

CORRESPONDENCE



Treatment of Acute Otitis Media in Children

TO THE EDITOR: Hoberman et al. (Jan. 13 issue)¹ report that antibiotics reduced “the time to resolution of symptoms and reduced the overall symptom burden” in children with acute otitis media, and they reject the null hypothesis on the basis of statistical benefit in three of four “primary” outcomes. There is no explanation of, or correction for, the use of four primary outcomes. The Consolidated Standards of Reporting Trials recommend against more than one primary outcome because of “the problems of interpretation associated with multiplicity of analyses.”²

More troubling, the study protocol (available with the full text of the article at NEJM.org) identifies only one primary outcome, “time to resolution.” Of the remaining three outcomes called “primary” in the article, one is not in the protocol and two are explicitly identified as secondary.

On the basis of the study protocol, the primary outcome showed no benefit over placebo ($P=0.14$), and the null hypothesis cannot be rejected. Moreover, diarrhea, the outcome identified in the protocol as the “primary safety outcome,” was associated with harm when the study drug was compared with placebo ($P=0.05$). These results do not support the reported conclusions and appear to be an argument against antibiotic use in this population.

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No potential conflict of interest relevant to this letter was reported.

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;364:105-15.

2. Consolidated Standards of Reporting Trials (CONSORT).

Transparent reporting of trials. (http://www.consort-statement.org/consort-statement/3-12---methods/item6a_outcomes.)

TO THE EDITOR: We question the conclusions of Hoberman et al.; it is not unreasonable to conclude that acute otitis media is a disease most often treatable with time alone. Had a correction for multiple comparisons been applied, there would have been no statistically significant differences between the treatment and placebo groups. The low daily doses of acetaminophen administered and the lack of topical analgesia may have biased the results against the null for symptom control as an outcome.^{1,2} Moreover, the visual inspection of the time-to-event curves (Fig. 2 of their article) indicates that the between-group differences are not clinically meaningful. In addition, the study design does not provide a comparison of immediate treatment with a wait-and-see prescription, an approach resulting in treatment of patients with acute otitis media that warrants antibiotics while limiting antibiotic use overall.³ As such, the study design compared treatment with placebo when a beneficial, standard therapy (the wait-and-see prescription) might have more appropriately served as an active control.⁴ Further comparative trials that include the wait-and-see approach are warranted before concluding that acute otitis media uniformly requires immediate antibiotic treatment.

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1. Hoberman A, Paradise JL, Reynolds EA, Urkin J. Efficacy of Auralgan for treating ear pain in children with acute otitis media. *Arch Pediatr Adolesc Med* 1997;151:675-8.
2. Bolt P, Barnett P, Babl FE, Sharwood LN. Topical lignocaine for pain relief in acute otitis media: results of a double-blind placebo-controlled randomized trial. *Arch Dis Child* 2008;93:40-4.
3. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;322:336-42.
4. Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. *JAMA* 2006;296:1235-41.

TO THE EDITOR: The article on acute otitis media by Hoberman et al. may overstate the benefit of antimicrobial therapy for acute otitis media. Their study, which used validated scoring instruments to quantify the time to resolution of symptoms of acute otitis media, produced results that were consistent with previous published data showing a marginal benefit from antibiotics for acute otitis media.¹⁻⁴ These investigators also used subjective assessments of otoscopic signs to identify clinical failure, sometimes in otherwise asymptomatic patients. The authors did not disclose the proportion of patients with clinical failure at day 10 to 12 who had concurrent symptom scores lower than the minimum score of 3 required for entry into the study, but the article suggests the number exceeds 37%. The temporal disparity between resolution of symptoms and resolution of otoscopic signs of acute otitis media became the authors' basis for describing a significant benefit from antibiotics for acute otitis media. Remnant effusions may persist for days or weeks after an episode of acute otitis media has resolved, but they are not necessarily an indication for saturation of the population of patients who have acute otitis media with broad-spectrum antibiotics. One observer's half-full middle-ear space might be another observer's half-empty one.

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Dr. Grubb and Mr. Spaugh report holding ownership positions in Walls Precision Instruments, a manufacturer of a medical device for tympanocentesis, a procedure sometimes performed in the management of acute otitis media. No other potential conflict of interest relevant to this letter was reported.

1. Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. *JAMA* 2006;296:1235-41.
2. Marchetti F, Ronfani L, Nibali SC, Tamburlini G. Delayed prescription may reduce the use of antibiotics for acute otitis media: a prospective observational study in primary care. *Arch Pediatr Adolesc Med* 2005;159:679-84.
3. Takata GS, Chan LS, Shekelle P, Morton SC, Mason W, Marcy SM. Evidence assessment of management of acute otitis media: I. The role of antibiotics in treatment of uncomplicated acute otitis media. *Pediatrics* 2001;108:239-47.
4. Damoiseaux RA, van Balen FA, Hoes AW, Verheij TJ, de Melker RA. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. *BMJ* 2000;320:350-4.

TO THE EDITOR: The two recent trials reported in the *Journal* by Hoberman et al. and Tähtinen et al.¹ and the accompanying editorial² on antibiotics for acute otitis media in children overstate the impact of antibiotics in clinical practice. The apparent effect size is greater than that reported in previous meta-analyses^{3,4} for two reasons. First, their end point combined symptoms with the proxy of the appearance of the tympanic membrane (of doubtful clinical importance in a normally spontaneously remitting disease). Second, they used a much narrower definition of acute otitis media than is typical in practice (in this study, clinicians received special training, inclusion criteria were stringent, and most patients were not eligible for enrollment because they were insufficiently ill). Sicker patients benefit more from any effective treatment. Some clinicians may think that they have freer license to prescribe antibiotics in children who are much less ill. Though the two trials showed statistically significant benefits associated with antibiotics, we think restricted prescribing is still appropriate. Instead of simply deciding to treat all children, we should carefully balance harms and benefits, which generally means restricting antibiotics to the small group of younger, sicker children.⁴

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1. 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;364:116-26.
2. Klein JO. Is acute otitis media a treatable disease? *N Engl J Med* 2011;364:168-9.
3. Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2004;1:CD000219.
4. Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;368:1429-35.

TO THE EDITOR: Tähtinen et al. evaluated a population with a pneumococcal vaccination rate of 2%, so the treatment effect of antibiotics in this population was probably overestimated. The overall number needed to treat was 3.8; however, the number needed to harm associated with adverse events was 6. It is difficult to establish whether these results apply to the population of vaccinated children in North America.

Amoxicillin–clavulanate, the drug used in the studies by Tähtinen et al. and Hoberman et al., is not considered to be first-line therapy for otitis media in children. A recent systematic review¹ concluded that amoxicillin is as good as other more expensive medications, and pooled results of seven studies showed a number needed to treat of 8 for amoxicillin–ampicillin. In the study by Hoberman et al., the number needed to treat was 17 for initial resolution of symptoms by day 7 with amoxicillin–clavulanate and the number needed to harm was 6 for diarrhea and 3 for dermatitis. Of interest, the two current studies showed a resolution rate with placebo of 55 to 74%.

Neither of these studies refutes the recommendation of the American Academy of Pediatrics for a 48- to 72-hour wait-and-see-prescription for otitis media,² nor do they prove that amoxicillin–clavulanate is the best choice of antibiotic.

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No potential conflict of interest relevant to this letter was reported.

1. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. *JAMA* 2010;304:2161-9.
2. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. *Pediatrics* 2004;113:1451-65.

TO THE EDITOR: Hoberman et al. and Tähtinen et al. suggest that amoxicillin–clavulanate is beneficial in young children with acute otitis media,

but their studies raise some questions. First, do they think that their results are applicable with a significant benefit in everyday practice? Most community episodes of acute otitis media are diagnosed by pediatricians who are not qualified otoscopists, and so there is a high risk of overdiagnosis.¹ Without specific education and diagnostic validation, the universal use of antibiotics could do more harm than good. Second, why was amoxicillin–clavulanate used in both studies? Many guidelines suggest that amoxicillin is the first-choice antibiotic for acute otitis media,^{2,3} and the use of broader-spectrum antimicrobial therapy for unselected cases is debatable.

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1. Marchisio P, Mira E, Klersy C, et al. Medical education and attitudes about acute otitis media guidelines: a survey of Italian pediatricians and otolaryngologists. *Pediatr Infect Dis J* 2009;28:1-4.
2. Leibovitz E, Broides A, Greenberg D, Newman N. Current management of pediatric acute otitis media. *Expert Rev Anti Infect Ther* 2010;8:151-61.
3. Marchisio P, Bellussi L, Di Mauro G, et al. Acute otitis media: from diagnosis to prevention: summary of the Italian guideline. *Int J Pediatr Otorhinolaryngol* 2010;74:1209-16.

DR. HOBERMAN AND COLLEAGUES REPLY: Newman and Shreves question our number of primary outcomes and our adherence to the study protocol. To measure symptomatic response adequately, and with official sanction to use coprimary patient-reported outcomes,¹ we settled on two — not four — primary outcomes: time to resolution of symptoms and symptom burden over time; each of these outcomes was measured in two ways. The four resulting measures were interrelated and were derived from a single set of symptom scores. We considered adjustment for multiple comparisons unnecessary; in general its application is debatable.^{2,3} Three of our four measures were described in the Primary Outcome Measure section of the protocol's Final Analysis Plan. The fourth was listed as secondary, but because it was closely related to one of the primary measures, we linked the two to form a single outcome. Diarrhea prompted discontin-

uation of treatment by the parents of only 6 of 144 children. We described the differences in symptom scores favoring antibiotic treatment as “modest”; more persuasive were the large differences in rates of clinical failure (16% among children who received amoxicillin-clavulanate vs. 51% among children who received placebo by day 10 to 12) as manifested by otoscopic evidence of continuing infection.

As Spiro and colleagues suggest, more aggressive analgesic administration might have resulted in smaller between-group differences in symptomatic response; differences in clinical-failure rates, however, would have been unaffected, and the use of topical therapy would have compromised otoscopic assessments. The cited trials of the approach involving the wait-and-see prescription lacked blinding (of parents), validation of diagnoses, and objective assessment of the outcome.^{4,5} In one of the trials,⁵ antibiotic prescriptions were eventually filled for 53% of children younger than 2 years of age in the group assigned to the wait-and-see prescription, suggesting that prompt treatment for those children might have been preferable.

It was not “remnant effusions,” as Grubb and Spaugh suggest, that we considered indicative of persisting middle-ear infection; rather, it was persistence of bulging of the tympanic membrane in addition to otalgia or marked erythema of the membrane. With all data included, the numbers needed to harm for the occurrence of diarrhea and of diaper dermatitis were 10 and 6, respectively. The number needed to treat to prevent clinical failure by day 10 to 12 was 3.

No data provide evidence to support the assertion by Del Mar and colleagues that the appearance of the tympanic membrane is “of doubtful clinical importance” in assessing outcome. Our stringent diagnostic criteria distinguished between children with and without acute otitis media, not between sicker and less sick subgroups of patients with the disease. We excluded no children for being “insufficiently ill.” Children who presented with low symptom scores were excluded only because symptomatic response was a study outcome; all such children had bulging tympanic membranes.

In response to Crocco and to Principi and colleagues: we chose amoxicillin-clavulanate for our proof-of-concept study as the most effective antimicrobial agent available. The use of amoxicillin may or may not have led to similar results;

it remains our preferred first-line antimicrobial agent.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Guidance for industry — patient-reported outcome measures: use in medical product development to support labeling claims. Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, 2009. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.)
2. Cook RJ, Farewell VT. Multiplicity in the design and analysis of clinical trials. *J R Stat Soc A* 1996;159:93-110.
3. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998;316:1236-8.
4. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavy J. Pragmatic randomized controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;322:336-42.
5. Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. *JAMA* 2006;296:1235-41.

DRS. RUOHOLA AND TÄHTINEN REPLY: We appreciate the comments about our study and that of Hoberman et al. The two studies were independent of each other, and neither aimed to evaluate the optimal duration of treatment, dose of medication, or antimicrobial agent for acute otitis media. Also, the studies did not evaluate the wait-and-see prescription. Amoxicillin-clavulanate was chosen to avoid underestimation of the treatment effect because of nonoptimal antimicrobial coverage.

Our inclusion criteria were criticized for being stringent. No child was excluded for being insufficiently ill, and only three children were excluded because of severe symptoms. Previously, we found that the children who were included and the children who were excluded had equal symptoms.¹ Other investigators have found that pneumococcal vaccination causes only minor changes in the incidence and bacterial cause of acute otitis media.² We used a stringent diagnostic definition because we saw no rationale to study the efficacy of antimicrobial treatment in children who do not have true acute otitis media but rather only a red eardrum or clear fluid in the middle ear. Overdiagnosis is also our major concern.

Our primary outcome was integrated into the

diagnostic criteria. As Figure 4 of our article showed, acute otitis media is not always spontaneously remitting: otoscopic signs had not improved at all or had deteriorated by the end-of-treatment visit in 38% of placebo recipients. Even according to an alternative definition of treatment failure, solely based on symptoms, antimicrobial treatment was beneficial. Our component of symptomatic failure was based on parental assessment of the child's overall condition, because no symptom is specific to acute otitis media and the spectrum of symptoms varies among children and also among days in one child. Our holistic approach, easily applicable in clinical practice, did not measure any individual symptom; rather, it measured all symptoms simultaneously, including adverse events. Thus, the comparison of the number needed to treat and the number needed to harm does not provide balance because, in our study, the clinical effects of harms are included in the number needed to treat.

We share the concern about the liberal use of antimicrobial agents. We agree that sicker patients benefit more from treatment, and this is what

our study showed — “sicker” patients were those with bulging eardrums. If antimicrobial treatment were restricted only to those patients, we would expect the use of antimicrobials to be decreased.

We acknowledge the diagnostic challenges and are aware that more education, as well as new technology, is urgently needed. However, we think that basing guidelines on the acceptance of the poor quality of diagnostics is not justified because they would lead to the withholding of treatment from children with true acute otitis media.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Laine MK, Tähtinen PA, Ruuskanen O, Huovinen P, Ruohola A. Symptoms or symptom-based scores cannot predict acute otitis media at otitis-prone age. *Pediatrics* 2010;125(5):e1154-e1161.
2. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. *JAMA* 2010;304:2161-9.

Dialysis Catheters and Recombinant Tissue Plasminogen Activator

TO THE EDITOR: Hemmelgarn et al. (Jan. 27 issue)¹ evaluated prophylactic recombinant tissue plasminogen activator (rt-PA) for preventing dialysis catheter malfunction. I have a few caveats regarding their interpretation of the results.

The authors used a surrogate outcome (blood flow during dialysis) to define catheter malfunction. A more clinically meaningful end point, many would think, is the need for catheter removal. Among those catheters in the heparin group in which malfunction developed, 50% required rt-PA instillation, but only 7.5% required removal because of malfunction (see Table 5 in the Supplementary Appendix, available with the full text of the article at NEJM.org). In other words, rt-PA instillation usually restored catheter patency. Rather than instilling rt-PA weekly, it might be more cost-effective to use heparin locks alone and reserve rt-PA instillation for catheters in which malfunction develops.

The authors observed less catheter-related bacteremia in the rt-PA group, which they attributed to prevention of bacterial biofilm. They enrolled only patients with incident-dialysis catheters. It is

unknown whether rt-PA prevents catheter-related bacteremia in prevalent-dialysis catheters, which already have an established biofilm. Antimicrobial locking solutions, which reduce the incidence of catheter-related bacteremia in patients with catheters for both incident and prevalent dialysis,² may be preferred to prophylactic rt-PA instillation.

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No potential conflict of interest relevant to this letter was reported.

1. Hemmelgarn BR, Moist LM, Lok CE, et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med* 2011;364:303-12.
2. Allon M. Prophylaxis against dialysis catheter-related bacteremia: a glimmer of hope. *Am J Kidney Dis* 2008;51:165-8.

THE AUTHORS REPLY: We agree with Allon that rt-PA has been shown to be an effective strategy to treat catheter malfunction. As we found in our study, rt-PA as prophylaxis can reduce the risk of catheter malfunction and the requirement for