ORIGINAL ARTICLE

Antibiotic Therapy to Prevent the Development of Asymptomatic Middle Ear Effusion in Children With Acute Otitis Media

A Meta-analysis of Individual Patient Data

Laura Koopman, MSc; Arno W. Hoes, MD, PhD; Paul P. Glasziou, MD, PhD; Cees L. Appelman, MD, PhD; Peter Burke, FRCGP, MRCP(Ire); David P. McCormick, MD; Roger A. Damoiseaux, MD, PhD; Nicole Le Saux, MD, PhD; Maroeska M. Rovers, PhD

Objectives: To determine predictors of the development of asymptomatic middle ear effusion (MEE) in children with acute otitis media (AOM) and to assess the effect of antibiotic therapy in preventing the development of MEE in these children.

Data Sources: A systematic literature search was performed using PubMed, EMBASE, the Cochrane databases, and the proceedings of international otitis media symposia.

Study Selection: A trial was selected if the allocation of participants to treatment was randomized, children aged 0 to 12 years with AOM were included, the comparison was between antibiotic therapy and placebo or no (antibiotic) treatment, and MEE at 1 month was measured.

Data Extraction: Data from 5 randomized controlled trials were included in the meta-analysis of individual patient data (1328 children aged 6 months to 12 years). We identified independent predictors of the development of asymptomatic MEE and studied whether these children benefited more from antibiotic therapy than children with a lower risk. The primary outcome was MEE (defined as a type B tympanogram) at 1 month.

Data Synthesis: The overall relative risk of antibiotic therapy in preventing the development of asymptomatic MEE after 1 month was 0.9 (95% confidence interval, 0.8-1.0; *P*=.19). Independent predictors of the development of asymptomatic MEE were age younger than 2 years and recurrent AOM. No statistically significant interaction effects with treatment were found.

Conclusion: Because of a marginal effect of antibiotic therapy on the development of asymptomatic MEE and the known negative effects of prescribing antibiotics, including the development of antibiotic resistance and adverse effects, we do not recommend prescribing antibiotics to prevent MEE.

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OTITIS MEDIA (OM) IS ONE of the most common diseases in infants and children.[1,2] Acute OM (AOM) and OM with effusion (OME) are different stages of the OM continuum.[3] Children with OME experience up to 5 times more episodes of AOM than children without OME, whereas 50% of children with AOM will develop asymptomatic middle ear effusion (MEE) after an episode of acute infection.[4] The effusion may lead to a conductive hearing loss of 15 to 40 dB, and this hearing loss could have an adverse effect on language development, cognitive development, behavior, and quality of life.[5] However, previous research has not been conclusive because more recent studies[6-8] demonstrate little or no effect of MEE on language and cognitive development.

Findings from a recent study[9] showed that antibiotic therapy is mainly beneficial in children younger than 2 years with bilateral AOM and in children with AOM and otorrhea for pain or fever at 3 to 7 days. For most other children with AOM, an observational policy seems justified.[9] Because antibiotic therapy may also affect the development of asymptomatic MEE,[10-12] the question is whether treatment might be more beneficial in preventing the development of this MEE in specific subgroups of children. Our meta-analysis of individual patient data (IPD) (ie, a meta-analysis on the individual original data of performed trials) offers the unique opportunity to identify subgroups that are more or less likely to benefit. Therefore, in this IPD meta-analysis, we aimed (1) to determine predictors of the development of asymptomatic MEE in children with AOM

Author Affiliations are listed at the end of this article.

and (2) to assess the effect of antibiotic therapy in preventing the development of asymptomatic MEE in these children.

METHODS

SELECTION OF THE TRIALS

A systematic literature search was performed in December 2005 using PubMed, EMBASE, the Cochrane databases, and the proceedings of international symposia on recent advances in OM. To be selected for the IPD meta-analysis, trials had to be randomized, they had to include children aged 0 to 12 years with AOM, the comparison had to be between antibiotic therapy and placebo or no (antibiotic) treatment, and MEE at 1 month had to be measured.

DATA COLLECTION AND END POINTS

The primary investigators of all selected trials were asked to provide the raw data of their trials. The obtained data were thoroughly checked for consistency, plausibility, and integrity of randomization and follow-up. Any queries were resolved by the responsible trial investigator or statistician. Based on a literature search and the availability of information in routine clinical practice, the following baseline candidate predictors of MEE were selected: age (<2 vs ≥ 2 years), sex (boys vs girls), and season (autumn and winter vs spring and summer), as well as the dichotomous (yes vs no) variables of pain, fever, crying, coughing, siblings, otorrhea, runny nose, recurrent AOM, bilateral AOM, having been breastfed, smoking in the household, red tympanic membrane, bulging tympanic membrane, and perforation of the tympanic membrane. The primary outcome variable was MEE at 1 month diagnosed as tympanometry (type B tympanograms were indicative of the presence of MEE).

DATA ANALYSIS

Data were available for 85% (range, 18%-100%) of the predictor variables and for 91% (range, 76%-99%) of the outcome variables. To decrease bias and to increase statistical efficiency, we imputed the missing data per trial using the linear regression method (Missing Value Analysis function) and commercially available software (SPSS for Windows version 12.0; SPSS Inc, Chicago, Illinois).[13,14] Such imputation is based on the correlation between each variable with missing values and all other variables, as estimated from the complete set of subjects from that particular trial.

To decide whether pooling of the data was justified, heterogeneity between studies was assessed using I^2.[15] Because I^2 was lower than 25%, pooling was performed.

First, independent predictors of the development of asymptomatic MEE at 1 month were identified.[16] To eliminate possible effects of antibiotic therapy on the findings, we only included children from the control groups in this prognostic analysis. Predictors having a univariate association with the outcome ($P \leq .10$) were included in multivariate logistic regression analyses. The model was reduced by excluding predictors with $P > .05$ from the model. The predictive accuracy of the model was estimated by the reliability (goodness of fit) using Hosmer-Lemeshow tests.[17] The ability of the prognostic model to discriminate between children with and without a poor outcome was estimated by the area under the receiver operating characteristic curve of the model.[18] In addition, we calculated the absolute risks of the development of asymptomatic MEE across combinations of independent predictors.

Second, the individual predictors were used to study whether children at risk of asymptomatic MEE at 1 month benefited more from antibiotic therapy than those with a lower risk. Fixed-effects logistic regression analysis was performed to study whether the interaction between the subgrouping variable and treatment was statistically significant.[19] This approach tests and estimates the difference between treatment effects across subgroups directly (ie, it involves a single statistical test irrespective of the number of subgroups). Stratified analyses were performed to quantify the effect in the subgroups studied. Relative risks, risk differences, and their 95% confidence intervals (CIs) were calculated. Finally, we performed sensitivity analyses among trials that included a placebo treatment or trials that included the same dose regimen. All analyses were performed according to the intent-to-treat principle.

RESULTS

Nineteen trials were identified that studied the effectiveness of antibiotic therapy in children with AOM. Thirteen trials were excluded because of inadequate randomization, receipt of another antibiotic treatment by the control arm, or unavailability of information on the outcome included in our meta-analysis. Five research groups provided their data[20-24]; the data from the other trial were unavailable.[25] The numbers of children in the trials ranged from 121 to 512. In total, 44.0% of 1328 children were younger than 2 years, 50.2% were male, 51.8% had recurrent AOM, 34.3% had bilateral AOM, and 94.4% had a red tympanic membrane (**Table 1** and **Table 2**).

PROGNOSTIC MODEL

In total, 660 children in the control arms of the trials were included in the prognostic analyses. Of these, 334 (50.6%) developed asymptomatic MEE. The independent predictors associated with the development of asymptomatic MEE at 1 month were age younger than 2 years (odds ratio, 2.2; 95% CI, 1.6-3.0) and recurrent AOM (odds ratio, 1.5; 95% CI, 1.1-2.1). The prognostic model showed a good fit ($P = .88$, Hosmer-Lemeshow goodness-of-fit test), and the area under the receiver operating characteristic curve was 0.61 (95% CI, 0.57-0.66).

Table 3 gives absolute risks of the development of asymptomatic MEE at 1 month in children with certain combinations of independent prognostic factors. The absolute risk of developing asymptomatic MEE was highest (64% [95% CI, 58%-70%]) in children younger than 2 years. The absolute risk was lowest (30% [95% CI, 25%-35%]) in children 2 years or older without recurrent AOM.

OVERALL EFFECT OF ANTIBIOTIC THERAPY ON OME DEVELOPMENT

There was no statistically significant overall effect of antibiotic therapy in preventing the development of asymptomatic MEE at 1 month ($P = .19$). The overall relative risk of antibiotic therapy in preventing the development of asymptomatic MEE after 1 month was 0.9 (95% CI, 0.8-1.0), and the risk difference showed a small benefit of antibiotic treatment (4% [95% CI, –2% to 9%]).

Table 1. Characteristics of 5 Included Trials

Source	No. of Patients	Participants	Interventions	Duration of Intervention, d	Outcomes
Appelman et al,[20] 1991	121	Children aged 6 mo to 12 y with recurrent AOM visiting a GP	Amoxicillin-clavulanate vs placebo	7	Fever after 3 d, pain after 3 d, otorrhea; otoscopy and tympanometry after 1 mo
Burke et al,[21] 1991	232	Children aged 3 to 10 y with AOM	Amoxicillin vs placebo	7	Symptom diary (including fever and ear pain) by the parents; home visits by researcher after 24 h and 5-7 d; otoscopy and tympanometry after 1 and 3 mo
Damoiseaux et al,[22] 2000	240	Children aged 6 mo to 2 y with AOM visiting a GP	Amoxicillin vs placebo	10	Symptoms (including fever and ear pain) at day 4 assessed by a GP; otoscopy and tympanometry after 6 wk and 3 mo
Le Saux et al,[23] 2005	512	Children aged 6 mo to 5 y with AOM seen at clinics or the emergency department	Amoxicillin vs placebo	10	Telephone follow-up (including fever) at days 1, 2, and 3 and between 10 and 14 d; tympanometry at 1 and 3 mo
McCormick et al,[24] 2005	223	Children aged 6 mo to 12 y with AOM	Amoxicillin immediately vs delayed treatment	10	Symptom diary (including fever and ear pain) kept by the parents; analgesics consumption; nasopharyngeal carriage; adverse events; absence from school; tympanometry after 12 and 30 d

Abbreviations: AOM, acute otitis media; GP, general practitioner.

Table 2. Baseline Characteristics of 1328 Included Children[a]

Characteristics	No. (%)		
	Placebo	Antibiotics	Total
Age <2 y	290 (43.9)	294 (44.0)	**584** (44.0)
Male sex	330 (50.0)	337 (50.4)	**667** (50.2)
Recurrent AOM	355 (53.8)	333 (49.9)	**688** (51.8)
Siblings	472 (77.9)	456 (75.9)	**928** (76.9)
Winter season	500 (75.8)	505 (75.6)	**1005** (75.7)
Ever being breastfed	137 (58.5)	138 (60.3)	**275** (59.4)
Passive smoke exposure	187 (38.3)	192 (39.4)	**379** (38.9)
Crying	415 (83.8)	404 (82.6)	**819** (83.2)
Cough	381 (77.0)	365 (74.6)	**746** (75.8)
Common cold	427 (77.8)	430 (77.3)	**857** (77.6)
Ear pain	567 (85.9)	579 (86.7)	**1146** (86.3)
Fever	272 (50.2)	271 (48.9)	**543** (49.5)
Bilateral AOM	220 (33.3)	236 (35.3)	**456** (34.3)
Otorrhea	19 (15.4)	16 (13.7)	**35** (14.6)
Perforation	8 (6.5)	7 (6.0)	**15** (6.3)
Red tympanic membrane	621 (94.1)	633 (94.8)	**1254** (94.4)
Bulging tympanic membrane	264 (40.0)	271 (40.6)	**535** (40.3)

Abbreviation: AOM, acute otitis media.
[a] Percentages do not total 100 because in some included studies certain characteristics were not measured.

Table 3. Absolute Risks of the Development of Middle Ear Effusion at 1 Month for the Overall Effect and for Each of the Subgroups of Children With Acute Otitis Media (AOM)

Predicting Variable	No. (%) of All Children	Absolute Risk (95% Confidence Interval), %
Overall effect	648 (100.0)	49 (46-52)
Age <2 y without recurrent AOM	174 (26.9)	55 (50-60)
Age <2 y with recurrent AOM	171 (26.4)	64 (58-70)
Age ≥2 y without recurrent AOM	96 (14.8)	30 (25-35)
Age ≥2 y with recurrent AOM	207 (31.9)	49 (44-54)

EFFECT OF ANTIBIOTIC THERAPY ON OME DEVELOPMENT IN SUBGROUPS OF CHILDREN

The largest treatment effect was found in children 2 years and older without recurrent AOM; 35.7% in the placebo group and 24.3% in the antibiotic group developed asymptomatic MEE after 1 month (risk difference, –11.5%; 95% CI, –21.4% to –1.5%). The smallest treatment effect was found in children younger than 2 years with recurrent AOM; 64.7% in the placebo group and 63.3% in the antibiotic group developed asymptomatic MEE after 1 month (risk difference, –1.5%; 95% CI, –13.0% to 10.1%). However, none of the (combined) subgrouping variables showed a statistically significant interaction effect with treatment (**Table 4**). Sensitivity analyses that included placebo-controlled trials or trials using the same dose of antibiotics produced similar results.

COMMENT

Combining data from the control groups of 5 randomized trials, we found that age younger than 2 years and recurrent AOM were independent predictors of the development of asymptomatic MEE at 1 month. Only a small beneficial effect of antibiotic therapy was found in preventing the development of asymptomatic MEE in children 2 years and older without recurrent AOM. However, none of the (combined) subgrouping variables showed a statistically significant interaction effect with treatment.

Regarding the efficacy of antimicrobial prophylaxis for middle ear effusion, the results are in agreement with the findings of 2 previous studies,[11,26] which also reported small beneficial effects. However, the children in these

Table 4. Overall Effect and Stratified Subgroup Results Presented as Risk Differences and Relative Risks

Subgroup	No.	Placebo Group, %	Antibiotics Group, %	Risk Difference (95% CI)	Relative Risk (95% CI)	*P* Value for Interaction
Overall effect	**1328**	50.6	47.0	–3.6 (–9.0 to 1.8)	0.93 (0.82 to 1.04)	. . .
Age, y						
<2	584	60.6	57.5	–3.2 (–11.2 to 4.8)	0.95 (0.81 to 1.08)	
≥2	744	42.7	38.8	–3.9 (–11.0 to 3.1)	0.91 (0.73 to 1.08)	.89
Recurrent AOM						
No	640	46.2	38.5	–7.7 (–15.4 to –0.1)	0.83 (0.65 to 1.01)	
Yes	688	54.4	55.6	1.2 (–6.2 to 8.6)	1.02 (0.89 to 1.16)	.10
Age and recurrent AOM						
<2 y Without recurrent AOM	317	57.0	53.0	–3.9 (–14.9 to 7.0)	0.93 (0.73 to 1.13)	
<2 y With recurrent AOM	267	64.7	63.3	–1.5 (–13.0 to 10.1)	0.98 (0.80 to 1.16)	
≥2 y Without recurrent AOM	323	35.7	24.3	–11.5 (–21.4 to –1.5)	0.68 (0.34 to 1.02)	
≥2 y With recurrent AOM	421	47.7	50.7	3.0 (–6.5 to 12.6)	1.06 (0.87 to 1.26)	.44

Abbreviations: AOM, acute otitis media; CI, confidence interval; ellipsis, not applicable.

previous studies were not experiencing AOM when they entered the trial. The results are also in agreement with current guidelines,[27,28] which do not recommend prescribing antibiotics with the aim to prevent the development of MEE.

The major strength of our study is the large number of children that could be analyzed. By reanalyzing the data of 5 trials, we were able to include 1328 children (of whom 660 were not initially treated using antibiotics), which gave us the power to predict the absolute risk of the development of asymptomatic MEE in children with AOM, as well as the opportunity to study whether subgroups benefited more from treatment using antibiotics.

To appreciate our results, some possible limitations should be discussed. First, we were only able to study asymptomatic MEE at 1 month, as this was the only point in time at which tympanograms were obtained in all available trials. However, we expect that after a longer period (eg, 3 or 6 months) the spontaneous resolution rate will be higher, resulting in an even smaller antibiotic effect.

Second, because myringotomy is considered unethical in the treatment of AOM in most Western countries, MEE was defined as a type B tympanogram. This may have resulted in some misclassification. However, because the sensitivity and specificity of a type B tympanogram are high (81% and 74%,[29] respectively), we believe that results accurately reflect the treatment effect.

Third, we did not study all possible subgroups, but we selected only those at higher risk of the development of MEE at 1 month. The strength of this approach is that our prognostic analyses revealed only a few relevant subgroups, limiting the numbers of subgroup analyses performed and subsequent false-positive findings (type I errors) caused by multiple testing. Furthermore, other subgroups that might benefit more from treatment using antibiotics (eg, those with Down syndrome or cleft palate) could not be studied in this IPD meta-analysis because these subgroups were excluded from the individual trials. The experience of many clinicians that these subgroups of children might benefit more from antimicrobial prophylaxis has not yet been demonstrated in randomized controlled trials, to our knowledge. Because the question whether to treat these children using antimicrobial prophylaxis is relevant for clinical practice, future trials studying these specific subgroups seem justified.

Fourth, the children in the included trials were prescribed antibiotics for 7 or 10 days. Prescribing antibiotics for a longer period might be more effective. However, in this era of increasing antibiotic resistance, we should study the effectiveness regarding the recommended duration, and a period of 5 to 10 days is recommended in all international AOM guidelines.[30-33]

In conclusion, only a small beneficial effect of antibiotic therapy was found in preventing the development of asymptomatic MEE in children 2 years and older without recurrent AOM. Because of this marginal effect and the known negative effects of prescribing antibiotics, including the development of antibiotic resistance and adverse effects, we do not recommend prescribing antibiotics to prevent MEE. However, more research is needed to identify relevant subgroups of children who have MEE that might benefit from other treatments.

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Author Affiliations: Julius Center for Health Sciences and Primary Care (Ms Koopman and Drs Hoes, Appelman, Damoiseaux, and Rovers) and Departments of Pediatrics and Otolaryngology, Wilhelmina Children's Hospital (Dr Rovers), University Medical Center Utrecht, Utrecht, the Netherlands; Department of Primary Health Care, Institute of Health Sciences, University of Oxford, Oxford (Dr Glasziou), and Community Clinical Sciences Division, Department of Primary Medical Care, Southampton University, and Aldermoor Health Centre, Southampton (Dr Burke), England; Department of Pediatrics, University of Texas Medical Branch at Galveston (Dr McCormick); and Division of Infectious Diseases, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Canada (Dr Le Saux).
Correspondence: Laura Koopman, MSc, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Stratenum 6.131, PO Box 85500, 3508 GA Utrecht, the Netherlands (l.koopman@umcutrecht.nl).
Author Contributions: Ms Koopman and Drs Hoes, Glasziou, Appelman, Damoiseaux, and Rovers had full ac-

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