To the Editor: Hoberman et al. (Jan. 13 issue) 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.”

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.

David H. Newman, M.D.
Mount Sinai School of Medicine
New York, NY
davidnewman44@mac.com

Ashley E. Shreves, M.D.
St. Luke’s–Roosevelt Hospital Center
New York, NY

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

2. Consolidated Standards of Reporting Trials (CONSORT).

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. 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. 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. Further comparative trials that include the wait-and-see approach are warranted before concluding that acute otitis media uniformly requires immediate antibiotic treatment.

This Week’s Letters

1775 Treatment of Acute Otitis Media in Children
1779 Dialysis Catheters and Recombinant Tissue Plasminogen Activator
1780 Iniparib in Metastatic Triple-Negative Breast Cancer
1781 Glycerol Kinase Deficiency in Adult Hypoglycemic Acidemia
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. 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.

Mark S. Grubb, M.D.
David C. Spaugh, B.B.A.
Northwest Pediatric Research Associates
Puyallup, WA
mgrubb@nwpediatricresearch.org

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.


TO THE EDITOR: The two recent trials reported in the Journal by Hoberman et al. and Tähtinen et al. and the accompanying editorial 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 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.

Chris Del Mar, M.D.
Paul Glasziou, Ph.D.
Bond University
Gold Coast, QLD, Australia
cdelmar@bond.edu.au

Maroeska Rovers, Ph.D.
University Medical Center Utrecht
Utrecht, the Netherlands

No potential conflict of interest relevant to this letter was reported.
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 underestimated. 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 review 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, nor do they prove that amoxicillin–clavulanate is the best choice of antibiotic.

Anthony G. Crocco, M.D.
Alberta Children’s Hospital
Calgary, AB, Canada
anthonycrocco@hotmail.com

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


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. 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, and the use of broader-spectrum antimicrobial therapy for unselected cases is debatable.

Nicola Principi, M.D.
Susanna Esposito, M.D.
Fondazione Istituto di Ricerca e Cura a Carattere Scientifico
Ca’ Granda Ospedale Maggiore Policlinico
Milan, Italy
susanna.esposito@unimi.it
Paola Marchisio, M.D.
Università degli Studi di Milano
Milan, Italy

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


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, 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.

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 use of topical therapy would have compromised 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.

Alejandro Hoberman, M.D.
Jack L. Paradise, M.D.
Howard E. Rockette, Ph.D.
University of Pittsburgh
Pittsburgh, PA
hoberman@chp.edu

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


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. Other investigators have found that pneumococcal vaccination causes only minor changes in the incidence and bacterial cause of acute otitis media. 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
Dialysis Catheters and Recombinant Tissue Plasminogen Activator

TO THE EDITOR: Hemmelgarn et al. (Jan. 27 issue) 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, may be preferred to prophylactic rt-PA instillation.

Michael Allon, M.D.
University of Alabama at Birmingham
Birmingham, AL
mdallon@uab.edu

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


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...