A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

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ABSTRACT

BACKGROUND
The efficacy of antimicrobial treatment in children with acute otitis media remains controversial.

METHODS
In this randomized, double-blind trial, children 6 to 35 months of age with acute otitis media, diagnosed with the use of strict criteria, received amoxicillin–clavulanate (161 children) or placebo (158 children) for 7 days. The primary outcome was the time to treatment failure from the first dose until the end-of-treatment visit on day 8. The definition of treatment failure was based on the overall condition of the child (including adverse events) and otoscopic signs of acute otitis media.

RESULTS
Treatment failure occurred in 18.6% of the children who received amoxicillin–clavulanate, as compared with 44.9% of the children who received placebo (P<0.001). The difference between the groups was already apparent at the first scheduled visit (day 3), at which time 13.7% of the children who received amoxicillin–clavulanate, as compared with 25.3% of those who received placebo, had treatment failure. Overall, amoxicillin–clavulanate reduced the progression to treatment failure by 62% (hazard ratio, 0.38; 95% confidence interval [CI], 0.25 to 0.59; P<0.001) and the need for rescue treatment by 81% (6.8% vs. 33.5%; hazard ratio, 0.19; 95% CI, 0.10 to 0.36; P<0.001). Analgesic or antipyretic agents were given to 84.2% and 85.9% of the children in the amoxicillin–clavulanate and placebo groups, respectively. Adverse events were significantly more common in the amoxicillin–clavulanate group than in the placebo group. A total of 47.8% of the children in the amoxicillin–clavulanate group had diarrhea, as compared with 26.6% in the placebo group (P<0.001); 8.7% and 3.2% of the children in the respective groups had eczema (P=0.04).

CONCLUSIONS
Children with acute otitis media benefit from antimicrobial treatment as compared with placebo, although they have more side effects. Future studies should identify patients who may derive the greatest benefit, in order to minimize unnecessary antimicrobial treatment and the development of bacterial resistance. (Funded by the Foundation for Paediatric Research and others; ClinicalTrials.gov number, NCT00299455.)
Acute otitis media is the most common bacterial infection during early childhood. Antimicrobial agents have been the primary treatment for this infection since the 1950s, when the first studies showed that antimicrobial therapy improved the outcome. Nevertheless, there is no consensus regarding the optimal management of acute otitis media. Because the treatment of acute otitis media is a major reason for the use of antimicrobial agents in the outpatient setting, experts have called for these agents to be used judiciously. Several guidelines for the management of acute otitis media recommend an observation period before antimicrobial therapy is even considered. These recommendations are based largely on meta-analyses that concluded that for 1 child to have relief of symptoms, 7 to 17 children must be treated with antimicrobial agents. However, some experts have suggested that the original studies included in the meta-analyses had important limitations, such as biases in patient selection, varying diagnostic criteria, and suboptimal spectrum or dosage of antimicrobial agents.

We conducted a randomized, double-blind, placebo-controlled study of the efficacy of antimicrobial therapy in the age group with the highest incidence of acute otitis media. Our aim was to assess the efficacy of antimicrobial treatment for acute otitis media when strict diagnostic criteria are used and the antimicrobial coverage and dosage of the active treatment are adequate.

Methods

Patients and Diagnostic Criteria

Children 6 to 35 months of age with acute symptoms were eligible for our diagnostic screening. A list of the exclusion criteria, along with descriptions and explanations, is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Children in whom acute otitis media was diagnosed per protocol were eligible for inclusion in the study. Three overall criteria were required for the diagnosis of acute otitis media (see videos 1, 2, and 3). First, middle-ear fluid had to be detected by means of pneumatic otoscopic examination that showed at least two of the following tympanic-membrane findings: bulging position, decreased or absent mobility, abnormal color or opacity not due to scarring, or air–fluid interfaces. Second, at least one of the following acute inflammatory signs in the tympanic membrane had to be present: distinct erythematous patches or streaks or increased vascularity over full, bulging, or yellow tympanic membrane. Third, the child had to have acute symptoms, such as fever, ear pain, or respiratory symptoms. A parent of each child provided written informed consent. The protocol, which is available at NEJM.org, was approved by the ethics committee of the Hospital District of Southwest Finland. The authors vouch for the accuracy and completeness of the reported data and the fidelity of this report to the study protocol.

Study Design

This was a randomized, double-blind, placebo-controlled study that was initiated by the investigators and was conducted independently of any commercial entities. Our objective was to study the efficacy of antimicrobial treatment with respect to the resolution of symptoms and signs of acute otitis media. The hypothesis was that amoxicillin–clavulanate would reduce the risk of treatment failure.

At the enrollment visit (day 1), the patient’s symptoms, medical history, and demographic and clinical characteristics were recorded, a nasopharyngeal sample was obtained, and a clinical examination was performed that included thorough otoscopic and tympanometric examinations. Details of nasopharyngeal sampling, bacterial culturing, analyses of resistance of the bacteria to antimicrobial agents, and otoscopic examinations are provided in the Supplementary Appendix.

Eligible patients were randomly assigned to receive amoxicillin–clavulanate (40 mg of amoxicillin per kilogram of body weight per day plus 5.7 mg of clavulanate per kilogram per day, divided into two daily doses) or placebo for 7 days. The placebo was similar to the active treatment in appearance and taste. (For a description of the study drugs, the randomization procedure, and the procedure for concealment of study assignments, see the Supplementary Appendix.) Parents were given a diary and were asked to record symptoms, doses of study drugs and any other medications, absenteeism of the child from day care and of the parent from work, and adverse events. Fever was defined as a body temperature of 38°C or higher. We encouraged the use of analgesic and antipyretic agents and allowed the use of analgesic ear drops and decongestant nose drops or sprays.
The first visit after the enrollment visit was scheduled for 2 days after the initiation of the study drug (day 3). The end-of-treatment visit was scheduled for the day after the last dose of study drug was administered (i.e., on day 8). At that visit, diaries and from reports by the study physicians were ascertained from entries by the parents in the diary and from reports by the study physicians after they questioned the parents.

**OUTCOMES**

The primary outcome was the time to treatment failure, which was a composite outcome consisting of six independent components: no improvement in overall condition by the first scheduled visit (day 3) (i.e., unless parents thought that their child’s overall condition was improving, the case was categorized as treatment failure), a worsening of the child’s overall condition at any time, no improvement in otoscopic signs by the end-of-treatment visit on day 8 (see videos 4 through 8), perforation of the tympanic membrane at any time, severe infection (e.g., mastoiditis or pneumonia) necessitating systemic open-label antimicrobial treatment at any time, and any other reason for stopping the study drug (e.g., an adverse event or nonadherence to the study drug) at any time. The time of treatment failure was the study day on which the study physician confirmed any one of the components for the first time. Several components could be confirmed concurrently, but this was not a requirement. The first two components were based on the parents’ assessment of their child’s overall condition, including adverse events (healthy, better, no improvement, or worse) as reported to the study physician; the other four components were based on recordings in the diary. The treatment result, as of the end-of-treatment visit, was based on the parents’ assessment of the child’s overall condition as reported to the study physician and on the otoscopic signs. Adverse events were ascertained from entries by the parents in the diary and from reports by the study physicians after they questioned the parents.

**STATISTICAL ANALYSIS**

We estimated that with 260 patients, the study would have 90% power to detect an absolute reduction of 15 percentage points in the rate of treatment failure in the amoxicillin–clavulanate group as compared with the placebo group, assuming a 25% rate of treatment failure in the placebo group, with a type I error of 0.05. We planned to enroll 320 patients to account for a possible 20% rate of withdrawal from the study.

The Kaplan–Meier method was used to analyze time-to-event data with the use of the log-rank test; hazard ratios and confidence intervals were calculated on the basis of a Cox regression model. Categorical outcomes were compared with the use of the chi-square test. Student’s t-test was used to compare means. Absolute percentage-point differences in rates and 95% confidence intervals are provided.

All analyses were performed on data from the intention-to-treat population. All reported P values are two-sided and have not been adjusted for multiple testing. All analyses were performed with the use of SPSS software, version 16.0.

**RESULTS**

**STUDY PATIENTS**

The intention-to-treat population comprised 319 patients — 161 in the amoxicillin–clavulanate group and 158 in the placebo group (Fig. 1 and Table 1). The rate of adherence to the study drug was approximately 94% as assessed according to diary entries and approximately 99% as assessed according to the amount of returned study drug capsules. Adherence to the study drug was estimated. Parents were told to contact a study physician whenever they thought that their child’s condition had not improved satisfactorily or had worsened; an additional visit was arranged on any day of the week. Whenever possible, the same study physician examined the patient at consecutive visits. At each visit, the study physician first asked the parents for their assessment of their child’s overall condition, which was recorded as healthy, better, no improvement, or worse. The child was then examined by the physician. At any visit, the physician could switch from the study drug to rescue treatment if the child’s overall condition or otoscopic signs warranted the change (see the Supplementary Appendix). Parents were encouraged to keep their children in the study for follow-up assessments even if they had discontinued the study drug.
Primary Outcome

Treatment failure occurred in 30 of the 161 children (18.6%) who received amoxicillin–clavulanate and in 71 of the 158 children (44.9%) who received placebo (P < 0.001). The Kaplan–Meier analysis showed that a separation between the curves for the two groups was already apparent at the first scheduled visit, on day 3 (Fig. 2A). At that time, 13.7% of the children in the amoxicillin–clavulanate group and 25.3% in the placebo group had treatment failure. The separation between the curves continued to widen during the subsequent follow-up and peaked at the end-of-treatment visit on day 8. Overall, amoxicillin–clavulanate reduced the risk of treatment failure by 62% (hazard ratio, 0.38; 95% confidence interval [CI], 0.25 to 0.59; P < 0.001). To avoid treatment failure in 1 child, 3.8 children (95% CI, 2.7 to 6.2) needed to be
treated with amoxicillin–clavulanate. Each of the six components of the primary outcome occurred less often in the amoxicillin–clavulanate group than in the placebo group (Fig. 3). The determination of treatment failure was based on overall condition in 27 children in the amoxicillin–clavulanate group and 48 in the placebo group; on overall condition and otoscopic signs in 0 and 106.

Table 1. Selected Baseline Characteristics of the Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amoxicillin–Clavulanate Group (N = 161)</th>
<th>Placebo Group (N = 158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — mo</td>
<td>Mean 16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Range 6–35</td>
<td>6–35</td>
</tr>
<tr>
<td>Previous episodes of acute otitis media — no.</td>
<td>Mean 2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Range 0–10</td>
<td>0–10</td>
</tr>
<tr>
<td>Time since previous episode of acute otitis media — mo*</td>
<td>Mean 3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Range 0–22</td>
<td>0–15</td>
</tr>
<tr>
<td>≥1 dose of pneumococcal conjugate vaccine — no. (%)</td>
<td>3 (1.9)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>≥1 dose of influenza vaccine — no. (%)</td>
<td>17 (10.6)</td>
<td>24 (15.2)</td>
</tr>
<tr>
<td>≥1 dose of <em>Haemophilus influenzae</em> type b vaccine — no. (%)</td>
<td>161 (100.0)</td>
<td>158 (100.0)</td>
</tr>
<tr>
<td>Symptoms — no. (%)</td>
<td>Highest measured temperature within the previous 24 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤38°C: no fever</td>
<td>97 (60.2)</td>
</tr>
<tr>
<td></td>
<td>38.0–38.9°C</td>
<td>40 (24.8)</td>
</tr>
<tr>
<td></td>
<td>39.0–39.9°C</td>
<td>21 (13.0)</td>
</tr>
<tr>
<td></td>
<td>≥40°C</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Ear pain</td>
<td>Reported by parents 123 (76.4)</td>
<td>126 (79.7)</td>
</tr>
<tr>
<td></td>
<td>Reported by child</td>
<td>24 (14.9)</td>
</tr>
<tr>
<td></td>
<td>Respiratory symptoms</td>
<td>156 (96.9)</td>
</tr>
<tr>
<td></td>
<td>Otoscopic signs at enrollment — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral acute otitis media†</td>
<td>60/159 (37.7)</td>
</tr>
<tr>
<td></td>
<td>Full or bulging tympanic membrane</td>
<td>149/161 (92.5)</td>
</tr>
<tr>
<td></td>
<td>Bulla formation</td>
<td>19/161 (11.8)</td>
</tr>
<tr>
<td>Pathogenic bacteria in nasopharyngeal sample — no./total no. (%)</td>
<td>Any‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150/157 (95.5)</td>
<td>153/158 (96.8)</td>
</tr>
<tr>
<td></td>
<td>*Streptococcus pneumoniae§</td>
<td>100/157 (63.7)</td>
</tr>
<tr>
<td></td>
<td>*H. influenzae</td>
<td>31/157 (19.7)</td>
</tr>
<tr>
<td></td>
<td>*Moraxella catarrhalis</td>
<td>117/157 (74.5)</td>
</tr>
<tr>
<td></td>
<td>*S. pyogenes</td>
<td>2/157 (1.3)</td>
</tr>
</tbody>
</table>

* Data were missing for three patients in the amoxicillin–clavulanate group and two patients in the placebo group.
† Data were missing for two patients in the amoxicillin–clavulanate group and two patients in the placebo group, in whom an adequate view of the contralateral tympanic membrane was not possible owing to thick cerumen.
‡ All strains were susceptible to amoxicillin–clavulanate.
§ Strains with intermediate susceptibility to penicillin were detected in 18 samples in the amoxicillin-clavulanate group and 21 samples in the placebo group. In the amoxicillin–clavulanate group, one strain of *S. pneumoniae* was fully resistant to penicillin.
6 children in the two groups, respectively; on otoscopic signs in 2 and 15 children, respectively; and on any reason to stop the study drug in 1 and 2 children, respectively (Table 2 in the Supplementary Appendix). In a subgroup analysis, the treatment effect was similar in children with unilateral acute otitis media and in those with bilateral acute otitis media (Table 3 in the Supplementary Appendix).

SECONDARY OUTCOMES
Rescue treatment was initiated in 11 of the 30 children in the amoxicillin–clavulanate group (36.7%) and in 53 of the 71 children in the placebo group (74.6%) who had treatment failure (P<0.001). The need for rescue treatment was decreased by 81% with amoxicillin–clavulanate as compared with placebo (hazard ratio, 0.19; 95% CI, 0.10 to 0.36; P<0.001) (Fig. 2B). Thus, rescue treatment was required in the case of 6.8% and 33.5% of all the children in the amoxicillin–clavulanate group and placebo group, respectively (Fig. 3, and Table 2 in the Supplementary Appendix).

Contralateral acute otitis media developed in 13 of the 159 children in the amoxicillin–clavulanate group (8.2%) and 29 of the 156 children in the placebo group (18.6%) for whom data were available (P=0.007) (Fig. 3). There was no significant between-group difference in the use of analgesic or antipyretic agents (Fig. 3). Among the children who received analgesic or antipyretic agents, the mean duration of treatment was 3.6 days and 3.4 days in the amoxicillin–clavulanate and placebo groups, respectively (P=0.45). Absenteeism from day care was reported for 107 of 672 follow-up days (15.9%) among day-care attendees and for 144 of 568 follow-up days (25.4%) among day-care attendees in the placebo group (a reduction of 9.4 percentage points with amoxicillin–clavulanate; 95% CI, −13.9 to −4.9; P<0.001). Parents of day-care attendees in the amoxicillin–clavulanate group missed significantly fewer workdays than did parents of day-care attendees in the placebo group (81 days [12.1%] vs. 101 days [17.8%], a reduction of 5.7 percentage points; 95% CI, −9.7 to −1.8; P=0.005).

At the end-of-treatment visit, there was a significantly better treatment result with respect to both overall condition and otoscopic signs with amoxicillin–clavulanate than with placebo (P<0.001 for both outcomes) (Fig. 4). Overall condition had not improved or had worsened in 11 children (6.8%) in the amoxicillin–clavulanate group, as compared with 47 children (29.7%) in the placebo group (22.9 percentage points less with amoxicillin–clavulanate; 95% CI, −31.4 to −14.4). Otoscopic signs had not improved or had worsened in 8 children (5.0%) and 60 children (38.0%) in
the amoxicillin–clavulanate and placebo groups, respectively (a decrease of 33.0 percentage points with amoxicillin–clavulanate; 95% CI, −42.0 to −24.0). In 1 child (0.6%) in the amoxicillin–clavulanate group and 10 children (6.3%) in the placebo group, both overall condition and otoscopic signs had worsened (a decrease of 5.7 percentage points with amoxicillin–clavulanate; 95% CI, −9.7 to −1.7), whereas 13 children (8.1%) in the amoxicillin–clavulanate group and 4 (2.5%) in the placebo group were completely healthy with respect to overall condition and otoscopic signs (an increase of 5.5 percentage points with amoxicillin–clavulanate; 95% CI, 0.6 to 10.5).

Treatment with amoxicillin–clavulanate significantly accelerated the resolution of fever, poor appetite, decreased activity, and irritability. The effect of treatment on the resolution of fever was already seen 6 hours after the first dose had been administered, and the effect on the resolution of the symptoms of poor appetite, decreased activity, and irritability was seen on the second study day. There was no significant effect of amoxicillin–clavulanate on the resolution of ear pain as reported by parents, ear pain as reported by the children, ear rubbing, restless sleep, or excessive crying (Fig. 2 in the Supplementary Appendix).

After the end of the study-treatment period, children who had received amoxicillin–clavulanate had less pathogenic bacteria in the nasopharynx than did children who had received placebo (Table 4 in the Supplementary Appendix). However, antimicrobial resistance was identified from the nasopharyngeal samples of one child in the amoxicillin–clavulanate group. On study days 1 and 8, we detected an isolate of *Streptococcus pneumoniae* that first showed intermediate resistance and later showed full resistance to penicillin.

**ADVERSE EVENTS**

An adverse event occurred in 85 children (52.8%) in the amoxicillin–clavulanate group and in 57 children (36.1%) in the placebo group (an increase of 16.7 percentage points with amoxicillin–clavulanate; 95% CI, 5.8 to 27.6; P = 0.003) (Table 2). There were no cases of mastoiditis. Two children in the placebo group had severe infection — one had pneumococcal bacteremia and the other had radiographically confirmed pneumonia. The most com-
mon adverse event was diarrhea, which affected 77 children (47.8%) in the amoxicillin–clavulanate group and 42 (26.6%) in the placebo group (an increase of 21.2 percentage points with amoxicillin–clavulanate; 95% CI, 10.6 to 31.9). No watery or bloody diarrhea was reported, and diarrhea did not result in discontinuation of the study drug. Eczema was significantly more common in the amoxicillin–clavulanate group than in the placebo group. Children with severe infections and perforations of the tympanic membrane were given rescue treatment. All other adverse events resolved spontaneously by the end-of-treatment visit (day 8), except in three children with diarrhea in each group and in one child in the placebo group in whom exanthema developed on day 8 and lasted for 4 days.

**Discussion**

Our study shows that amoxicillin–clavulanate is superior to placebo for the treatment of acute otitis media. The primary outcome, the time to treatment failure, incorporated six independent components, including acute symptoms and otoscopic signs that are required for the diagnosis of acute otitis media. Moreover, our composite outcome measured the net effect of the treatment, because the assessment of the child’s overall condition included adverse events. This study was not powered to assess the effect of treatment on each component of the composite primary outcome. Nonetheless, amoxicillin–clavulanate significantly reduced two components — worsening of the child’s overall condition and lack of improvement in otoscopic signs — as well as the combined occurrence of perforations of the tympanic membrane and severe infections. Antimicrobial treatment had a more beneficial effect on acute otitis media in our study than in previous randomized, double-blind, placebo-controlled studies.21-30 Previous studies have shown that the higher the failure rate is in the placebo group, the more antimicrobial treatment is shown to be superior. In a study by Kaleida et al.,26 failure rates in the placebo group were 8% among patients who were not severely ill and 24% among those who were severely ill, and the respective absolute differences in failure rates between the antimicrobial-therapy group and the placebo group were 4 percentage points and 12 percentage points, respectively. In the placebo group in our study, the failure rate was even higher — 44.9%, with a 26-percentage-point difference between the groups. The number needed to treat for 1 child to benefit from antimicrobial therapy, as calculated on the basis of the results of our study, is 3.8, as compared with 7 to 17 on the basis of the meta-analyses.11-15,31,32 A marked difference between the amoxicillin–clavulanate group and the placebo group was also seen in the need for rescue treatment. Rescue treatment was initiated in the children receiving antimicrobial treatment.
The resolution of several symptoms was accelerated with amoxicillin–clavulanate therapy, as compared with placebo. This was an unexpected finding, since most patients in both groups received analgesic or antipyretic agents, and it has been emphasized that symptoms often resolve spontaneously.\textsuperscript{33,34} Furthermore, although bacteria can virtually always be found in the middle ear during an episode of acute otitis media,\textsuperscript{35,36} the symptoms are not specific to acute otitis media but instead resemble those that are manifested during viral-type respiratory infections.\textsuperscript{37} Since we analyzed the treatment effect on symptoms with a time-to-event approach, as suggested by some experts,\textsuperscript{38,39} we were able to observe that the effect of amoxicillin–clavulanate became apparent early. The earliest treatment effect was seen with respect to the resolution of fever. The rapid resolution of fever during the first day of antimicrobial treatment is well documented in the case of childhood pneumonia.\textsuperscript{40,41} In the current study, the effect of the treatment on other symptoms was seen on the second study day. From the third study day onward, rescue treatment was initiated significantly more often in children in the amoxicillin–clavulanate group. As highlighted by Mygind et al., assessment of the treatment effect on symptoms should take into account the need for rescue treatment for the most symptomatic patients.\textsuperscript{22} Despite the tendency for symptoms to resolve spontaneously, which was also seen in our study, our results challenge the view that antimicrobial treatment of acute otitis media should be withheld to see whether symptoms will resolve without such treatment.

Since no symptom is specific to acute otitis media in children of preverbal age, it is also important to examine the treatment effect on the site of the infection itself — namely, the middle ear. At the end of treatment, otoscopic signs had not improved or had worsened in 5.0% and 38.0% of children in the amoxicillin–clavulanate and placebo groups, respectively. Whether these children were at risk for the persistent presence of fluid in the middle ear is a question for further research. The results of this study are consistent with the results of our previous study of acute otitis media with tympanostomy-tube otorrhea, which showed that antimicrobial therapy in our study approximately as often as in previous studies.\textsuperscript{21,24,26–30} In contrast, a third of the children in the placebo group in our study needed rescue treatment, as compared with an average of 12% in other studies. Our decision to provide rescue treatment for children who had improvement in overall condition but no improvement in otoscopic signs can be criticized. Nonetheless, these children still had clinically manifest acute otitis media after a 1-week observation period. Even when these children were excluded from the analysis, children in the placebo group needed rescue treatment significantly more often than did those in the amoxicillin–clavulanate group. The greater beneficial effect of antimicrobial therapy in our study than in previous studies results primarily from methodologic differences. Only children who met stringent diagnostic criteria for acute otitis media were included in our study, and we did not exclude patients according to the severity of symptoms or otoscopic signs. In addition, we used an active treatment with adequate dosage and antimicrobial coverage.
Antimicrobial Treatment of Acute Otitis Media

From a different perspective, our results can also be interpreted as showing that half the children in the placebo group did not have treatment failure and two thirds did not need rescue treatment. These findings suggest that not all patients with acute otitis media need antimicrobial treatment. It will be important in the future to characterize patients who do not need antimicrobial treatment. The identification of prognostic markers, together with the use of stringent diagnostic criteria, could reduce the use of antimicrobial agents in the treatment of acute otitis media. Reduced use of antimicrobial agents may limit the development of resistant bacteria and increase the chances that the subsequent use of antimicrobial agents, when truly indicated, would be beneficial.

In conclusion, our study provides evidence that in children 6 to 35 months of age, the treatment of acute otitis media with an antimicrobial agent that gives adequate coverage — such as amoxicillin–clavulanate — is beneficial. Antimicrobial treatment reduces the risk of treatment failure by improving both overall condition and otoscopic signs.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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