of interest declared.

Less straightforward, however, were the advance decisions we needed to make about outcome measures, and about which of the measures should be designated as primary. The two outcomes of principal interest to us were resolution of infection and abatement of symptoms.

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--i.e., TM bulging--persisted.

Abatement of symptoms

To rate symptoms we used the Acute Otitis Media Severity of Symptoms (AOM-SOS) scale,[3,4] comprising seven 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 two main components--time to resolution of symptoms and symptom burden over time--and we measured each of these components in two ways, giving a total of four discrete measures.

Choice of primary outcome

Our original predilection was to designate resolution of infection as our primary outcome, reflecting our belief that 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 (FDA) recommendation at the time,[6] we designated abatement of symptoms as our primary trial outcome, and resolution of infection as one of several secondary outcomes.

Main study findings

On each of our four measures of symptomatic response, results were modestly more favorable among children who received amoxicillin-clavulanate than among those who received placebo. Three of the between-group differences were statistically significant (*P* values 0.01, 0.02, and 0.04, respectively); one was not (*P* value 0.14). More substantial were the differences favoring the amoxicillin-clavulanate group in the rates of clinical failure: by Day 4–5, 4% versus 23%; and by Day 10–12, 16% versus 51% (both *P* values <0.001). No child was categorized as having met our criteria for clinical failure on the basis of symptoms alone.[1]

Reactions to study findings

Reactions to the report of our findings were mixed. On the one hand, an editorial accompanying our report and that of a similarly designed Finnish study[7] with similar outcomes commented, "The investigators … have provided the best data yet … more young children with a certain diagnosis of acute otitis media recover more quickly when they are treated with an appropriate antimicrobial agent."[8]

Other commenters,[9] 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 the Table, and bring to light the following relationships:

- However clinical failure was defined, it was experienced by fewer children treated with amoxicillin-clavulanate than with placebo.
- The magnitude of the difference in outcome between the amoxicillin-clavulanate and placebo groups varied substantially depending on the criteria used for defining clinical failure: absolute between-group differences in the percentage of children with clinical failure ranged from 35% to 12%; the number needed to treat thus ranged from 3 to 8.
- 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).
- Limiting symptoms of interest, in determining outcome, to persistent ear rubbing or tugging and/or fever (Set 4)--as had been the case in a number of earlier studies[10]--substantially reduced the number of children meeting criteria for clinical failure, as compared with considering the AOM-SOS scale in its entirety (Set 3), but resulted in little or no change in the magnitude of absolute differences between the two treatment groups.

Taken together, these findings underscore the need to resolve the question of whether symptomatic response or response based on otoscopic findings is the more telling measure of disease outcome, and relatedly, whether young children in whom otoscopic evidence of infection persists after antimicrobial treatment (or after no treatment), 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 under 2 or 3 years of age 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.

Acknowledgments

Source of Funding:

This work was supported in part by Grant 3U01AI066007-02S1 from the National Institute of Allergy and Infectious Diseases.

References

1. 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; 364:105–115. [PubMed: 21226576]
2. Hoberman A, Dagan R, Leibovitz E, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. Pediatr Infect Dis J. 2005; 24:525–532. [PubMed: 15933563]
3. Shaikh N, Hoberman A, Paradise JL, et al. Development and preliminary evaluation of a parent-reported outcome instrument for clinical trials in acute otitis media. Pediatr Infect Dis J. 2009; 28:5–8. [PubMed: 19077917]
4. Shaikh N, Hoberman A, Paradise JL, et al. Responsiveness and construct validity of a symptom scale for acute otitis media. Pediatr Infect Dis J. 2009; 28:9–12. [PubMed: 19077916]
5. Niemelä M, Uhari M, Jounio-Ervasti K, Luotonen J, Alho OP, Vierimaa E. Lack of specific symptomatology in children with acute otitis media. Pediatr Infect Dis J. 1994; 13:765–768. [PubMed: 7808842]
6. Guidance for industry -- acute bacterial otitis media; developing drugs for treatment. Revision 1. Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research; Food and Drug Administration website; 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070947.pdf [Accessed September 19, 2012.]
7. 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; 364:116–126. [PubMed: 21226577]
8. Klein JO. Is acute otitis media a treatable disease? [editorial]. N Engl J Med. 2011; 364:168–169. [PubMed: 21226583]

9. Newman DH, Shreves AE, Spiro DM, et al. Treatment of acute otitis media in children [letters]. N Engl J Med. 2011; 364:1775–1777. [PubMed: 21542756]

10. Damoiseaux RA, van Balen FAM, Hoes AW, Verheij TJ, de Melker RA. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children age under 2 years. BMJ. 2000; 320:350–354. [PubMed: 10657332]

Table

Clinical Failure Rates in Children with Acute Otitis Media, According to Study Group and Hypothetical Criteria Used for Defining Clinical Failure, Based on Data from Hoberman et al.[1]

Criteria Sets Used for Defining Clinical Failure At or Before Day 10–12[*]	Amoxicillin-Clavulanate Group (N = 139)[†]	Placebo Group (N = 139)[†]	Between-Group Difference (95% CI)	*P* Value	Number Needed to Treat (95% CI)
	no. (%) of children with clinical failure according to specified criteria for failure[‡]				
Set 1					
Any degree of TM bulging[§], AOM-SOS score ≥0	23 (17)	71 (51)	35% (23%, 45%)	<0.001	3 (4, 2)
Any degree of TM bulging; AOM-SOS score ≥1	17 (12)	51 (37)	24% (15%, 34%)	<0.001	4 (7, 3)
Any degree of TM bulging; AOM-SOS score ≥2	16 (12)	43 (31)	19% (10%, 29%)	<0.001	5 (10, 4)
Any degree of TM bulging; AOM-SOS score ≥3	15 (11)	37 (27)	16% (7%, 25%)	0.001	6 (14,4)
Set 2					
Moderate or marked TM bulging, AOM-SOS score ≥0	18 (13)	63 (45)	32% (22%, 42%)	<0.001	3 (5, 2)
Moderate or marked TM bulging; AOM-SOS score ≥1	14 (10)	45 (32)	22% (13%, 31%)	<0.001	5 (8, 3)
Moderate or marked TM bulging; AOM-SOS score ≥2	13 (9)	38 (27)	18% (9%, 27%)	<0.001	6 (11, 4)
Moderate or marked TM bulging; AOM-SOS score ≥3	12 (9)	32 (23)	14% (6%, 23%)	0.002	7 (16, 4)
Set 3					
AOM-SOS score ≥1 without regard to TM bulging	70 (50)	87 (63)	12% (<1%, 23%)	0.053	8 (171, 4)
AOM-SOS score ≥2 without regard to TM bulging	44 (32)	63 (45)	14% (2%, 25%)	0.03	8 (50, 4)
AOM-SOS score ≥3 without regard to TM bulging	28 (20)	50 (36)	16% (5%, 26%)	0.005	6 (20, 4)
Set 4					
Ear tugging or rubbing and/or fever[¶], without regard to TM bulging	19 (14)	45 (32)	19% (9%, 28%)	<0.001	5 (11, 4)
Ear tugging or rubbing and/or fever, with any degree of TM bulging	12 (9)	37 (27)	18% (9%, 27%)	<0.001	6 (11, 4)
Ear tugging or rubbing, without regard to TM bulging	10 (7)	30 (22)	14% (6%, 23%)	<0.01	7 (16, 4)
Ear tugging or rubbing, with any degree of TM bulging	9 (6)	30 (22)	15% (7%, 23%)	<0.001	7 (15, 4)

Abbreviations: CI, confidence interval; TM, tympanic membrane; AOM-SOS, Acute Otitis Media Severity of Symptoms scale.[6,7]

[*] 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 Day 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.

[§] At each examination, bulging was rated as slight, moderate, marked, or absent in each ear. When findings in the two ears differed, findings in the more affected ear were used in the analysis.

[¶] As indicated in the parental AOM-SOS recordings.