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Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years

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Abstract

Objective To determine the effect of antibiotic treatment for acute otitis media in children between 6 months and 2 years of age.

Design Practice based, double blind, randomised, placebo controlled trial.

Setting 53 general practices in the Netherlands.

Subjects 240 children aged 6 months to 2 years with the diagnosis of acute otitis media.

Intervention Amoxicillin 40 mg/kg/day in three doses.

Main outcome measures Persistent symptoms at day four and duration of fever or pain or crying, or both. Otoscopy at days four and 11, tympanometry at six weeks, and use of analgesic.

Results Persistent symptoms at day four were less common in the amoxicillin group (risk difference 13%; 95% confidence interval 1% to 25%). The median duration of fever was two days in the amoxicillin group versus three in the placebo group (P = 0.004). No significant difference was observed in duration of pain or crying, but analgesic consumption was higher in the placebo group during the first 10 days (4.1 v 2.5 doses, P = 0.004). In addition, no otoscopic differences were observed at days four and 11, and tympanometric findings at six weeks were similar in both groups.

Conclusions Seven to eight children aged 6 to 24 months with acute otitis media needed to be treated initially by their own general practitioner. Children aged between 6 and 24 months were eligible if they presented with acute otitis media—defined as infection of the middle ear of acute onset and a characteristic ear drum picture (injection along the handle of the malleus and the annulus of the tympanic membrane or a diffusely red or bulging ear drum)—or acute otorrhoea. In addition, one or more symptoms of acute infection (fever, recent earache, general malaise, recent irritability) had to be present, in line with the Dutch guidelines.

Methods

Study population

The study was conducted between February 1996 and May 1998 in the Netherlands, where all patients are treated initially by their own general practitioner. Children aged between 6 and 24 months were eligible if they presented with acute otitis media—defined as infection of the middle ear of acute onset and a characteristic ear drum picture (injection along the handle of the malleus and the annulus of the tympanic membrane or a diffusely red or bulging ear drum)—or acute otorrhoea. In addition, one or more symptoms of acute infection (fever, recent earache, general malaise, recent irritability) had to be present, in line with the Dutch guidelines.

The following exclusion criteria were applied: antibiotic treatment in the preceding four weeks; proved allergy to amoxicillin; compromised immunity; craniofacial abnormalities; Down’s syndrome; or being entered in this study before. The 53 participating general practitioners were trained to classify ear drums by using a standard set of slides depicting a range of common ear drum appearances with the emphasis on discriminating between acute otitis media and oitis media with effusion. The study protocol was approved by the ethical committee of the Children’s Hospital of the University Medical Centre Utrecht; and all parents of the children gave written informed consent before enrolment.

Intervention

Patients received either amoxicillin suspension 40 mg/kg/day in three divided doses for 10 days or placebo suspension. Most patients in the Netherlands...
with acute otitis media receive decongestant nose
drops, so all patients received one drop of oxymetazo-
line 0.025% in each nostril three times a day (Nasivin, 
Merck) for seven days. The use of paracetamol was 
allowed when the child was in pain, the amount being 
recorded in the diary. For each dose children under 1 
year old received a 120 mg suppository and older chil-
dren received 240 mg.

At the baseline visit the doctor recorded the history, 
the presence or absence of certain risk factors for acute 
otitis media, and the results of otoscopy. Parents were 
instructed to keep a 10 day diary showing occurrence 
of aural and gastrointestinal symptoms and adminis-
tration of study medication, paracetamol, and nose 
drops. Follow up visits were scheduled on days four 
and 11 at the general practitioner’s clinic, inquiry was 
made about remaining symptoms, and the ear drum 
was examined. At six weeks all children were visited at 
home by the first author (RD), and information was 
obtained about present and past symptoms, antibiotic 
use, and any referral to a paediatrician or otolaryn-
gologist since day 11. Further otoscopy and tympan-
omeetry was also carried out.

**Outcome measures**

The primary outcome measure was persistent symp-
toms at day four, assessed by the doctor and defined as 
persistent earache, fever (≥38°C), crying, or being irri-
table. In addition the prescription of another antibiotic 
because of clinical deterioration before the first follow 
up visit was to be considered a persistent symptom.

Secondary outcome measures were clinical treat-
ment failure at day 11, defined as persistent fever, ear-
ache, crying, being irritable, or no improvement in the 
appearance of the tympanic membrane, defined as 
persistent redness, bulging, or perforation of one or 
both tympanic membranes; the duration of fever 
(≥38°C), pain, or crying, defined as the number of days 
until the first day on which these signs were considered 
absent and remained absent as recorded in the diary by 
the parents; the mean number of doses of analgesics 
given, based on the diaries; adverse effects mentioned 
in the diaries; and the percentage of children with mid-
dle ear effusion at six weeks. The diagnosis of effusion 
was based on combined otoscopy and tympanome-
try. Type B and C2 tympanograms (modified Jerger’s 
classification) were regarded as indicative of the 
presence of fluid in the middle ear.17 18

**Sample size and data analysis**

Calculation of the sample size was based on the 
assumption of a minimum difference of 20% in 
primary outcome between the groups, with an α of 5%, 
a discriminating power of 80%, and an estimated 60% 
persistent symptoms in the placebo group.1 2 The total 
number of children required in each treatment arm 
was 70.

All analyses were carried out with SPSS on an inten-
tion to treat basis. We performed best and worst case 
analyses when necessary because of loss to follow up.

The prevalence of persistent symptoms at day four, 
clinical treatment failure at day 11, occurrence of middle 
ear effusion at six weeks, and side effects in the two 
groups were compared by calculating differences in risk 
with 95% confidence intervals. Durations of fever and of 
pain or crying, or both, were plotted by means of 
Kaplan-Meier curves, and differences between the treat-
ment groups were tested by the log rank test. When 
diary data were incomplete and the last entry recorded 
fever or pain, the child was censored in the survival 
analysis. The difference in the mean analgesic consump-
tion in the two groups was tested with the Mann-
Whitney U test. All reported P values are two sided.

To adjust for possible confounding due to unequal 
distribution of baseline characteristics we used logistic 
regression analysis with the primary outcome measure 
as the dependent variable.

**Assignment and blinding**

After we obtained consent the children were randomly 
assigned to treatment with amoxicillin or with a 
placebo suspension with the same colour and taste. 
The suspensions were supplied to the participating 
doctors in a double blind fashion with computerised 
two block randomisation; doctors, parents, and investi-
gators remained blinded throughout the study. During 
the trial the code of the allocation schedule was kept in 
the pharmacy of the University Medical Centre, 
Utrecht, and was broken only if severe complications 
or side effects occurred.

**Results**

**Participant flow and follow up**—Of the 425 children with 
acute otitis media registered, 362 were eligible, and 
from these 240 were randomly assigned to one of the 
treatment groups (figure). Children in the antibiotic 
group and the placebo group differed in the 
prevalence of recurrent acute otitis media, regular 
attendance at a day care centre, and parental smoking 
habits (table 1).

**Outcome at day four—**Persistent symptoms at day 
four occurred in 69 out of 117 children (50%) in the 
amoxicillin group and in 89 of 123 (72%) in the 
placebo group (difference in risk 13%; 95% confidence 
interval 1% to 25%) (table 2). Adjustment for 
recurrence, day care, and smoking as possible 
confounders in the logistic regression analyses showed 
an odds ratio of 1.79 (1.03 to 3.13). Among children 
with persistent symptoms four (one in the amoxicillin 
group and three in the placebo group) received other 
antibiotics. Three of these children were admitted to 
hospital (one in the amoxicillin group, two in the 
placebo group); one (placebo group) was admitted on 
the third day with meningitis but because of deteriora-
tion this child had already been started on another 
antibiotic on day two. The culture of cerebrospinal fluid 
yielded negative results, but the Gram stain suggested 
 streptococcal meningitis. The two other children were 
admitted because of dyspnoea (amoxicillin group) and 
dehydration (placebo group). All four recovered 
without residual symptoms. Inclusion of the one child 
lost to follow up (amoxicillin group) in either outcome 
group did not materially change the findings.

**Outcome at day 11—**Clinical treatment failure at day 
11 occurred in 72 out of 112 children (64%) in the 
amoxicillin group and in 84 of 120 (70%) in the 
placebo group (6%; -6% to 18%) (table 2). Eleven 
children received other antibiotics (three in the amoxi-
cillin group, eight in the placebo group) and were 
recorded as treatment failures. One of these children 
(placebo group) needed admission to the hospital
because of deterioration of symptoms of acute otitis media. Six children (three in each group) were lost to follow-up between day four and day 11, and in one case (amoxicillin group) the evaluation of the ear drum was missing, although the symptoms were gone. A best case scenario (amoxicillin group analysed as “cured” and placebo group as “not cured”) did not show any significant difference in clinical treatment failure at day 11 (9%; −3% to 21%).

Duration of fever and pain or crying—The median time to cessation of fever was two days with amoxicillin and three days with placebo (P = 0.004; log rank test). Median time to cessation of pain or crying was eight days with amoxicillin and nine days with placebo (P = 0.432; log rank test).

Analgesic consumption—During the first three days, mean analgesic consumption in the amoxicillin group was 1.7 doses and in the placebo group 2.5 doses (P = 0.018). Over the whole 10 days these figures were 2.3 and 4.1, respectively (P = 0.004).

Outcome at six weeks—At six weeks 212 children were examined. Middle ear effusion was present in 69/107 (64%) in the amoxicillin group and in 70/105 (67%) in the placebo group (3%; −10% to 16%). The proportion of children with bilateral effusion was 48% in both groups. In addition, no clear differences were observed between the two groups as regards recurrent acute otitis media, use of antibiotics in this period, referrals to the otolaryngologist or paediatrician, or surgery.

Adverse effects—De novo diarrhoea was reported on day four in 17% (20/117) of the amoxicillin group and in 10% (12/123) of the placebo group (difference −7%; −16% to 2%). On day 10 these figures were 12% (14/117) and 8% (10/123), respectively (difference −4%; −12% to 4%). Of the children lost to follow up, five were withdrawn (all between day four and day 11) because of possible side effects, two because of diarrhoea (both in the amoxicillin group) and three because of skin rashes (all in the placebo group).

Compliance—According to the diaries the mean number of doses of study medication taken was 24.6 (82% of possible total) in the amoxicillin group and 23.2 (76%) in the placebo group (P = 0.9). According to

### Table 1 Baseline characteristics of 240 children randomised in trial of antibiotic use for treatment of acute otitis media. Figures are numbers of children except for mean age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amoxicillin (n=117)</th>
<th>Placebo (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (months)</td>
<td>13.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>Breastfed for &gt;6 months</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>≥2 children in family</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Season of inclusion (Oct-March)</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>Smoking in household</td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>Attendance at day care centre</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Medical history:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent URTI</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>Recurrent AGM in family</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Allergy</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Recurrent AGM</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>Clinical presentation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 days complaints</td>
<td>57</td>
<td>54</td>
</tr>
<tr>
<td>Earache</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Fever</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>Perforation</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Bilateral AGM</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>Bulging ear drum</td>
<td>25</td>
<td>29</td>
</tr>
</tbody>
</table>

URTI=upper respiratory tract infection. AGM=acute otitis media.
the suspension remaining in the returned bottles, 80% of the children in both groups had received the full amount, and 95% received at least 80% of the amount prescribed.

Discussion

In this study resolution of symptoms on day four was more common in those treated with amoxicillin than in those taking placebo. At day 11, no significant differences in symptoms and otoscopy results were observed. Amoxicillin shortened the duration of fever by one day, and analgesics were used more often in the placebo group.

The significant reduction of the duration of fever observed in the amoxicillin group is in accord with the results of Burke et al in children aged 3 to 10 years.7 We observed no difference between the two groups in pain or crying. This was also reported by Burke et al, and the amounts of analgesics taken in their study were comparable with those in ours.3 The fact that more analgesics were used in the placebo group could explain the lack of difference in duration of pain or crying.

The number of children with persistent symptoms in our study was high compared with other studies.2 18 Burke et al, however, included only older children and in young children symptoms are often prolonged.18 Contrary to our results complete resolution of symptoms was not mentioned by Kaleida et al.19 Our diagnoses were based on acute signs of infection and abnormality of the ear drum; this has shown to be adequate in other studies1 4 and is in accord with day to day practice in the Netherlands. An abnormal ear drum had to be seen because diagnosis based only on symptoms is not specific.20 According to the baseline characteristics the results in our sample are generalisable to the population seen in primary care in the Netherlands.1 2

What is already known about this

Several meta-analyses have shown that the effectiveness of antibiotics for acute otitis media is limited in terms of clinical improvement

For children under 2 years of age—a risk group with regard to poor outcome—the evidence of the effectiveness of antibiotics for this common condition is not conclusive

What this paper adds

This randomised study shows that seven to eight children, aged 6 to 24 months, with acute otitis media need to be treated with amoxicillin to improve symptomatic outcome at day four in one child

This is not sufficiently important clinically to prescribe antibiotics for every child with acute otitis media in this age group

Watchful waiting at the first visit is therefore justified for these children

Table 2 Main outcome measures in infants with acute otitis media randomised to receive amoxicillin or placebo

<table>
<thead>
<tr>
<th>Measure</th>
<th>Amoxicillin</th>
<th>Placebo</th>
<th>Difference in % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of symptoms* at day 4</td>
<td>69/114 (60)</td>
<td>89/123 (72)</td>
<td>13 (1 to 25)</td>
<td>0.031</td>
</tr>
<tr>
<td>No improvement in ear drum at day 4</td>
<td>68/111 (61)</td>
<td>99/120 (83)</td>
<td>6 (4 to 15)</td>
<td>0.301</td>
</tr>
<tr>
<td>Clinical treatment failure† at day 11</td>
<td>72/112 (64)</td>
<td>84/120 (70)</td>
<td>6 (6 to 18)</td>
<td>0.351</td>
</tr>
<tr>
<td>Median duration of fever (days)</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0.004</td>
</tr>
<tr>
<td>Median duration of pain/crying (days)</td>
<td>8</td>
<td>9</td>
<td>1</td>
<td>0.432</td>
</tr>
<tr>
<td>Mean consumption of analgesia in first 10 days (dose)</td>
<td>2.3</td>
<td>4.1</td>
<td>1.8</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Defined as still having earache or having fever, crying, being irritable, or having received other antibiotics.
†Defined as still having symptoms or no improvement, or both, in tympanic membrane.
‡Defined as still having symptoms or no improvement, or both, in tympanic membrane.
¶Mann-Whitney U test.
§Log rank test for Kaplan-Meier plot.
||

The treatment regimen we used (amoxicillin 40 mg/kg/daily) is still the treatment of first choice.22 The dosage was deemed sufficient because incidences of resistant Streptococcus pneumoniae and Haemophilus influenzae in the Netherlands remain low at < 1%32 and 6% (data on file 1998, Dutch National Institute of Public Health and Environmental Protection), respectively, and compliance in this study was good.

As primary outcome measure we combined earache, crying, and irritability because in these little children it is difficult to establish earache as such. We have shown that seven to eight children aged 6 to 24 months with acute otitis media needed to be treated to improve symptomatic outcome at day four in one child. This is not sufficiently important clinically to prescribe antibiotics for every affected child within this age group. Routine prescription of antibiotics would not prevent all cases of meningitis.24 Our conclusion is that watchful waiting at the first visit is justified for these children. Instead of antibiotics analgesics could be given for proper resolution of symptoms but more research is needed as to whether this is a good alternative.

We thank all the general practitioners who included patients for this trial.

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Competing interests: Nasivin nose drops for this study were donated by E Merck Nederland BV.

Contributors: RAMJD was responsible for the planning of the study, data collection and analysis. FAMvB, and RAdM designed the protocol and were the supervisors of RAMJD. AWH and TJMV assisted with the analysis of the results. The manuscript was prepared by RAMJD and commented on by all authors. RAMJD is the study guarantor.

After some 30 years of medical development focusing largely on hospitals, organ specialisation, and high technology, the 1960s saw the revitalisation of general practice (in some countries known as family practice—see note at the end of the article), allowing this field of medicine to develop into a cornerstone of the healthcare system. At the end of the millennium academic general practice is now established in all developed countries. General practice is recognised as a special discipline and in many countries as a medical specialty equally important as and complementary to other specialties. Participation in specific training programmes has therefore become mandatory for anyone who wishes to become a specialist in this field. The time has come to reflect on the education of general practitioners, which depends on the scientific content of general practice. A proper starting point is to consider the ideal content of the discipline as it would be described in a definition.

Old definitions of general practice

Many definitions of primary care and general practice have been proposed. One of the most frequently quoted is the Leeuwenhorst definition from 1974: “The general practitioner is a licensed medical graduate who gives personal, primary and continuing care to individuals, families and a practice population irrespective of age, sex and illness. It is the synthesis of these functions which is unique.” Other definitions also focus on the patient on an individual in a family and cultural context, continuity of care, and the sustained relationship with patients. Hence most textbooks describe the particulars of the general practitioner in terms of working methods such as continuity, comprehensiveness, work in a society (or even in patients’ homes), a family approach, and good communication. Other definitions and descriptions of general practice gave prominence to systems, settings, and methods creating opportunities for good general practice.

We question whether these dimensions in themselves distinguish between those doctors who are general practitioners and those who are not. Not only that, but they may hamper change and promote failure. They are rooted in a model of long term, full time, year round service in a stable community. Although rewarding for the doctor, this is a difficult role, with high personal and social costs for doctors in a modern society.

We contend that many definitions confuse the setting with the role and the person. They do not help us in defining the academic agenda for universities or...