SPECIAL ARTICLE

# Predictors of Pain and/or Fever at 3 to 7 Days for Children With Acute Otitis Media Not Treated Initially With Antibiotics: A Meta-analysis of Individual Patient Data

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## ABSTRACT

OBJECTIVE. The goal was to determine the predictors of a prolonged course for children with acute otitis media.

METHODS. A meta-analysis of data with the observation groups of 6 randomized, controlled trials was performed. Participants were 824 children, 6 months to 12 years of age, with acute otitis media. The primary outcome was a prolonged course of acute otitis media, which was defined as fever and/or pain at 3 to 7 days.

RESULTS. Of the 824 included children, 303 had pain and/or fever at 3 to 7 days. Independent predictors of a prolonged course were age of <2 years and bilateral acute otitis media. The absolute risk of pain and/or fever at 3 to 7 days for children <2 years of age with bilateral acute otitis media (20% of all children) was 55%, and that for children ≥2 years of age with unilateral acute otitis media (47% of all children) was 25%.

CONCLUSIONS. The risk of a prolonged course was 2 times higher for children <2 years of age with bilateral acute otitis media than for children ≥2 years of age with unilateral acute otitis media. Clinicians can use these features (ie, age of <2 years and bilateral acute otitis media) to inform parents more explicitly about the expected course of their child's otitis media and to explain which features should prompt parents to contact their clinician for reexamination of the child.

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**Key Words**
prognosis, acute otitis media, meta-analysis

**Abbreviations**
AOM—acute otitis media
OR—odds ratio
CI—confidence interval

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ACUTE OTITIS MEDIA (AOM) is one of the most common childhood infections, the leading cause of doctors' visits, and the most frequent reason children receive antibiotics or undergo surgery.[1] The high incidence of and high rate of spontaneous recovery from AOM suggest that it is a natural phenomenon, inevitable (like a common cold), and part of the gradual maturation of the child's anatomy and immune system. However, untreated AOM can lead occasionally to suppurative complications, such as acute mastoiditis.

The treatment of AOM is still controversial.[2] Many children are given antibiotics, although systematic reviews suggest that there is only marginal benefit for most children.[3–5] An estimated 8 to 17 children need to be treated for 1 child to benefit from earlier resolution of symptoms.[3–5] The effects of prescription of antibiotics are important, because prescription could increase antibiotic resistance[6,7], increase revisit rates, and increase the likelihood of seeking medical care for future illnesses.[8]

Currently we have no tools to discriminate between children with mild, self-limiting episodes of AOM and those at risk of a prolonged course. To date, only Little et al[9] have examined which children with AOM are at risk for a prolonged course. They showed that the presence of fever and vomiting increased the risk of a prolonged course. Prognostic studies require relatively large numbers of participants developing the outcome of interest (in general, 10 participants per prognostic determinant studied).[10] The power of the 2 earlier studies was therefore very limited. We determined the predictors of a prolonged course from the combined individual patient (control) data of 6 randomized, controlled trials.

## METHODS

### Selection of Trials

A systematic literature search was performed with PubMed, Embase, the proceedings of International Symposia on Recent Advances in Otitis Media, and the Cochrane Library. To be selected for the individual patient data meta-analysis, trials needed to be randomized, they needed to include children 6 months to 12 years of age with AOM, and the comparison needed to be between antibiotics and a placebo or no treatment (observation group). The primary investigators of all selected trials were asked for the raw data from their trials.

### Patients

Only patients in the observation groups of the available randomized, controlled trials were selected for this prognostic study.

### Outcomes

The primary outcome was a prolonged course of AOM, which was defined as pain and/or fever at 3 to 7 days. We used this composite end point because both factors are relevant from clinical and patient (parental) perspectives. Fever was defined as a temperature of ≥38°C, and pain (yes versus no) was measured with diaries completed by the parents. Both outcome measures needed to be dichotomized, because several trials measured them only in that way. Fever and pain were also studied separately (secondary outcomes).

### Predictors

On the basis of a literature search and the availability of information in routine clinical practice, the following baseline candidate predictors were selected: age (<2 years versus ≥2 years), gender (boys versus girls), season (autumn/winter versus spring/summer), having been breastfed (yes versus no), smoking in the household (yes versus no), siblings (yes versus no), family history of AOM (yes versus no), recurrent AOM (yes versus no), fever (yes versus no), pain (yes versus no), bilateral AOM (yes versus no), otorrhea (yes versus no), runny nose (yes versus no), crying (yes versus no), coughing (yes versus no), red tympanic membrane (yes versus no), bulging tympanic membrane (yes versus no), and perforation of the tympanic membrane (yes versus no).

### Statistical Methods

To determine whether pooling was justified, heterogeneity between studies was assessed with the $I^2$ statistic.[11] Because the $I^2$ value was <25%, pooling was performed.

The association between each prognostic factor and the presence or absence of fever and/or pain at 3 to 7 days was examined with univariate logistic regression analyses. Predictors that were associated with the outcome in univariate analyses ($P \leq .10$) were included in multivariate logistic regression analyses. The model was reduced through exclusion of predictors with $P$ values of >.05. The predictive accuracy of the models was estimated on the basis of their reliability (goodness of fit) with Hosmer-Lemeshow tests.[12] The model's ability to discriminate between children with and without poor outcomes was estimated as the area under the receiver operating characteristic curve of the model.[13] The receiver operating characteristic curve area is a suitable parameter to summarize the discriminative or predictive value and can range from 0.5 (no discrimination, like a coin flip) to 1.0 (perfect discrimination). In addition, we calculated the absolute risks of a prolonged course across combinations of independent predictors.

We also calculated the proportions of children with a prolonged course on each consecutive day within each subgroup of the identified independent predictors. The resulting survival curves were based on diary records of the presence of symptoms completed by the parents in 5 of the 6 included trials. Finally, sensitivity analyses, including only those trials that measured the outcomes

on the same day, used the same dosage, or included a placebo, were performed.

### Missing Values

Information was available for 72% of the predictor variables (range: 28%–100%) and for 90% of the outcome variables (range: 81%–98%). Data are seldom missing at random; it has been shown that removal of subjects with a missing value for ≥1 of the predictors studied (complete case analysis) commonly leads to biased results and certainly to loss of power.[14,15] To decrease bias and to increase statistical efficiency, it is better to impute missing data than to perform a complete case analysis. Accordingly, we imputed the missing data for each trial by using the linear regression method (missing value analysis) available in SPSS 12.0 for Windows (SPSS, Chicago, IL). Such imputation is based on the correlation between each variable with missing values and all other variables, as estimated for the set of complete subjects. We imputed missing values only within trials. Some predictor and outcome variables are therefore still missing because they were not measured at all in 1 of the included trials.

## RESULTS

We identified 19 trials that studied the effectiveness of antibiotics in children with AOM. Nine trials were excluded because of inadequate randomization or lack of availability of information on the outcomes included in our meta-analysis or because the trial was conducted with a special study population.[16–24] The principal investigators of 6 trials provided their data.[25–30] The data from the other 4 trials were not available.[31–34] The mean number of children studied in the 6 included trials ranged from 121 to 512. The mean age was 3.4 years (range: 6 months to 12 years); 50% of the children were boys, 52% had recurrent AOM, and 27% had bilateral AOM.

In total, 824 patients (ie, all children with AOM who were assigned to the observation group in the 6 available randomized trials) were included for determination of the predictors of a prolonged course. The characteristics of these 824 included children are shown in Table 1. Of the 824 included children, 91 (11%) had fever at 3 to 7 days, 257 (31%) had pain at 3 to 7 days, and 303 (37%) had pain and/or fever at 3 to 7 days.

Table 2 shows the univariate predictors of both the primary and secondary outcomes. Univariate predictors of pain and/or fever at 3 to 7 days were age of <2 years, family history of otitis media, fever at inclusion, bilateral AOM, otorrhea, and red tympanic membrane. Predictors of fever at 3 to 7 days were age of <2 years, winter season, fever at inclusion, pain at inclusion, bilateral AOM, runny nose, and abnormal tympanic membrane. Predictors of pain at 3 to 7 days were age of <2 years, having siblings, bilateral AOM, otorrhea, and red tympanic membrane.

Table 3 shows the independent predictors of pain and/or fever, pain, and fever at 3 to 7 days. Independent predictors of pain and/or fever at 3 to 7 days were age of <2 years (odds ratio [OR]: 2.1; 95% confidence interval [CI]: 1.5–2.9) and bilateral AOM (OR: 1.7; 95% CI: 1.2–2.4). The prognostic model showed a good fit (goodness-of-fit test, $P = .93$), and the AUC was 0.63 (95% CI: 0.59–0.68). Independent predictors of pain at 3 to 7 days were age of <2 years (OR: 2.0; 95% CI: 1.4–2.9) and bilateral AOM at baseline (OR: 1.8; 95% CI: 1.3–2.6). The goodness of fit of this model was good ($P = .59$), and the AUC was 0.64 (95% CI: 0.59–0.68). Age of <2 years (OR: 1.6; 95% CI: 1.0–2.6) and fever at baseline (OR: 3.0; 95% CI: 1.8–4.9) were independent predictors of fever at 3 to 7 days. The goodness-of-fit test for this model indicated a good fit of the prognostic model ($P = .92$), and the AUC was 0.67 (95% CI: 0.61–0.73). There was no significant interaction between the independent predictors (all $P > .6$).

**TABLE 1 Characteristics of the 824 Included Children**

| | No. (%) |
|---|---|
| Personal factors | |
| Age | |
| <2 y | 287 (35) |
| ≥2 y | 537 (65) |
| Gender | |
| Boys | 411 (50) |
| Girls | 413 (50) |
| Season | |
| Autumn/winter | 620 (75) |
| Spring/summer | 204 (25) |
| Being breastfed | |
| Yes | 255 (31) |
| No | 143 (17) |
| Recurrent AOM | |
| Yes | 429 (52) |
| No | 395 (48) |
| Symptoms at baseline | |
| Fever at inclusion | |
| Yes | 287 (35) |
| No | 419 (51) |
| Pain at inclusion | |
| Yes | 724 (88) |
| No | 100 (12) |
| Bilateral AOM | |
| Yes | 220 (27) |
| No | 440 (53) |
| Otorrhea | |
| Yes | 65 (8) |
| No | 268 (27) |
| Tympanic membrane | |
| Red | |
| Yes | 754 (91) |
| No | 70 (9) |
| Bulging | |
| Yes | 342 (42) |
| No | 482 (58) |
| Perforated | |
| Yes | 19 (2) |
| No | 268 (33) |

The percentages do not always add to 100 because of missing data.

TABLE 2 **Crude Association (OR) of Potential Predicting Factors With Fever at 3 to 7 Days, Pain at 3 to 7 Days, and Composite End Point of Poor Outcome (Defined as Pain and/or Fever at 3–7 Days)**

| Predictors | OR (95% CI) | | |
|---|---|---|---|
| | Pain and/or Fever at 3–7 d | Pain at 3–7 d | Fever at 3–7 d |
| Personal factors | | | |
| Age of <2 y | 2.04 (1.52–2.74)[a] | 1.86 (1.37–2.52)[a] | 2.09 (1.35–3.24)[a] |
| Male gender | 0.90 (0.68–1.19) | 0.93 (0.69–1.25) | 1.20 (0.77–1.85) |
| Winter season | 0.85 (0.61–1.17) | 0.76 (0.54–1.06) | 2.11 (1.15–3.89)[a] |
| Breastfed | 0.86 (0.57–1.30) | 0.88 (0.58–1.33) | 0.65 (0.32–1.33) |
| Passive smoking | 0.80 (0.57–1.12) | 0.97 (0.69–1.37) | 1.04 (0.63–1.71) |
| Siblings | 1.25 (0.84–1.88) | 1.36 (0.88–2.10) | 1.02 (0.59–1.76) |
| Family history | 1.51 (0.91–2.49)[a] | 1.40 (0.84–2.31) | 1.24 (0.48–3.21) |
| Recurrent AOM | 1.09 (0.82–1.45) | 1.35 (1.00–1.82)[a] | 0.89 (0.58–1.38) |
| Symptoms at baseline | | | |
| Fever at inclusion | 1.29 (0.95–1.75)[a] | 0.93 (0.67–1.28) | 3.31 (2.04–5.37)[a] |
| Pain at inclusion | 1.09 (0.71–1.69) | 1.33 (0.83–2.14) | 0.56 (0.31–0.99)[a] |
| Bilateral AOM | 2.09 (1.50–2.92)[a] | 2.21 (1.56–3.13)[a] | 1.53 (0.97–2.40)[a] |
| Otorrhea | 2.04 (1.16–3.58)[a] | 1.94 (1.11–3.39)[a] | 0.36 (0.81–1.59) |
| Runny nose | 1.36 (0.88–2.11) | 1.19 (0.75–1.90) | 2.36 (1.14–4.89)[a] |
| Crying | 1.06 (0.65–1.75) | 1.01 (0.60–1.72) | 0.83 (0.44–1.56) |
| Coughing | 0.88 (0.62–1.24) | 0.75 (0.52–1.07) | 1.59 (0.88–2.87) |
| Tympanic membrane | | | |
| Red | 1.91 (1.08–3.36)[a] | 1.73 (0.96–3.13)[a] | 2.94 (0.91–9.53)[a] |
| Bulging | 0.94 (0.71–1.26) | 0.86 (0.63–1.16) | 1.30 (0.84–2.01) |
| Perforated | 1.65 (0.64–4.22) | 1.43 (0.56–3.64) | |

[a] Statistically significant predictor ($P \leq .10$).

TABLE 3 **Independent Predictors of Fever at 3 to 7 Days, Pain at 3 to 7 Days, and Prolonged Course (Defined as Pain and/or Fever at 3–7 Days)**

| Variable | OR (95% CI) | *P* | ROC Curve Area (95% CI) |
|---|---|---|---|
| Pain and/or fever at 3–7 d | | | 0.63 (0.59–0.68) |
| Age of <2 y | 2.07 (1.47–2.91) | <.0001 | |
| Bilateral AOM | 1.70 (1.19–2.41) | .003 | |
| Pain at 3–7 d | | | 0.64 (0.59–0.68) |
| Age of <2 y | 2.02 (1.41–2.89) | <.0001 | |
| Bilateral AOM | 1.80 (1.25–2.60) | .002 | |
| Fever at 3–7 d | | | 0.67 (0.61–0.73) |
| Age of <2 y | 1.58 (0.98–2.55) | .06 | |
| Fever | 3.02 (1.84–4.94) | <.0001 | |

ROC indicates receiver operating characteristic.

Figure 1 shows the proportions of children experiencing fever and/or pain during the follow-up period. Table 4 shows the absolute risks of fever and/or pain, fever, and pain at 3 to 7 days for children with certain combinations of independent prognostic factors. The absolute risk of pain and/or fever at 3 to 7 days was highest for children <2 years of age with bilateral AOM (ie, 55%; 95% CI: 47%–63%; 20% of all children). The risk for children ≥2 years of age with unilateral AOM was 25%; 95% CI: 20%–30%; 47% of all children). The results of the complete case and sensitivity analyses (including only the trials that measured the outcome at the same time, used the same dosage, or included a placebo) were in agreement with the overall results.

## DISCUSSION

Combining data from the observation groups of 6 randomized trials, we found that age of <2 years and bilateral AOM were independent predictors of a prolonged course of AOM. The absolute risk of pain and/or fever at 3 to 7 days for children <2 years of age with bilateral AOM (20% of all children) was 55%, whereas the risk for children ≥2 years of age with unilateral AOM (47% of all children) was 25%.

Reliably identifying prognostic factors for a prolonged course has been difficult, because individual studies were too small for valid reliable analyses. Meta-analyses of the original data of the individual trials have been proposed as a major improvement, because they have

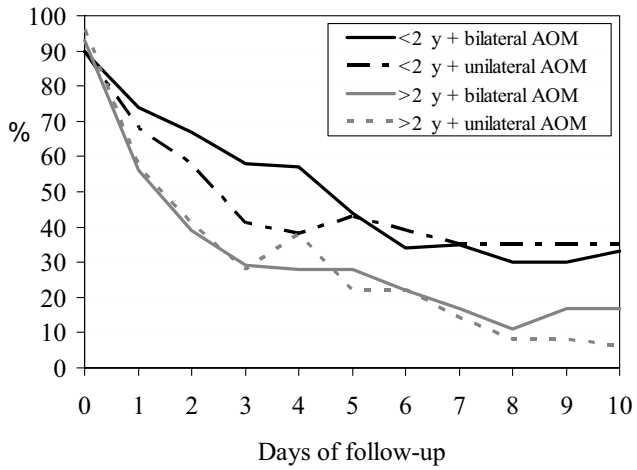


FIGURE 1
Proportions of children with AOM with a prolonged course (defined as pain and/or fever) in the subgroups with the predicting variables during the follow-up period.

greater power for informative prognostic analyses, allowing more-thorough assessment of whether differences are spurious.[35] By reanalyzing the data of 6 trials, we were able to include 824 children. Moreover, with exclusion of the children from the antibiotic treatment groups, the results represent the natural history of untreated AOM. To our knowledge, this is the first study that attempts to predict the absolute risks of a prolonged course in children with AOM.

Some of our findings deserve additional discussion. First, 6 of the 10 relevant randomized trials were included in our meta-analysis. The main-effect results for the 4 trials whose individual patient data were not available were very similar to those for the included trials (ie, antibiotics had a marginal effect); therefore, it is not expected that inclusion of these data would have changed the results of this meta-analysis. The major advantage of such a large study is that it minimizes the possibility of both type I and II errors. Because our study included 300 children who developed the outcome, we had the power to evaluate ~30 predicting variables, whereas we studied only 18.

Second, the results are based on data for children participating in trials, who may not be representative of those visiting general practitioners. For example, more severely affected children may be underrepresented in the trials. However, because we had access to raw data from 6 randomized trials, the numbers in the specific high-risk groups that are often underrepresented in a single trial were higher than in all studies performed to date. Furthermore, the population of children included in our meta-analysis seemed representative of those visiting general practitioners in daily life, because the proportions of children <2 years and ≥2 years of age in our study were similar to those in national surveys (ie, 35% vs 33% and 65% vs 67%, respectively).[36]

Third, because not all trials used objective diagnostic methods (eg, pneumatic otoscopy or tympanometry), some children might not have suffered from an ear infection. However, results of sensitivity analyses with the 3 trials that did use these diagnostic methods[27,29,30] were in agreement with the overall results.

Fourth, we included only children allocated to the observation arm in our analyses, which is appropriate because treatment with antibiotics would influence the course of the disease and result in an invalid natural history model. Fifth, some predictor and outcome variables (eg, fever and pain) might have been more informative if analyzed on a continuous scale. Some trials did measure these items on a continuous scale but, because others did not, we needed to recode these items as dichotomous variables. Other possible important outcomes, such as severity of pain, night disturbance, and

TABLE 4 **Absolute Risks of Fever at 3 to 7 Days, Pain at 3 to 7 Days, and Prolonged Course (Defined as Pain and/or Fever at 3–7 Days) for Each Subgroup of Predicting Variables**

| Predicting Variables | No. (%) of All Children | Absolute Risk (95% CI), % |
|---|---|---|
| Pain and/or fever at 3–7 d | | |
| Age of <2 y plus bilateral AOM | 134 (20) | 55 (47–63) |
| Age of <2 y plus unilateral AOM | 132 (20) | 40 (32–48) |
| Age of ≥2 y plus bilateral AOM | 86 (13) | 35 (25–45) |
| Age of ≥2 y plus unilateral AOM | 308 (47) | 25 (20–30) |
| Pain at 3–7 d | | |
| Age of <2 y plus bilateral AOM | 134 (20) | 46 (38–54) |
| Age of <2 y plus unilateral AOM | 132 (20) | 33 (25–41) |
| Age of ≥2 y plus bilateral AOM | 86 (13) | 30 (20–40) |
| Age of ≥2 y plus unilateral AOM | 308 (47) | 19 (15–23) |
| Fever at 3–7 d | | |
| Age of <2 y plus fever | 153 (22) | 23 (16–30) |
| Age of <2 y plus no fever | 134 (19) | 8 (3–13) |
| Age of ≥2 y plus fever | 134 (19) | 15 (9–21) |
| Age of ≥2 y plus no fever | 285 (40) | 6 (3–9) |

Percentages may change because of missing data.

duration of symptoms before study entry, were not measured in all trials and therefore could not be studied. Consequently, we cannot rule out the possibility that some children had relatively mild complaints.

To date, 2 studies that tried to identify predictors of antibiotic use have been performed.[9,37] They also found that fever was a prognostic factor for antibiotic usage (indicating a poor outcome). Neither of them, however, studied bilateral AOM, and Little et al[9] dichotomized age at 3 years, which seemed not to predict a poor outcome. A cutoff value of 2 years of age seems to be more relevant, because it is known that protective immunity against infections with encapsulated bacteria, such as the species that cause AOM, depends on the ability to produce specific antibodies against bacterial capsular polysaccharides, which is inadequate until 2 years of age.[38] The anatomic features of the eustachian tubes and the nasopharynx also differ with age.[39,40] Consequently, children <2 years of age seem to be more susceptible to AOM. Moreover, guidelines often recommend treating children <2 years of age with antibiotics, whereas an initial observation period is recommended for children ≥2 years of age.[41–43] We also studied different cutoff points, which showed that children <3 years of age also had a higher risk of a prolonged course but the absolute risks were much smaller (ie, the absolute risk of pain and/or fever at 3–7 days for children <3 years of age with bilateral AOM was 33%).

## CONCLUSIONS

The risk of fever and/or pain at 3 to 7 days was 2 times as high for children <2 years of age with bilateral AOM, compared with children ≥2 years of age with unilateral AOM. Clinicians can use these features (ie, age of <2 years and bilateral AOM) to inform parents more explicitly about the expected course of their child's AOM and to explain which features should prompt parents to contact their clinician for reexamination of the child.


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