Prognostic Factors for Treatment Failure in Acute Otitis Media

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abstract

BACKGROUND AND OBJECTIVES: Antimicrobial treatment is effective in the management of acute otitis media (AOM), but approximately half of the children may recover without antimicrobial agents. By identifying patients who may not require antimicrobial treatment for the management of AOM, the use of antimicrobial agents could be substantially reduced. Our aim was to identify subgroups of children with AOM who would benefit most from antimicrobial treatment and children who could be suitable for initial observation.

METHODS: This is a secondary analysis of randomized, double-blind, placebo-controlled trial. Children 6 to 35 months of age with AOM *(N* = 319) were randomly allocated to receive amoxicillin-clavulanate (40/5.7 mg/kg per day) or placebo for 7 days. Our primary outcome was time until treatment failure.

RESULTS: Treatment failure occurred in 31.7% of all children. Older age (24–35 months) and peaked tympanogram at entry decreased the hazard for treatment failure (hazard ratio, 0.53; 95% confidence interval [CI], 0.29 to 0.96; *P* = .04; and hazard ratio, 0.43; 95% CI, 0.21 to 0.88; *P* = .02, respectively). The rate difference for treatment failure between antimicrobial treatment and placebo groups was highest among children with severe bulging of the tympanic membrane (11.1% vs 64.1%; rate difference −53.0%; 95% CI, −73.5% to −32.4%), resulting in a number needed to treat of 1.9.

CONCLUSIONS: Children with severe bulging of the tympanic membrane seem to benefit most from antimicrobial treatment of AOM. On the other hand, children with peaked tympanogram (A and C curves) may be optimal candidates for initial observation.

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WHAT'S KNOWN ON THIS SUBJECT: Antimicrobial treatment is effective in the management of acute otitis media, but approximately half of the children may recover without antimicrobial agents. Prognostic factors for treatment failure remain uncertain.

WHAT THIS STUDY ADDS: Children with severe bulging of the tympanic membrane benefit most from antimicrobial treatment of acute otitis media, and children with peaked tympanogram may be treated with observation. Clinicians can use these results when discussing the treatment decisions with the parents.

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Acute otitis media (AOM) is one of the most common bacterial infections in young children and a major indication for antimicrobial treatment in the outpatient setting.[1] Recent studies have shown antimicrobial agents to be effective in the management of AOM. However, even when stringent diagnostic criteria are used, approximately half of the children recover without antimicrobial treatment.[2,3] Because bacterial resistance to antimicrobial agents is a major public health problem worldwide, every effort should be made to avoid unnecessary antimicrobial treatment. Some unnecessary antimicrobial treatment could be avoided by identifying patients who may be less likely to require it for the management of AOM.

Several AOM studies have attempted to identify patients who benefit most from antimicrobial treatment.[2,4–8] The results, however, have been inconsistent and the prognostic factors have differed based on study designs, study populations, or the antimicrobial agents that were used. A meta-analysis with individual patient data summarized data from 6 individual studies and concluded that children <2 years of age with bilateral AOM and children with otorrhea seem to benefit the most from antimicrobial treatment.[9] This meta-analysis was used as one of the main references in the recently published clinical practice guideline for the diagnosis and management of AOM by the American Academy of Pediatrics (AAP).[10] The new guideline emphasizes stringent diagnostic criteria for AOM and offers an initial observation option for children <2 years of age with nonsevere unilateral AOM and for all children >2 years of age with nonsevere AOM. However, it was concluded that the most efficient and acceptable methods of initial observation should be studied to establish the balance between benefits and potential risks to the child.

We conducted a randomized, double-blind, placebo-controlled study of the efficacy of antimicrobial treatment of AOM in children 6 to 35 months of age.[3] The aim of this preplanned secondary analysis was to identify subgroups of children who would benefit most from antimicrobial treatment and children who could be suitable for initial observation with analgesic treatment and close follow-up.

METHODS

Study Design and Diagnostic Criteria

This is a secondary analysis of a randomized, double-blind, placebo-controlled study conducted within primary care between March 2006 and December 2008 in Turku, Finland.[3] Children 6 to 35 months of age with acute symptoms were eligible for diagnostic screening. Three overall criteria were required for the diagnosis of AOM. First, middle ear fluid had to be detected by pneumatic otoscopy showing at least 2 of the following tympanic-membrane findings: bulging position, decreased or absent mobility, abnormal color or opacity not because of scarring, or air-fluid interfaces. Second, at least 1 of the following acute inflammatory signs on the tympanic membrane had to be present: distinct erythematous patches, streaks, or increased vascularity over either a full, bulging or yellow tympanic membrane. Third, the child had to have acute symptoms, such as fever, ear pain, or respiratory symptoms. The exclusion criteria have been described in detail elsewhere.[3] A parent of each child provided written informed consent. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland.

Study Visits

At the enrollment visit (day 1), the patient's symptoms, medical history, and demographics were recorded. After that, a clinical examination, including thorough otoscopic and tympanometric examinations, was performed. All 5 study physicians were trained otoscopists, and the authors made over 90% of the diagnoses with an excellent agreement (κ values from 0.80 to 0.92). Eligible patients were randomly assigned to receive amoxicillin-clavulanate (40/5.7 mg/kg per day, divided into 2 daily doses) or placebo for 7 days. The placebo was similar to the active treatment in appearance and taste. The randomization procedure, concealment of the study drugs, and the handling of the study drugs have been described in detail elsewhere.[3] At the end of the enrollment visit the study physician took a nasopharyngeal sample for the detection of pathogenic bacteria and respiratory viruses.[11]

All children had the first scheduled follow-up visit within 48 to 72 hours after study entry, and the end-of-treatment visit was 1 day after the last dose of study drug or the rescue treatment. At all visits, the study physician first asked the parents for their assessment of the child's overall condition, which was recorded as healthy, better, no improvement, or worse. Then a clinical examination, including pneumatic otoscopy examination, was performed. If the child's overall condition had not improved satisfactorily or had worsened, the physician could switch from the study drug to rescue treatment, which was an open label antimicrobial treatment, primarily amoxicillin-clavulanate (40/5.7 mg/kg per day) for 7 days. The allocation of each participant was kept blinded until the completion of the whole trial, although the initial study drug was discontinued. Additional visits were arranged whenever needed.

Outcome

Our primary outcome was the time until treatment failure. Treatment failure consisted of 6 independent components: no improvement in overall condition by day 3, a worsening of the child's overall condition at any time, no improvement in otoscopic signs by day 8, perforation of the tympanic membrane at any time, development of severe infection, or any other reason to discontinue the study drug (eg, adverse event or nonadherence to the study drug) at any time. In this secondary analysis, our main aim was to identify prognostic factors that were more or less common in children with treatment failure.

Statistical Analysis

The sample calculation was determined for our main hypothesis of the efficacy of the antimicrobial treatment of AOM. We estimated that with 260 patients the study would have 90% power to detect a reduction of 15% in treatment failure in the antimicrobial treatment group assuming a 25% rate of treatment failure in the placebo group, with a type I error of 5%. Accounting for a possible dropout rate of 20%, we planned to enroll 320 children in the study.

The 14 prognostic factors were chosen based on literature search and they were the following: age (24–35 months vs 6–23 months); recurrent AOM (≥4 previous episodes of AOM); bilateral AOM; severe bulging of the tympanic membrane (convexity markedly increased beyond the edges of tympanic membrane, resembling a doughnut); peaked tympanogram (height ≥0.2 mmho and width ≤300 daPa [ie, type A, C1, or C2 curve]); fever ≥38°C; ear pain as reported by the child or the parents; ear rubbing; decreased activity; nasopharyngeal *Streptococcus pneumoniae*; nasopharyngeal *Haemophilus influenzae*; nasopharyngeal *Moraxella catarrhalis*; any nasopharyngeal respiratory virus; and severe illness according to the AOM treatment guideline by AAP (ie, moderate or severe ear pain or fever ≥39°C).[10]

Because our primary outcome included the time aspect, we used Cox proportional hazards model to identify any prognostic factor that would have an effect on treatment outcome. First, we examined the association between each prognostic factor and time until treatment failure and group by prognostic factor interaction with Cox regression model. Then, we used a multivariable model to identify independent risk factors for treatment failure by including all prognostic factors and interaction terms that were associated with the outcome ($P \leq .10$). All Cox regression models were adjusted for treatment allocation. If an interaction remained significant in the multivariable model, we performed stratified analyses of the hazard ratios for both treatment groups.

To further study the effect of antimicrobial treatment in each prognostic factor group, we calculated the proportions of children with treatment failure in antimicrobial treatment and placebo groups, the rate differences between the groups, and the number needed to treat (NNT) to prevent treatment failure in 1 child.

All analyses were performed according to the intention-to-treat principle. Reported *P* values are 2-sided and have not been adjusted for multiple testing. Analyses were performed with the use of IBM SPSS Statistics, version 21.0 (IBM Corporation, Armonk, NY).

RESULTS

Study Population

The intention-to-treat population comprised 319 children; 161 in the antimicrobial treatment group and 158 in the placebo group (Fig 1). The median age of participants was 14 months (range 6–35 months), 57.1% (182/319) of them were boys, and 99.4% (317/319) were white. The proportion of children who attended daycare was 54.2% (173/319). All children had received at least 1 dose of *H influenzae* type b vaccine, and 2.2% (7/319) of children had received any pneumococcal vaccination. At study entry, 91.8% (293/319) of children had a full or bulging tympanic membrane, 76.5% (244/319) had purulent fluid, and 9.7% (31/319) had hemorrhagic redness of tympanic membrane. The distributions of the prognostic factors in the entire cohort and in the treatment groups are shown in Table 1 and Fig 2.

Prognostic Factors in the Entire Cohort

In the entire cohort, treatment failure occurred in 101 of 319 (31.7%) children. The proportion of children with treatment failure was lower among children 24 to 35 months of age compared with children 6 to 23 months of age (12/60 [20.0%] vs 89/259 [34.4%], $P = .04$) (Table 1). In addition, a peaked tympanogram (A and C curves) at entry decreased the risk for treatment failure (8/57 [14.0%] vs 93/262 [35.5%], $P = .02$). The results of the Cox regression models are shown in Table 1. In the multivariable model, older age (24–35 months) and peaked tympanogram (A and C curves) decreased the hazard for treatment failure (Table 1). Because there was a significant interaction between treatment allocation and the degree of bulging of the tympanic membrane ($P = .02$ for interaction), we performed stratified analyses for antimicrobial treatment and placebo groups separately. Our subgroup analysis showed that severe bulging of the tympanic membrane almost doubled the hazard for treatment failure among children in the placebo group compared with moderate,

mild, or no bulging of the tympanic membrane (hazard ratio, 1.96; 95% confidence interval [CI], 1.20 to 3.20; $P = .007$). If the child received antimicrobial treatment, severe bulging of the tympanic membrane did not affect the risk for treatment failure (hazard ratio, 0.51; 95% CI, 0.20 to 1.34; $P = .17$). Among children with severe bulging of the tympanic membrane, the reasons for treatment failure were: worsening of the child's overall condition, 53.3% (16/30); no improvement in overall condition by day 3, 23.3% (7/30); no improvement in otoscopic signs by day 8, 13.3% (4/30); perforation of the tympanic membrane, 6.7% (2/30); and any other reason to discontinue the study drug, 3.3% (1/30).

Failure Rates in Treatment Groups

In the antimicrobial treatment group, treatment failure occurred in 18.6% (30/161) of children, and the number of children with treatment failure did not differ significantly with respect to any of the prognostic factors (Fig 2). In the placebo group, 44.9% (71/158) of children encountered treatment failure. The treatment result in each prognostic factor group consistently favored antimicrobial treatment. The percentage-point difference in treatment failure between the antimicrobial treatment and placebo groups was highest among children with severe bulging of the tympanic membrane (11.1% vs 64.1%; rate difference −53.0%; 95% CI, −73.5% to −32.4%), resulting in an NNT of 1.9 (Fig 2).

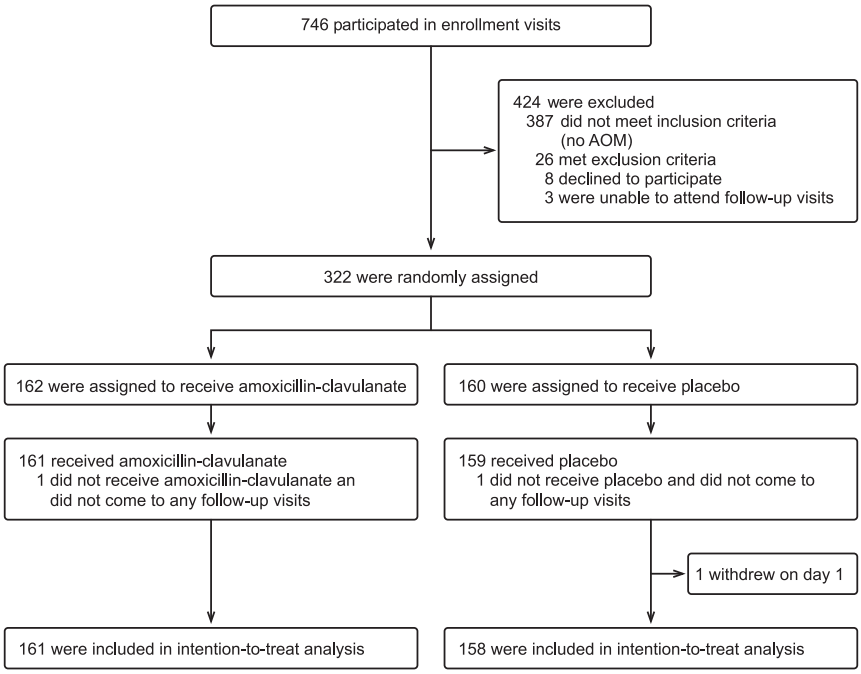

FIGURE 1
Enrollment, random assignment, and follow-up of the study patients.

DISCUSSION

First, our main finding is that children with severe bulging of the tympanic membrane seem to benefit most from antimicrobial treatment. In this subgroup, 64% of children in the placebo group encountered treatment failure compared with 11% in the antimicrobial treatment group. The interaction between bulging of the tympanic membrane and treatment group suggested that the effect of antimicrobial treatment varies depending on the severity of bulging. The NNT among children with severe bulging of the tympanic membrane was 1.9, indicating that 2 children need to be treated with antimicrobial agents to prevent treatment failure in 1 child. This NNT is much lower than the one presented in the recent Cochrane Review in which the authors concluded that 20 children need to be treated to prevent residual pain at 2 to 3 days in 1 child.[12] Our results are in line with the study by Hoberman et al.[2] They also used stringent diagnostic criteria for AOM and showed that children with severe bulging benefit most from antimicrobial treatment. These results are logical because bulging of the tympanic membrane has been shown to be associated with the presence of a bacterial pathogen in the middle ear.[4,13–15] Furthermore, bulging of the tympanic membrane was the finding judged best to differentiate AOM from otitis media with effusion by AOM experts.[16] The recently published AAP guideline for the diagnosis and management of AOM highlights the use of bulging of the tympanic membrane as the most relevant diagnostic criteria for AOM and recommends antimicrobial treatment of all children <2 years of age with severe symptoms or bilateral disease.[10] However, on the basis of our results, all young children with severe bulging of the tympanic membrane seem to benefit from antimicrobial treatment regardless of the severity of their symptoms or the number of ears infected.

Second, our results indicate that tympanometry can be useful in determining which children could be treated without antimicrobial agents. In our study population, peaked tympanogram (A and C curves) significantly decreased the risk for treatment failure. We used stringent diagnostic criteria and virtually all children in our study had either full or bulging tympanic membrane as assessed by pneumatic otoscopy.[3] Nevertheless,

TABLE 1 Treatment Failure Rates and Hazard Ratios in Each Prognostic Factor Group

	No. of Children With Treatment Failure (%) ($N = 319$)	Hazard Ratio for Treatment Failure (95% CI)[a]	*P* for the Hazard Ratio[a]	*P* for the Interaction (Prognostic Factor × Treatment Group)
Entire cohort	101/319 (31.7)			
Personal factors				
Age			.04	.60
24–35 mo	12/60 (20.0)	0.53 (0.29 to 0.96)		
6–23 mo	89/259 (34.4)	Reference		
≥4 previous episodes of AOM			.57	.83
Yes	20/58 (34.5)	1.15 (0.71 to 1.88)		
No	81/261 (31.0)	Reference		
Otoscopic signs at enrollment				
Bilateral AOM[b]			.48	.76
Yes	44/127 (34.6)	1.15 (0.78 to 1.72)		
No	55/188 (29.3)	Reference		
Severe bulging of the tympanic membrane			.03	.02
Yes	30/84 (35.7)	1.75 (1.07 to 2.85)		
No	71/235 (30.2)	Reference		
Peaked tympanogram[c]			.02	.31
Yes	8/57 (14.0)	0.43 (0.21 to 0.88)		
No	93/262 (35.5)	Reference		
Symptoms at entry				
Fever ≥38°C			.18	.43
Yes	37/110 (33.6)	1.32 (0.88 to 1.98)		
No	64/209 (30.6)	Reference		
Ear pain			.46	.44
Yes	79/254 (31.1)	0.84 (0.52 to 1.34)		
No	22/65 (33.8)	Reference		
Ear rubbing			.29	.66
Yes	59/203 (29.1)	0.81 (0.54 to 1.20)		
No	42/116 (36.2)	Reference		
Decreased activity			.30	.19
Yes	36/135 (26.7)	0.81 (0.53 to 1.21)		
No	65/184 (35.3)	Reference		
Severity of illness				
Severe illness according to AAP criteria[d]			.92	.88
Yes	63/197 (32.0)	1.02 (0.68 to 1.53)		
No	38/122 (31.1)	Reference		
Microbial etiology in nasopharyngeal sample[e]				
S pneumoniae			.74	.37
Yes	60/191 (31.4)	1.07 (0.72 to 1.60)		
No	39/125 (31.2)	Reference		
H influenzae			.72	.92
Yes	26/79 (32.9)	0.92 (0.59 to 1.45)		
No	73/237 (30.8)	Reference		
M catarrhalis			.96	.12
Yes	72/233 (30.9)	0.99 (0.64 to 1.54)		
No	27/83 (32.5)	Reference		
Any respiratory virus			.47	.80
Yes	90/276 (32.6)	1.29 (0.65 to 2.56)		
No	9/40 (22.5)	Reference		

[a] Hazard ratios and *P* values are adjusted for treatment group. If the prognostic factor showed an association with treatment failure (ie, age 24–35 mo and a peaked tympanogram) or a significant interaction was found (severe bulging of the tympanic membrane × treatment group), the hazard ratios and *P* values are adjusted for treatment group, for the other prognostic factors, and for the interaction term.

[b] Data on bilaterality were missing for 4 children in whom an adequate view of the contralateral tympanic membrane was not possible because of thick cerumen.

[c] Peaked tympanogram was defined as a tympanogram with height (static acoustic admittance) ≥0.2 mmho and width ≤300 daPa (ie, type A, C1, or C2 curve). The selected tympanogram was obtained from the ear with most severe otoscopic findings.

[d] Severe illness according to AAP criteria: moderate or severe ear pain or fever ≥39°C.

[e] Data on microbiologial etiology were missing for 3 children because parents refused the nasopharyngeal sampling from their children.

Subgroup	Antimicrobial Treatment	Placebo	RD (95% CI) Between the Treatment Groups	NNT
	Number (%) of children with treatment failure			
All children	30/161 (18.6)	71/158 (44.9)	–26.3 (–36.5 to –16.1)	3.8
Age				
24 to 35 months	2/26 (7.7)	10/34 (29.4)	–21.7 (–42.1 to –1.3)	4.6
6 to 23 months	28/135 (20.7)	61/124 (49.2)	–28.5 (–40.0 to –16.9)	3.5
≥ 4 previous episodes of AOM				
Yes	6/30 (20.0)	14/28 (50.0)	–30.0 (–54.5 to –5.5)	3.3
No	24/131 (18.3)	57/130 (43.8)	–25.5 (–36.8 to –14.3)	3.9
Bilateral AOM[a]				
Yes	13/60 (21.7)	31/67 (46.3)	–24.6 (–41.2 to –8.0)	4.0
No	17/99 (17.2)	38/89 (42.7)	–25.5 (–38.5 to –12.5)	3.9
Severe bulging of the tympanic membrane				
Yes	5/45 (11.1)	25/39 (64.1)	–53.0 (–73.5 to –32.4)	1.9
No	25/116 (21.6)	46/119 (38.7)	–17.1 (–28.8 to –5.4)	5.8
Peaked tympanogram[b]				
Yes	4/32 (12.5)	4/25 (16.0)	–3.5 (–21.7 to 14.7)	28.5
No	26/129 (20.2)	67/133 (50.4)	–30.2 (–41.8 to –18.6)	3.3
Fever ≥38°C				
Yes	12/64 (18.8)	25/46 (54.3)	–35.6 (–53.5 to –17.7)	2.8
No	18/97 (18.6)	46/112 (41.1)	–22.5 (–35.0 to –10.0)	4.4
Ear pain				
Yes	21/125 (16.8)	58/129 (45.0)	–28.2 (–39.5 to –16.8)	3.5
No	9/36 (25.0)	13/29 (44.8)	–19.8 (–43.0 to 3.3)	5.1
Ear rubbing				
Yes	19/104 (18.3)	40/99 (40.4)	–22.1 (–34.6 to –9.6)	4.5
No	11/57 (19.3)	31/59 (52.5)	–33.2 (–50.7 to –15.7)	3.0
Decreased activity				
Yes	10/76 (13.2)	26/59 (44.1)	–30.9 (–45.9 to –15.9)	3.2
No	20/85 (23.5)	45/99 (45.5)	–21.9 (–35.8 to –8.1)	4.6
Severe illness according to AAP criterion[c]				
Yes	18/98 (18.4)	45/99 (45.5)	–27.1 (–40.1 to –14.1)	3.7
No	12/63 (19.0)	26/59 (44.1)	–25.0 (–41.5 to –8.6)	4.0
***Streptococcus pneumoniae*[d]**				
Yes	20/101 (19.8)	40/90 (44.4)	–24.6 (–37.8 to –11.5)	4.1
No	8/57 (14.0)	31/68 (45.6)	–31.6 (–47.9 to –15.2)	3.2
***Haemophilus influenzae*[d]**				
Yes	5/31 (16.1)	21/48 (43.8)	–27.6 (–48.8 to –6.4)	3.6
No	23/127 (18.1)	50/110 (45.5)	– 27.3 (–39.1 to –15.6)	3.7
***Moraxella catarrhalis*[d]**				
Yes	18/118 (15.3)	54/115 (47.0)	–31.7 (–43.6 to –19.8)	3.1
No	10/40 (25.0)	17/43 (39.5)	–14.5 (–34.7 to 5.6)	6.9
Any respiratory virus[d]				
Yes	25/134 (18.7)	65/142 (45.8)	–27.1 (–38.2 to –16.1)	3.7
No	3/24 (12.5)	6/16 (37.5)	–25.0 (–51.4 to 1.4)	4.0

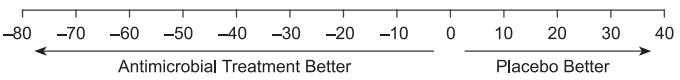

FIGURE 2

Treatment failure rates in antimicrobial treatment and placebo groups with rate differences and NNTs to prevent treatment failure in 1 child. [a] Data were missing for 2 children in the antimicrobial treatment group and 2 children in the placebo group in whom an adequate view of the contralateral tympanic membrane was not possible because of thick cerumen. [b] Peaked tympanogram was defined as a tympanogram with height (static acoustic admittance) ≥0.2 mmho and width ≤300 daPa (ie, type A, C1, or C2 curve). The selected tympanogram was obtained from the ear with most severe otoscopic findings. [c] Severe illness according to AAP criteria: moderate or severe ear pain or fever ≥39°C. [d] Data on microbiological etiology were missing for 3 children in the antimicrobial treatment group because parents refused the nasopharyngeal sampling from their children. RD, rate difference.

we obtained a peaked tympanogram in a subset of the children. Many of these children had bulging tympanic membrane because of positive pressure in the middle ear, but the amount of middle ear fluid may have been low. We performed the tympanometry before otoscopy and did our best to obtain a peaked tympanogram whenever possible. If we obtained a flat tympanogram, we repeated the tympanometry 3 times. As the AAP guideline states, AOM is a disease continuum, and we possibly examined some of the children at early stage of the disease when the fluid was still accumulating in the middle ear.[10] In fact, peaked tympanograms in our study were often associated with air-fluid interfaces as observed by

pneumatic otoscopy examination.[17] Among children with peaked tympanogram, the failure rates were low in both, antimicrobial treatment and placebo groups, and the NNT to prevent treatment failure in 1 child was 29. These results are directly applicable in clinical practice; by withholding antimicrobial treatment from children with peaked tympanogram (A and C curves), the use of antimicrobial agents and the development of antimicrobial resistance could be reduced without increasing the risks for the child.

Like in previous studies, older age appeared to be associated with a better outcome.[6,18,19] Although the majority of children in our study were <2 years of age, children 24 to 35 months seemed to be at lower risk for treatment failure. It should be noted, though, that our results were borderline significant and treatment failure occurred in 29% of children 24 to 35 months of age if they did not receive antimicrobial treatment.

In contrast to the meta-analysis by Rovers et al,[9] bilateral AOM did not increase the risk for treatment failure in our study. This may be because of the fact that AOM is a dynamic disease. The otoscopic signs change from day to day and unilateral AOM may become bilateral even during antimicrobial treatment.[3,20] Furthermore, our definition of treatment failure included both symptoms and otoscopic signs, whereas the study by Rovers et al[9] used the presence of fever and/or ear pain at 3 to 7 days as a primary outcome. Previously, we have shown that children with bilateral AOM have more severe otoscopic signs compared with children with unilateral AOM.[21] To sum up, it could be interpreted that the otoscopic signs themselves, not the laterality of AOM, are indicative of the severity of AOM.

An important finding was the lack of association of preexisting symptoms with treatment outcome. Furthermore, children classified as having severe illness according to the AOM treatment guideline by AAP (ie, moderate or severe ear pain or fever ≥39°C)[10] encountered treatment failure as often as children with nonsevere illness. The major problem is that, especially in preverbal children, symptoms are not specific to AOM and they overlap with the symptoms of concurrent viral respiratory tract infection.[22] Therefore, it could be questioned whether the AOM treatment decisions should be based solely on symptom severity. In the resolution of AOM, however, symptoms play an important role. We had a close follow-up schedule and examined every child at our study clinic on days 3 and 8. This kind of close follow-up is not feasible in clinical practice, and it seems like the current recommendation of revisit only if the child's symptoms do not improve within 2 to 3 days is both safe and reasonable.[10,23]

Our study has several strengths acknowledged by experts.[10,24] The study population consisted of children <3 years of age, which is the age group with the highest incidence of AOM. In addition, we used stringent diagnostic criteria and antimicrobial treatment with the optimal coverage. Our primary outcome, the time until treatment failure, is clinically relevant. This study also has its limitations. Our study was conducted before 10-valent pneumococcal conjugate vaccine was incorporated into the Finnish National Immunization Program. Thus, the bacterial etiology of AOM may differ from the etiology in a completely vaccinated population. Because this was a secondary analysis of our AOM treatment trial, it may be underpowered to detect an association between certain subgroup variables and treatment failure. In addition, subgroup analyses may result in false-positive results because of multiple comparisons. However, all our subgroups were prespecified, and stratified analyses were done only for those prognostic factors that showed a significant interaction with treatment in the Cox regression model. Our decision to include a grading system for bulging of the tympanic membrane could also be criticized. The evaluation of otoscopic signs is always subjective and prone to interobserver bias. Severe bulging is, however, a sign that is difficult to miss even for a less experienced otoscopist, and therefore this prognostic factor as an indication for antimicrobial treatment could be easily applied into clinical practice. Our results emphasize the importance of accurate diagnosis of AOM, which can only be obtained by careful removal of cerumen and by using a pneumatic otoscope with good light source and right sized speculum that enables an air tight seal at the external auditory canal.

CONCLUSIONS

Our main finding is that children with severe bulging of the tympanic membrane, regardless of the laterality of AOM, seem to benefit most from antimicrobial treatment. On the other hand, children with peaked tympanogram (A and C curves) may be optimal candidates for initial observation strategy.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
AOM: acute otitis media
CI: confidence interval
NNT: number needed to treat

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