Acute otitis media in infancy in general practice

A therapeutic and prognostic study

Roger Damoiseaux

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Acute otitis media in infancy in general practice

A therapeutic and prognostic study

Acute middenoorontsteking bij kinderen van 6 maanden tot 2 jaar in de huisartsenpraktijk

(met een samenvatting in het Nederlands)

Proefschrift

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ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen
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door

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geboren op 17 augustus 1961 te Schinnen

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Chapter 1

Acute otitis media in children aged under two years: introduction and aims of the study.

R.A.M.J. Damoiseaux

Adapted from: Tijdschr. v Huisartsgeneeskunde 1999; 16 Suppl 6: 10-12.

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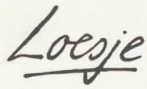

1.1 Introduction

In the Netherlands acute otitis media (AOM) is normally treated in general practice.[1] The first guidelines of the Dutch College of General Practitioners for management of this common childhood malady divided children into three groups by age: under 6 months, between 6 months and 2 years, and over 2 years of age.[2]
For those older than 2, symptomatic treatment and watchful waiting for 3 days were recommended, with antibiotics if symptoms persisted for more than 3 days. Van Buchem et al estimated that in a general practice population more than 90 per cent of such older children with AOM recovered within 3 days with symptomatic treatment (nose drops and analgesics) only.[3] A severe course (persistent illness with severe pain or high temperature, or both, after 3-4 days) was estimated to occur in fewer than 3 per cent of cases, and these children responded well to antibiotics. These findings justify this policy for children aged over 2.
For children aged under 6 months, antibiotics were recommended at the first visit, together with close monitoring; and even consideration of immediate referral. These recommendations were based on consensus opinion and the high risk of complications.[2]
For children aged between 6 months and 2 years the early guidelines recommended watchful waiting for 24 hours and antibiotics if there was no improvement in that time. The reason for the more intensive monitoring of this group was the higher risk of complications such as bacteremia and dehydration, compared with older children.[2] The revised guidelines do not distinguish this age group separately form the older children anymore.[4] In this first chapter we describe AOM in children under 2, and discuss important issues in this age group.

1.2 Epidemiology

Acute otitis media is a common disease in general practice, with an incidence of 200 per 1000 children under 2 per year.[1] A Dutch general practitioner with a list of 2300 patients may thus expect to see 10 to 15 such children a year with an episode of AOM. In a Dutch cohort study of 289 children followed from birth until their second birthday, 44 per cent had experienced at least one episode of AOM, diagnosed by a doctor.[5] In the United States of America these figures are higher: 60 per cent of children have had at least one episode of AOM by one year of age and as many as 80

per cent by age 3.[6] One reason for this difference could be that parents are familiar with the cautious policy of Dutch general practitioners in prescribing antibiotics, so children with AOM are not brought to a doctor straight away, whereas in other countries parents can expect antibiotics to be prescribed at the first visit.[7] Figures for incidence are normally based on cases presenting to medical facilities, so differing medical practices could account for apparent differences although true incidences could very well be the same.

1.3 Determinants and prognosis

Determinants for AOM can be divided in two groups: environment-related and host-related. Day care is a well accepted environment-related determinant, and a Finnish study reported that approximately 14 per cent of all otitis media episodes would have been avoided if all of the children had been cared for at home.[8] Breast-feeding and cessation of parental smoking would have a similar but smaller effect according to the same study. Whether passive smoking is a real determinant for AOM is still in doubt.[9] The protective effect of breast-feeding can last up to 4 months after it has been stopped.[5] Furthermore, it is known that AOM is commoner in wintertime.[1] Host-related determinants are a history of recurrent otitis media in a sibling and being male.[6]

Early onset of AOM is associated with a high recurrence rate[6,10,11] but little research has been done on determinants predictive of recurrence after an initial episode of AOM before age 2.

Apart from these clinical determinants, research has been done on genetic markers and levels of immunoglobulins as predictors of AOM.[12,13] The relevance of these findings for the general practitioner still needs to be established.

Children under 2 with an episode of AOM are at increased risk of persistence of middle ear effusion (MEE).[14,15,16] Whether determinants for persistent MEE in children in general, such as season, bilateral disease, type B tympanogram at time of diagnosis, or history of recurrence are also applicable to children under 2 still needs to be established.

1.4 Microbiology

The pathogens causing AOM in a general practice population have not been systematically investigated. In clinical populations bacteria are isolated in more than 80 per cent of children with AOM.[17] Streptococcus pneumoniae is the commonest organism isolated (25-50 per cent) and the next most important is non-typable Haemophilus influenzae (15-30 per cent). Other pathogens are Moraxella catarrhalis (3-20 per cent), group A streptococci, and Staphylococcus aureus (2-3 per cent).[18] Resistance of these bacteria to antibiotics is an increasing problem world-wide.[19] In the Netherlands the incidences of resistant Streptococcus pneumoniae and Haemophilus influenzae remain low at <1 per cent[20] and 6 per cent respectively (data on file 1998, Dutch National Institute of Public Health and Environmental Protection). Several studies have indicated a crucial role for respiratory viruses in the aetiopathogenesis of AOM.[21,22,23] Viruses associated with AOM in these studies were respiratory syncytial virus, influenza virus, rhinovirus and adenovirus. A virus has been demonstrated as the sole pathogen in middle ear fluid in 6 per cent of patients.[24]

1.5 Age related aspects of the pathogenesis

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. Physiologically, the antibody response to pneumococcal capsular polysaccharides is inadequate until age 2.[25] Children have high levels of maternal IgG at birth but these decline gradually to a nadir at about 6 months. There is a relationship between the maturation of the immune response and the changing pattern of susceptibility to infections in childhood.[26] Epidemiological studies show that children under 2 are more susceptible than older children to AOM.[6]

The anatomical features of the Eustachian tube and the nasopharynx differ with age and there is an association between recurrent AOM and the dimensions of the nasopharynx.[27,28] Also for this reason children under 2 are more susceptible to AOM.

1.6 Diagnosis and symptoms

The guidelines of the Dutch College of General Practitioners define AOM as an infection of the middle ear of acute onset, with 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 eardrum), or acute otorrhoea. In addition, one or more symptoms of acute infection (fever, recent earache, general malaise, recent irritability) must be present.[2] Internationally, pneumatic otoscopy is the recommended method of diagnosis. This is based on the fact that MEE needs to be present for the diagnosis of AOM.

Symptoms in children under 2 with AOM are different from those in older children.[29,30,31] They have more often non-specific symptoms such as diarrhoea, poor appetite, irritability, rubbing of the ear or fever.[29] Diagnosis on symptoms alone is not very specific and otoscopic examination of the eardrum is needed for a more specific diagnosis. Otorrhoea at this age is almost always due to AOM. A distinct red or bulging eardrum is highly specific for AOM.[32] An only slightly red drum is much less specific. Crying or an upper respiratory tract infection without AOM can also cause a slightly red eardrum. Furthermore, otoscopic examination in very young children is not always easy, and diagnostic certainty is lowest in this group.[7]

Little is known about the duration of symptoms in children under 2 with AOM, except that it is longer than in older children.[33]

1.7 Management

Antibiotics are currently thought to be the treatment of choice for AOM in nearly all countries.[7] This is rather surprising since their ability to effect clinical improvement seems limited.[34,35] Several authors have advocated restricting antibiotic treatment for AOM to children at increased risk of poor outcome or complications, notably those aged under 2,[36,37] but no study has shown that antimicrobial treatment improves outcome in such children.[36] The Netherlands is still the only country where only a minority of episodes of AOM are treated with antibiotics.[7] Recently the guidelines of the College of General Practitioners have been revised.[4] Children aged between 6 and 24 months are no longer regarded as a separate group and are now recommended for the same management as children over 2, i.e. symptomatic treatment for the first 3 days and antibiotics if symptoms then still persist. Whether this is the right policy has

still to be proven. The effectiveness of antibiotics for AOM in children aged under 2 years still needs to be established. Furthermore, little is known about the duration of symptoms during an AOM episode in this age group. Is 3 days really the ideal watchful waiting time in this group?
Finally, for the implementation of evidence-based medicine it is important to know what factors influence doctors in their actual prescribing of drugs. From studies with simulated cases we know that the decision to prescribe antibiotics is not based solely on biomedical factors: social information about the patient also plays a part.[38,39] To date, however little is known about the reasons for actual prescribing of antibiotics.[40]

1.8 Aims of the study

Children aged 6 to 24 months with AOM are a special group and until now little has been known about the effectiveness of antibiotic treatment, the duration of symptoms, and which children in this group are at risk for recurrent AOM or persistent MEE. The aims of this study can be described as follows:

- to determine the effectiveness of antibiotic treatment of AOM in children under 2 years of age by systematically reviewing the literature and assessing the methodological quality of published randomised clinical trials;
- to assess the effectiveness of amoxicillin in children aged 6 months to 2 years with AOM in general practice in a placebo controlled, double blind, randomised trial;
- to determine the duration of clinical symptoms in children under 2 years of age with AOM;
- to determine the clinical factors that predict recurrence of AOM or persistent MEE in the 6 months following an episode of AOM in these children;
- to determine whether serum levels of specific IgG1 and IgG2 antibodies for selected pneumococcal serotypes can predict recurrence within 6 months of an index episode in primary care;
- to assess whether a family history of recurrent AOM is related to low levels of IgG1 or IgG2 antibody levels against selected pneumococcal serotypes, as a possible indication of a genetic predisposition; and
- to determine reasons for the actual prescribing of antibiotics for AOM other than those provided by the guidelines of the Dutch College of General Practitioners on AOM.

1.9 A reader's guide to this thesis

Chapter 2: The effectiveness of antibiotic treatment of AOM in children under 2 years of age is described. A systematic literature review and a quantitative analysis with an assessment of the methodological quality of published trials comparing antibiotic treatment with non-antibiotic treatment are reported.

Chapter 3: The results of a primary care based, randomised, double blind trial of amoxicillin versus placebo for AOM in children aged 6 months to 2 years are presented. Outcome measures discussed are: persistent symptoms at day 4, duration of fever and pain/crying, otoscopy at days 4 and 11, tympanometry at 6 weeks, and use of analgesics.

Chapter 4: The duration of clinical symptoms in an episode of AOM in children aged under 2 is described, with identification of factors influencing the speed of resolution of symptoms.

Chapter 5: A description of the long-term prognosis of AOM in infancy is presented. Determinants of recurrent AOM and persistent MEE for 6 months are discussed.

Chapter 6: A prospective study in general practice of the value of IgG1 and IgG2 antibodies for selected pneumococcal serotypes in prediction of recurrence of AOM within 6 months after an episode of AOM in infancy is presented.

Chapter 7: The relation of a positive sibling history of recurrent AOM and low pneumococcal serotype-specific IgG2 levels in children with an episode of AOM is presented. The possibility of a genetic predisposition is discussed.

Chapter 8: A study of Dutch general practitioners' reasons for prescribing antibiotics for AOM other than those listed in the College guidelines is presented. The implications of these reasons for appropriate use of antibiotics are discussed.

Chapter 9: The overall conclusions of the study are presented, with a discussion in the light of the present knowledge. Some practical implications and proposals for future research are suggested.

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Chapter 2

Antibiotic treatment of acute otitis media in children under two years of age: evidence based?

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Published in: Br J Gen Pract 1998; 48: 1861-4

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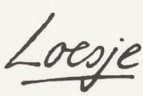

2.1 Abstract

Background: Appropriate use of antibiotics is one of the major issues in medicine today. In most countries, acute otitis media in children is treated with antibiotics; however the efficacy of antibiotic use in every acute otitis media is a controversial issue. It may be worthwhile looking for special risk groups that benefit more from antibiotic treatment for acute otitis media. Children under two years of age with acute otitis media are at risk of poor outcome.
Aim: To assess whether the current high prescription rates of antibiotics for acute otitis media in children under two years of age (being a risk group for poor outcome) are based on an established increased efficacy.
Method: Systematic literature review and a quantitative analysis with an assessment of the methodological quality of published trials, comparing antibiotic treatment with non antibiotic treatment in acute otitis media in children aged under two years.
Results: Six trials were included. Trials from before 1981 had a poor methodological quality. Four were suitable for the quantitative analysis. Only two of them were truly placebo controlled. Of these two, one included only recurrent acute otitis media and the other included only non-severe episodes. With these restricted data, no statistically significant difference was found between antibiotic-treated children and controls under two years of age with acute otitis media, judged on the basis of clinical improvement within seven days (common odds ratio 1.31; (95% CI: 0.83-2.08)).
Conclusion: The current high prescription rates of antibiotics among children under two years of age with acute otitis media are not sufficiently supported by evidence from published trials. New randomised placebo-controlled trials using reliable methodology are needed in this young age group.

2.2 Introduction

Although most children with acute otitis media (AOM) may need only symptomatic treatment, up to 86% of all episodes of the infection are treated with antibiotics.[1,2] Two recent meta-analysises on the effect of antibiotic treatment for AOM showed only a modest effect.[3,4] Rosenfeld et al. included 33 studies of children aged four weeks to 18 years, and the outcome of AOM was improved in only one in seven children treated with antibiotics.[3] Del Mar et al. included six studies of children aged seven months to 15 years and they found that even 17 children needed to be treated to

prevent pain in one child at 2-7 days after presentation.[4] Currently, no studies have identified subcategories of patients with AOM in whom antibiotic treatment is more effective.

Howie introduced the 'otitis prone' condition for children suffering six or more episodes of otitis media before the age of six.[5] Of his 'otitis prone' patients, 91% had their first AOM episode during the first year of life. Appelman found, in his study of children with recurrent AOM that those under two years of age were more likely to follow an abnormal course of illness, defined as pain and/or fever after three days.[6] Other authors report a higher recurrence rate and a higher rate of persistent middle ear effusion (MEE) in this age group.[7,8,9,10] This is probably the reason why antibiotic therapy is prescribed more often in children under two years with AOM than in older children.[2] Whether this strategy is justified by an established increased efficacy is not known.

We systematically reviewed the available literature to determine the efficacy of antibiotic treatment for AOM in children under two years of age.

2.3 Methods

We carried out a computer search using MEDLINE on articles published between 1966 and January 1997, and using EMBASE from 1974 until January 1997, using the following keywords: otitis media, child, clinical trial and placebo. In addition, the reference sections of these articles, and of several major review articles, were checked for missing trials meeting the inclusion criteria. Furthermore, an extensive hand search for clinical trials of therapy for AOM of all ages, performed by our group in 1991, was used.[11]

An article was included when the following criteria were met:

- Random allocation to the different treatment groups.
- Comparison of antibiotic treatment with non antibiotic treatment in AOM (not comparison of different antibiotics or different durations of treatment).
- Inclusion of children aged under two years, with separate presentation of the results for these young children.

The quality of the studies was assessed using the scoring system proposed by

Chalmers et al.[12] The items included in this scoring system are divided in four main categories (Box 1):

- study protocol,
- blinding procedures,
- testing procedures, and
- statistical analysis.

The items 'blinding of physicians and patients as to ongoing results' and 'multiple looks considered' were not considered in our analysis because no interim analysis

Box 1 Items for assessing the methodological quality of a trial proposed by Chalmers et al.

STUDY PROTOCOL (15 points)
- selection description
- reject log
- withdrawals
- therapeutic regimens definition
- control regimen (placebo)

BLINDING PROCEDURES (30 points)
- randomisation
- blinding of patients
- blinding of physicians as to therapy received
- blinding of physicians and patients as to ongoing results

TESTING PROCEDURES (15 points)
- prior estimate of numbers
- testing randomisation
- testing blinding
- testing compliance

STATISTICAL ANALYSIS (30 points)
- on major endpoints
- posterior ß estimate of observed difference for negative trials
- statistical inference
- appropriate statistical analysis
- handling of withdrawals
- side effects, statistical discussion
- retrospective analysis
- blinding of statistician
- multiple looks considered

were performed in the relatively short-term AOM trials. Because 'retrospective analysis' may be viewed both a positive and a negative aspect of a study, we did not include this item. Finally the item 'blinding of statistician' was not mentioned in any study and thus not included in our assessment. The maximum score was 79 points. All studies were scored independently by the four authors. The papers were blinded by removing all identifying information prior to distribution to the four reviewers. A consensus meeting was held to discuss any disagreements on assessment after the individual scoring, with differences resolved by discussion.
Where possible, data were extracted for a quantitative analysis. As an end point, symptomatic clinical improvement within seven days after start of treatment was used: the outcome measure presented most often in the trial reports. Otoscopic appearance, middle ear effusion, or bacteriological results were not considered as end points because they were presented infrequently in the available studies. An estimate of the common odds ratio (with approximate 95% confidence intervals) was computed according to the Mantel-Haenszel approach.[13]

2.4 Results

In total, 115 articles were identified after the computer search on MEDLINE and EMBASE. Based on the abstracts, only five articles met the inclusion criteria.[6,14,15,16,17] In the reference sections, one additional trial was found that met all the criteria.[18] Most papers(53) were excluded because they studied the efficacy of additional therapy compared with a placebo in antibiotic treated AOM. Other reasons for exclusion were that prevention of recurrent AOM(18), otitis media with effusion(14) or different duration of antibiotic treatment(9) were studied. Three trials were excluded because data of children younger than two years of age were missing.[1,19,20] In the reference sections, one additional trial had to be excluded for the same reason.[21] The remaining papers(13) were review articles or duplicate publications.
The characteristics of the six studies included in our analysis are shown in table 2.1. The diagnosis of AOM was based on otoscopic appearance of the tympanic membrane and clinical signs of acute infection in three studies,[6,16,17] and on otoscopy alone in two studies.[14,18] One study did not mention the diagnostic criteria.[15] Appelman included only recurrent AOM, and Kaleida compared antibiotic treatment with placebo in children under two years only in non-severe episodes. Severity in this study was assessed by temperature and otalgia score.

Two studies presented only separate data of children under three years of age.[14,18] In the study by Halsted et al, 80% of this group under 3 years were below two years of age.

A methodological quality assessment was carried out for all six studies. The methodological quality of the six studies ranged from 27% to 73% of the maximum score. The studies published after 1981 scored better (range 60% - 73%) than those published earlier (range 27% - 43%).

Efficacy

The results of the individual studies are mentioned in table 2.1. Four individual studies reported, at short term, a statistically significant reduction in clinical failure, persistent effusion at two weeks, persistent bacterial growth (at 2-7 days), or otoscopic signs of AOM in favour of antibiotic treatment.[15,16,17,18] Long-term results were mentioned in three studies, and no differences were seen between antibiotic therapy and placebo.[6,14,17]

We were able to extract data for quantitative analysis from four studies.[6,14,16,17] One study was excluded because the absolute number of children in the young age group was not reported.[18] Another was excluded because no data on clinical improvement were reported.[15] Clinical improvement in the four studies included in the quantitative analysis was assessed after a period lasting from 24 hours to six days after the start of treatment. The common odds ratio of clinical improvement in patients treated with antibiotics, compared with the reference group, was 1.31 (95% CI: 0.83 - 2.08) (table 2.2).

Restricting the quantitative analysis to studies with a methodological quality of 60% or more did not change the results (OR: 1.42 (95% CI: 0.85 -2.39)).[6,16,17] Exclusion of the study from Kaleida, in which only non-severe episodes were included, yielded an odds ratio of 1.10 (95% CI 0.56 - 2.15). Exclusion of the study of Appelman et al., which reported rather strong positive results, yielded an odds ratio of 1.20 (95% CI: 0.74 - 1.94).

2.5 Discussion

To assess the methodological quality of the trials, we used the method introduced by Chalmers et al.[12] Although many other methods have been proposed, most use similar

items. The paradigm for studies assessing drug efficacy is the double-blind, randomised, placebo controlled trial, and the reporting of these trials requires high

Table 2.1 Characteristics and methodological quality score of six trials.

Trial	Treatment	Controls	Sample size (<2yrs)	Follow up/Outcome measures	Method-ological quality	Results in young age group
Halsted (1968)	Ampicillin/ Penicillin-sulfa (+myringotomy)[1]	Placebo (+myringotomy)[1]	106 (80)	3-9 months/ clinical improvement, bacterial cure, recurrent attacks	43%	ND
Laxdal (1970)	Ampicillin/ Penicillin	Symptomatic	142 (±70)	21 days/ clinical failure	27%	AS (clinical failure)
Howie (1972)	Erytromycin/Ampi-cillin/ Sulfonamide (+myringotomy)[1]	Placebo (+myringotomy)[1]	280 (±280)	7 days/ persistent effusion, bacterial cure	33%	AS (persistent effusion, bacterial cure)
Engelhard (1989)	Amoxy/clav (+myringotomy)[2]	Placebo (+myringotomy)[2]	105 (105)	11 days/ clinical improvement, otoscopy	61%	AS (otoscopy)
Appelman (1991)	Amoxy/clav	Placebo	121 (27)	1 year/ irregular course (3 days) recurrent attacks	73%	ND
Kaleida (1991)	Amoxicillin	Placebo	536 (270)	1 year/ initial treatment failure persistent effusion	60%	AS (persistent effusion at two weeks)

[1] myringotomy for bacterial culture only

[2] myringotomy as part of treatment (only in half of the antibiotic group)

ND denotes no statistically significant difference in efficacy between antibiotic and control group

AS denotes antibiotic therapy superior to control treatment (end point for which antibiotic superior)

the methodological quality, expressed as a percentage of the maximum score

standards.[22] Trials before 1981 score moderately or poorly when judged by present standards. Conducting and reporting of a trial in that time did not require the same standards, but in order to assess the current value of their results judgement according

to the present standard seems reasonable. On the other hand, requirements could have been met by the earlier studies, but not mentioned in their reports because it was not required at that time.[12] This could result in an underestimation of the quality of the earlier trials.

Table 2.2 Clinical improvement within seven days following antibiotic treatment for AOM in children less than two years of age. Results of four randomised trials.

Basic data from trials				
	Patients improved/total no.patients evaluated (%)			
Trial	Antibiotic therapy	Control treatment	Odds Ratio	95% CI
Halsted	45/62 (73%)	20/27 (74%)	0.93	(0.29-2.87)
Engelhard	42/62 (68%)	23/32 (72%)	0.82	(0.29-2.3)
Appelman	11/15 (73%)	5/12 (42%)	3.85	(0.59-27.73)
Kaleida[1]	259/277 (94%)	229/254 (90%)	1.57	(0.8-3.09)
Total	357/416 (86%)	277/325 (85%)	-	-

Weighted Odds Ratio (Mantel-Haenszel): 1.31 (95% confidence interval 0.83 - 2.08)

[1] numbers from this study are based on evaluated episodes of AOM, not patients.

The conclusion of our pooled analysis should be judged with caution. Only four studies were involved and only two were truly placebo-controlled (table 2.1). Furthermore, diagnostic certainty of AOM in this young age group is lowest compared with that of all ages, and this makes satisfactory comparisons of different studies when addressing treatment efficacy in AOM in this age group even more hazardous.[2] In addition, one study included only recurrent AOM and another looked only at non-severe episodes.[6,17] Of the four studies, the study by Appelman et al. reported rather strong positive results compared with the other studies, suggesting heterogeneity of the trial's results. These results, however, were based on 27 patients only and, therefore, the 95% CI was very wide. Importantly, exclusion of this trial did not materially change the results of our quantitative analysis.

The choice of the treatment end-point is also important in interpreting treatment efficacy. To allow for pooling, we chose a broad end point. Rosenfeld et al. did the same in their meta-analysis, and mentioned that specific benefits of antibiotic therapy on the time course of individual symptom resolution could have been missed.[3] The endpoints for which antibiotic therapy was superior compared with placebo in the individual studies, were bacterial cure, resolution of middle ear effusion within two weeks and otoscopic appearance. These endpoints seemed not to be related to symptomatic clinical improvement.[3,15,16,17] To assess the effect of antibiotic therapy on outcome of AOM, the use of symptomatic clinical improvement seems most valuable, notably in view of the known relationship between the severity of symptomatology and medical utilisation.[23]

Our results are compatible with either a two-fold increase of clinical improvement, or a lower rate of symptomatic clinical improvement within seven days for antibiotic therapy in AOM in children under two years of age. The estimation of the odds ratio (1.31 (95% CI: 0.83 - 2.08)) for this young age group is lower than the estimation of the odds ratio (2.9 (95% CI: 1.76 - 4.88)) that Rosenfeld et al. found for all children. But if the event rate of an abnormal course with AOM in the young age group is high, even a small relative risk reduction will have a potentially important impact on clinical practice.[24]

We conclude that the current high prescription rates of antibiotics among children aged under two years with AOM, being a risk group with regard to poor outcome, are not sufficiently supported by evidence from the published trials. New randomised placebo-controlled trials using a reliable methodology are needed to assess the effect of antibiotics for AOM in this age group.

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Chapter 3

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

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WIE
MET BEIDE BENEN
OP DE GROND
BLIJFT STAAN
KOMT NIET VER

Loesje

3.1 Abstract

Objective: To determine the effect of antibiotic treatment for acute otitis media in children between six months and two years of age.
Design: Practice based, double blind, randomised, placebo-controlled trial.
Setting: 53 general practices in The Netherlands.
Subjects: 240 children aged six months to two years with the diagnosis of acute otitis media.
Intervention: Amoxicillin 40 mg/kg/day in three doses
Main outcome measures: Persistent symptoms at day 4 and duration of fever and pain or crying, or both. Otoscopy at days 4 and 11, tympanometry at six weeks, and use of analgesics.
Results: Persistent symptoms at day 4 were less common in the amoxicillin group (risk difference, (RD) 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 vs. 2.3 doses, P = 0.004). In addition, no otoscopic differences were observed at days 4 and 11, and tympanometric findings at six weeks were similar in both groups.
Conclusions: Seven to eight children aged 6 to 24 months with AOM needed to be treated with antibiotics to improve symptomatic outcome at day 4 in one child. This modest effect does not justify prescription of antibiotics at the first visit, provided close surveillance can be guaranteed.

3.2 Introduction

Antibiotics are currently the treatment of choice for acute otitis media in nearly all countries,[1] which is rather surprising as their effectiveness seems limited in terms of clinical improvement.[2,3,4,5,6,7] Although the world-wide crisis of multiple resistant strains of microbes underlines the importance of the prevention of overuse and misuse of antibiotics, The Netherlands is still the only country where only a minority of the episodes of acute otitis media are treated with antibiotics.[1] The outcome of acute otitis media in The Netherlands does not seem to be any worse than that in other countries.[1]

Several authors have advocated restriction of antibiotic treatment for acute otitis media to children at increased risk of poor outcome or complications,[5,8] notably children under two years of age,[4,9,10,11,12,13,14] although, surprisingly, there is virtually no empirical evidence as to the effectiveness of such treatment in these children.[15] We therefore assessed outcome in a primary-care-based randomised trial of amoxicillin versus placebo.

3.3 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.[8]

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 otitis media with effusion.[16] The study protocol was approved by the ethical committee of the Children's Hospital of the University Medical Center 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 oxymetazoline 0,025% in each nostril three times a day (Nasivin^{R}, 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 one year old received a 120 mg suppository and older children 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 administration of study medication, paracetamol, and nose drops. Follow up visits were scheduled on days 4 and 11 at the general practitioner's clinic, inquiry was made about remaining symptoms, and the eardrum 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 otolaryngologist since day 11. Further otoscopy and tympanometry was also carried out.

Outcome measures

The primary outcome measure was persistent symptoms at day 4, assessed by the doctor and defined as persistent earache, fever (>= 38°C), crying, or being irritable. In addition the prescription of another antibiotic because of clinical deterioration before the first follow up visit was also considered as persistent symptoms.
Secondary outcome measures were: -1- clinical treatment failure at day 11, defined as persistent fever, earache, 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; -2- The duration of fever (>= 38°C) or of pain/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; -3- the mean number of doses of analgesics given, based on the diaries; -4- the percentage of children with middle ear effusion at six weeks. The diagnosis of effusion was based on combined otoscopy and tympanometry. Type B and C2 tympanograms (modified Jerger's classification) were regarded as indicative of the presence of fluid in the middle ear;[17,18] -5- adverse effects mentioned in the diaries.

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 alpha of 5%; a discriminating power of 80%, and an estimated 60% persistent symptoms in the placebo group.[4] The total number of children required in each treatment arm was 79.

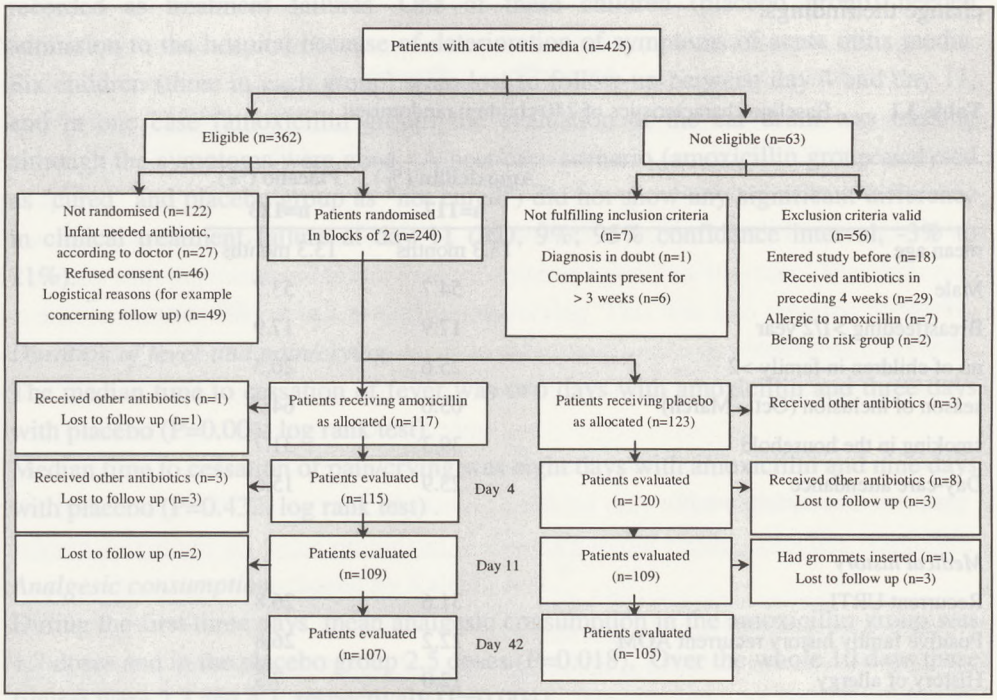
All analyses were carried out with SPSS on an intention to treat basis. We performed best and worst case analyses when necessary because of loss to follow up.
The prevalence of persistent symptoms at day 4, clinical treatment failure at day 11, occurrence of middle ear effusion at six weeks and side effects in the two groups were compared by calculating risk differences (RD) with 95% confidence intervals. Durations of fever and of pain/crying were plotted by means of Kaplan-Meier curves, and differences between the treatment 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 consumption in the two groups was tested using 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 investigators remained blinded throughout the study. During the trial the code of the allocation schedule was kept in the pharmacy of the University Medical Center Utrecht, and was broken only if severe complications or side effects occurred.

3.4 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 3.1) Children in the antibiotic group and the placebo group differed in the prevalence of recurrent acute otitis media, day care attendance (care for at least 5 children, not from the same family, during at least one day a week), and parental smoking habits. (table 3.1)

Figure 3.1 Trial profile



Outcome at day 4

Persistent symptoms at day 4 occurred in 69 out of 117 children (59%) in the amoxicillin group and in 89 of 123 (72%) in the placebo group (RD, 13%; 95% confidence interval, 1% to 25%) (table 3.2). Adjustment for recurrence, day care, and smoking, as possible confounders in the logistic regression analyses showed an odds ratio of 1.79 (95% confidence interval, 1.03 - 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 the hospital (one in the amoxicillin group, two in the placebogroup); one (placebo group) was admitted on the third day with meningitis but because of deterioration 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.

Table 3.1 Baseline characteristics of 240 children randomised

	Amoxicillin (%) n=117	**Placebo (%) n=123**
mean age	13.3 months	13.3 months
Male	54.7	53.7
Breastfeeding >1/2 year	17.9	17.9
no of children in family >2	25.6	20.3
season of inclusion (Oct – March)	65.0	64.2
smoking in the household	39.3	31.7
Day-care attendance	23.9	15.6
Medical history		
Recurrent URTI	31.6	26.8
Positive family history recurrent AOM	22.2	26.8
History of allergy	12.0	7.3
Recurrent AOM	28.2	40.7
Clinical presentation		
>3 days complaints	48.7	43.9
Earache	70.1	66.7
Fever	67.5	65.0
Perforation	15.4	17.1
Bilateral AOM	64.1	61.8
Bulging eardrum	22.2	23.6

AOM: acute otitis media
URTI: upper respiratory tract infection

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 (RD, 6%; 95% confidence interval, -6% to 18%) (table 3.2). Eleven children received other

antibiotics (three in the amoxicillin 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 4 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 (RD, 9%; 95% confidence interval, -3% to 21%).

Duration of fever and pain/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/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 (RD, 3%; 95% confidence interval, -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 pediatrician, or surgery.

Adverse effects

De novo diarrhoea was reported on day 4 in 17% (20/117) of the amoxicillin group and in 10% (12/123) of the placebo group (RD, -7%; 95% confidence interval, -16% to 2%). On day 10 these figures were 12 % (14/117) and 8% (10/123), respectively (RD, -4%; 95% confidence interval, -12% to 4%).

Table 3.2 Main outcome measures in infants with AOM randomised to receive amoxicillin or placebo.

	Amoxicillin No (%)	Placebo No (%)	RD	95%CI	p value
persistent symptoms[#] day4	69/117 (59)	89/123 (72)	13%	(1 - 25)	0.03[*]
no improvement eardrum day4	88/114 (77)	99/120 (83)	6%	(-4 - 16)	0.30[*]
clinical treatment failure[†] day11	72/112 (64)	84/120 (70)	6%	(-6 - 18)	0.35[*]
Median			*difference*		
duration of fever(days)	2	3	1		0.004[‡]
duration of pain/crying	8	9	1		0.432[‡]
Mean					
analgesic consumption first 10 days	2.3	4.1	1.8		0.004[§]

[#] Persistent symptoms defined as still having earache, and/or having fever, and/or crying, and/or being irritable, or having received other antibiotics.

[†] Clinical treatment failure defined as still having symptoms and/or no improvement of the tympanic membrane.

[*] Chisquare test.

[‡] Log rank test for Kaplan Meier plot.

[§] Mann-Witney U test

Of the children lost to follow-up, five were withdrawn (all between day 4 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 the suspension remaining in the returned bottles, 80% of the children in both groups had received the full amount, and 95% at least 80% of the amount prescribed.

3.5 Discussion

In this study resolution of symptoms on day 4 was more common in those treated with amoxicillin than in those taking placebo. At day 11, no significant differences in symptoms combined with 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.[2] We observed no difference between the two groups in pain/crying. This was also reported by Burke et al. and the amounts of analgesics taken in their study were comparable with those in ours.[2] The fact that more analgesics were used in the placebo group could explain the lack of difference in duration of pain/crying.

The number of children with persistent symptoms in our study was high compared with other studies.[2,19] Burke et al., however, included only older children and in young children symptoms are often prolonged.[4,9] 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 studies,[3,4] and is in accord with day-to-day practice in The Netherlands. An abnormal eardrum 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.[1,21]

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 pneumonia and Haemophilus influenzae in The Netherlands remain low at <1 %[23] 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 AOM needed to be treated to improve symptomatic outcome at day 4 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.

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Appendix chapter 3

Subgroup analyses were performed to study effect modification by age (dichotomized at 1 year), first versus recurrent episode, and uni- versus bilateral acute otitis media. All these factors are known to influence outcome in acute otitis media.[1,2,3,4] Interaction tests were used to assess statistical significance.[5]

Subgroup analyses suggested that the treatment effect of amoxicillin was more pronounced in children with a first episode of acute otitis media, children with bilateral acute otitis media and children younger than one year (table), but none of the interaction tests reached the conventional levels of statistical significance.

Table Subgroup analysis concerning persistent symptoms[#] at day 4 (%).

Subgroup	n	Amoxicillin	Placebo	RD	95%CI	p value[*]
Recurrent AOM	83	24/33 (73)	38/50 (76)	3%	(-16 - 22)	0.74
first episode	157	45/84 (54)	51/73 (70)	16%	(1 - 31)	0.04
unilateral AOM	89	27/42 (64)	31/47 (66)	2%	(-18 - 22)	0.86
bilateral AOM	151	42/75 (56)	58/76 (76)	20%	(5 - 35)	0.01
< one year	101	32/52 (61)	40/49 (81)	20%	(3 - 37)	0.03
> one year	139	37/65 (57)	49/74 (66)	9%	(-7 - 25)	0.26

[#] Persistent symptoms defined as still having earache, and/or fever, and/or crying, and or being irritable, or having received other antibiotics.

[*] Chisquare test.

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Appendix chapter 3

Subgroup analyses were performed to study effect modification by age (dichotomized at 1 year) versus recurrent episode, and otitis unilateral versus bilateral acute otitis media. All these factors are known to influence outcome in acute otitis media. Interaction tests were used to assess statistical significance.

Subgroup analyses suggested that the treatment effect of amoxicillin was more pronounced in children with a first episode of acute otitis media, children with bilateral acute otitis media and children younger than one year (table). Interaction tests reached the conventional levels of statistical significance.

Table Subgroup analysis concerning persistent symptoms* at day 4 (PP)

Subgroup	n	Amoxicillin	Placebo	RD	95% CI	p value
unilateral AOM	89	27/42 (64)	31/47 (66)	2%	(-18 - 22)	0.86
bilateral AOM	151	42/75 (56)	58/76 (76)	20%	(5 - 35)	0.01
< one year	101	32/52 (61)	40/49 (81)	20%	(3 - 37)	0.03
> one year	139	37/65 (57)	49/74 (66)	9%	(-7 - 25)	0.26

* Persistent symptoms defined as still having earache, and/or fever, and/or crying, and or being irritable, or having received other antibiotics.
Chi-square test.

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Chapter 4

Duration of clinical symptoms in children under two years of age with acute otitis media

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RELATIEF MENEER

Loesje

4.1 Abstract

Objective: To describe the course of symptoms during the first 10 days of episodes of AOM in children under 2 years of age.
Methods: Within the framework of a placebo controlled, double blind, randomised trial studying the effect of amoxicillin on acute otitis media in children under 2 in the Netherlands, symptoms were recorded in diaries by the parents. Durations of symptoms were plotted by means of Kaplan-Meier curves. Possible factors influencing the duration were included in a Cox regression.
Results: Data from 230 children were used in the analyses. The median duration of fever was 2 days and the median duration of the combination of earache and/or crying was 8 days. The duration of earache and/or crying was not influenced by any factor analysed (including treatment allocation).
Conclusion: Fifty percent of the children under 2 with an episode of AOM had symptoms lasting for more than 8 days. Treatment with antibiotics did not influence this period, so persistence of symptoms should not be a reason for changing antibiotic therapy.

4.2 Introduction

Acute otitis media (AOM) is seen most often in infancy.[1] The majority of older children are free of symptoms within 3 days.[2,3] Appelman et al showed that children under 2 are more likely to follow an abnormal course of illness, defined as pain and/or fever for more than 3 days.[4] Most studies evaluating these young children after 2 to 6 days do not describe complete relief of symptoms.[5,6,7] Nor do they describe the course of symptoms from day to day. So, little is known about the actual course of clinical symptoms during the first few days of an episode of AOM in such children.
Because therapy is often changed because symptoms are peristing,[8,9] it is important to know how long these children normally have symptoms during an episode of AOM. This study describes the course of symptoms during the first 10 days of such episodes and identifies factors influencing the speed of complete relief of symptoms.

4.3 Methods

Data for this study were collected within the framework of a placebo controlled, double blind, randomised clinical trial studying the effect of amoxicillin on AOM in children under 2 in the Netherlands. Children, aged 6 months to 2 years were eligible if they presented with AOM at the office of their general practitioner. Diagnosis was based on otoscopy (red or bulging eardrum, or otorrhoea) and presence of acute signs of infection (fever, pain, irritability).[9] Children with immunity disorders, craniofacial abnormalities, or Down's syndrome were excluded. At entry the children were randomly assigned to amoxicillin or placebo treatment groups. Analgesics were allowed but their use had to be recorded in a diary.

The parents were also to record for 10 days the occurrence of fever, crying, earache, or otorrhoea, and use of medication (including analgesics). The duration of a symptom was defined as the number of days up to the first day on which the parental record showed it as absent and remaining absent. Because of the difficulty of differentiating between earache and crying in infants these symptoms are presented both separately and together.

Factors analysed in relation to the duration of symptoms included age and sex, day care attendance, parental smoking, history of AOM in a sibling, unilateral vs. bilateral AOM, allergy, fever at entry, days with symptoms before entry, recurrent AOM (at least one previous episode), recurrent upper respiratory tract infections (six or more episodes in the previous 12 months), number of children in family, breastfeeding (for more than 6 months), season of entry, doses of analgesics taken.

Statistical methods

Durations of symptoms were plotted by means of Kaplan-Meier curves. When diary data were incomplete and the last entry recorded presence of a symptom, the child was censored in the survival analysis.[10]

In the analysis we aimed to investigate which of the factors listed above influenced the speed of dissipation of symptoms. The crude hazard ratios were estimated by univariate analysis by the Cox proportional hazard model. To estimate simultaneous influences, predictive factors with a probability less than 0.2 and the treatment allocation were included in a multivariate model.

The study protocol was approved by the ethical committee of the Children's Hospital of the University Medical Center Utrecht.

4.4 Results

Between February 1996 and May 1998, a total of 240 children were included in this study. Their baseline characteristics (assessed by the general practitioner) are presented in table 4.1. Of the 240 children, 117 were randomly allocated to antibiotic treatment and 123 to placebo. The mean number of analgesic doses taken in this study was 3.2 in 10 days. For 10 patients no diary was available so they were excluded from the analysis.

Fever

The median duration of fever was 2 (95% CI 1.7 - 2.3) days. On the tenth day 5 per cent of the children were still recorded as having fever. Placebo treatment was associated with a prolonged duration of fever, the hazard ratio (HR) in the multivariate analysis being 0.74 (95% CI 0.55 - 0.99). Use of more than two doses of analgesic (paracetamol) was also associated with a prolonged duration of fever, adjusted HR 0.70 (95% CI 0.52 - 0.94). Symptoms for more than 3 days before entry resulted in a shorter duration of fever, adjusted HR 1.34 (95% CI 1.01 - 1.77). None of the other factors mentioned before influenced the duration of fever.

Earache

The median duration of earache was 7 (95% CI 6.0 - 8.0) days. Earache was still being reported on day 10 in 24 per cent of the children. None of the factors mentioned previously influenced the duration of earache.

Crying

The median duration of crying was 6 (95% CI 5.2 - 6.8) days, and 19 per cent of the children were recorded as still crying on day 10. Use of more than two doses of analgesic was associated with prolonged crying, adjusted HR 0.67 (95% CI 0.49 - 0.92). None of the other factors mentioned before influenced the duration of crying.

Table 4.1 Baseline characteristics of 240 children assessed by the General practitioner.

Mean age	13.3 months
Male	54.2 %
Breastfeeding >1/2 year	17.9 %
No of children in family >2	22.9 %
Season of inclusion (Oct – March)	64.6 %
Smoking in the household	35.4 %
Day-care attendance	19.6 %
Medical history	
Recurrent URTI	29.2 %
Positive family history recurrent AOM	24.6 %
History of allergy	9.6 %
Recurrent AOM	34.6 %
Clinical presentation	
>3 days complaints	46.3 %
Earache	68.3 %
Fever	66.3 %
Perforation	16.3 %
Bilateral AOM	62.9 %
Bulging eardrum	22.9 %

AOM: acute otitis media
URTI: upper respiratory tract infection

Crying and/or earache

The median duration of the combination of crying and/or earache was 8 days (95% CI 6.9 - 9.1). On the tenth day 31 per cent of the children still had earache and/or were crying. None of the factors mentioned before influenced the duration of these symptoms combined.

Otorrhoea

At entry 36 children were recorded as having otorrhoea. The median duration was 4 days,and it was still present on day 10 in 7 (19 per cent) of them. Owing to the small numbers no Cox regression was performed. Of the total group of 204 without otorrhoea at the start of the study, 17 developed a new perforation of the drum with

otorrhoea during the first 10 days. The median duration of the otorrhoea in these latter children was 1 day.

4.5 Discussion

Fifty per cent of the children under age 2 with an episode of AOM in this study were free of fever after 2 days. The duration of earache and/or crying was much longer, 50 per cent suffering from earache and/or crying for more than 8 days. We are not aware of any other study looking at the course of clinical symptoms from day to day during the first 10 days of an episode of AOM in children under 2. Most studies assessed the children at one point only, and did not describe the course of symptoms. Appelman et al. reported that 11 out of 27 children (41 per cent) in this age group still had earache and/or fever after 3 days.[4] Kaleida et al. reported a failure rate of only 12 per cent between 24 - 72 hours, in patients under 2 with 'severe otitis'. Failure was defined as still having fever above 38.5°C or an otalgia score above a certain level but, unlike in our study, complete resolution of symptoms was not mentioned.[5] Carlin et al. reported clinical failure, defined as persistent fever, persistent otorrhoea, or continued irritability at day 3, in 11 per cent of 293 children with a mean age of 17.4 months (range 2 months to 12 years).[6] Dagan et al. reported that more than 60 per cent of 123 children under 2 with an episode of AOM had symptoms or redness or bulging of the drum at day 5. Symptoms and signs at otoscopy were not mentioned separately.[7] Children in our study seem to have had a longer duration of symptoms than in the studies just mentioned but in the survival analysis we counted children as having still symptoms even if they had been temporarily symptom-free for a day but symptoms had later returned. This could be an explanation for the differences seen.

The following studies are more in line with our findings. Jero et al. reported that 25 per cent of children under 2 with AOM (n=56) still had symptoms at 2 weeks.[11] Hathaway et al. reported that 37.5 per cent of such young children with AOM (n=56) had persistent AOM when assessed 10 to 21 days after the initial visit.[12]

Young age is often found to be a risk factor for prolonged symptoms.[4,6,11,13] Within this age group we found that the duration of fever was shortened by the use of antibiotics, as already reported before in our trial report.[14] The finding that the use of more analgesic medication was associated with prolonged fever and prolonged crying can be explained by the fact that analgesic was given when the child was suffering or was having fever, and thus prolonged crying or fever resulted in more analgesic being

given. The amounts of analgesics given in this study were probably too small to provide a proper level of analgesia. The fact that the presence of symptoms for more than 3 days before entry into the study resulted in a shorter duration of fever seems logical when the relatively short median duration of fever is taken into account.

The duration of earache in this young age group was not influenced by any of the factors investigated (including treatment allocation), nor was the combination of earache and/or crying. Earache or the combination of earache and/or crying was not associated with the amount of analgesics given, unlike crying alone, but the hazard ratios were similar to those found for crying alone.

Otorrhoea in the relatively small number (36) of children with it on enrolment lasted for more than 4 days in 18 (50 per cent). Eight per cent of the study population without otorrhoea on entry developed otorrhoea during the first 10 days. Pukander et al. reported spontaneous perforation in 4.6 per cent of 2254 AOM episodes in children aged under 16 years.[3] Most of these spontaneous perforations were reported among the youngest age groups.

In conclusion we can say that in children under 2 with an episode of AOM there is a 50 per cent chance of symptoms lasting more than 8 days. And this is not influenced by the use of amoxicillin, which is still the treatment of choice.[15] Therefore we think that persistence of symptoms should not be a reason for changing antibiotic therapy. Relief of symptoms by analgesics may be an alternative approach. There are few studies in which analgesics were given regularly and the optimal dose for use in AOM is not known.[16] More studies focusing on optimal symptomatic treatment for these young children with AOM may be worthwhile.

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Chapter 5

Long-term prognosis of acute otitis media in infancy: determinants for poor outcome

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R.A. de Melker

5.1 Abstract

Background: Children aged under 2 are at increased risk of recurrence of acute otitis media and persistent middle ear effusion after an episode of acute otitis media than are older children. Little is known about prognostic determinants for these two outcomes after an episode of acute otitis media within this age group.
Aim: To assess whether known determinants for children of all ages for recurrent acute otitis media and persistent middle ear effusion after an episode of acute otitis media also apply to children under 2, who are a separate risk group.
Method: Children less than 2 years of age with an episode of acute otitis media were followed prospectively for 6 months. Outcome measures were recurrence of acute otitis media and persistent middle ear effusion. Known determinants for children of all ages were included in a multivariate analysis for both outcome measures. A prognostic function was developed and its discriminating ability was assessed by ROC analysis.
Results: For recurrent acute otitis media data from 210 children were used and season, sex, and persistent symptoms for more than 10 days of the entry episode were found to be determinants. For persistent middle ear effusion data from 156 children were used and season, bilateral disease at entry, and sibling history of recurrent acute otitis media were found to be determinants. No sufficiently discriminatory prognostic model could be constructed for either outcome measure.
Conclusion: Prediction of poor outcome in individual young children, on the basis of these determinants, as indicated by the area under the curve of the prognostic function, remains poor.

5.2 Introduction

Acute otitis media (AOM) is one of the most common diseases in infants and children. After an uncomplicated episode of AOM a child can face two problems, recurrent AOM or persistent middle ear effusion (MEE). Children under 2 are at increased risk of recurrent AOM[1,2,3] and persistent MEE after an episode of AOM.[4,5,6] Known prognostic determinants other than young age, for recurrence after an episode of AOM include male sex, sibling history of recurrent AOM, not being breastfed, primary clinical treatment failure, bilateral disease, passive smoking, day care, season, history of recurrent AOM.[1,3,7,8,9,10,11,12] Other determinants for persistent MEE after AOM are

season, bilateral disease, type B tympanogram at diagnosis of AOM, history of recurrent AOM.[5,6, 12, 13,14,15]

Most studies on determinants for recurrent AOM or persistent MEE after an episode of AOM have been carried out on children aged 6 months to 12 years. Little research has been done on the predictive clinical factors in the high-risk group of children under age 2. In this prospective study we examined determinants for persistent MEE or recurrent AOM in the children under 2.

5.3 Methods

Patients

The study was conducted between February 1996 and December 1998 in the Netherlands, within the framework of a placebo controlled, double blind, randomised clinical trial studying the effect of amoxicillin for AOM.[16] Children aged between 6 and 24 months were eligible if they presented with AOM at the office of their family doctor. Diagnosis was based on otoscopy (red eardrum, bulging or otorrhoea) and presence of acute signs of infection (fever, pain, irritability), according to the guidelines of the Dutch College of General Practitioners. Children with a known immunological disorder, craniofacial abnormality, or Down's syndrome were excluded from this study. The ethical committee of the Children's Hospital of the University Medical Center Utrecht approved the protocol, and all parents of the children gave written informed consent before enrolment.

Follow-up

At entry the doctor recorded the medical history, the presence or absence of known determinants for otitis media, and the results of otoscopy. During the 10 days of treatment (amoxicillin or placebo) the child was seen twice at the doctor's office, inquiry was made about remaining symptoms and the ear drum was examined. The first author (RD) visited all included children at home at 6 weeks and, when the child had unilateral or bilateral effusion at 6 weeks, again at 3 months after their episode of AOM. At 6 months all children with effusion (uni- or bilateral) at 3 months were visited at home and otoscopy and tympanometry repeated; the parents of all other children were contacted by telephone. The parents were asked whether the child had suffered from another episode of AOM and whether this episode was verified by their family doctor.

Outcome criteria

The outcome criteria were: recurrent AOM, defined as at least one episode of AOM within 6 months of the end of treatment, and persistent MEE defined as uni- or bilateral MEE at all the follow-up visits at 6 weeks, 3 months and 6 months. MEE was diagnosed by tympanometry. Type B and C2 tympanograms (modified Jerger's classification) were regarded as indicative of the presence of fluid in the middle ear.[17,18] The positive predictive value of this combination, between 80 and 90 per cent, is also applicable to children aged 6 to 24 months.[19,20] When tympanometry was unsuccessful because of a lack of co-operation by a child, the subjects were excluded from the persistent MEE analysis. Children who had undergone an ENT operation (tympanostomy tubes, adenoidectomy) during the half-year follow-up because of persistent MEE or recurrent AOM, were considered to have persistent MEE.

Statistical methods

Prognostic parameters considered in relation to the outcome criteria included age and sex, history of at least one previous episode of AOM, day-care attendance (care for at least 5 children, not from the same family, during at least one day of the week), history of recurrent upper respiratory tract infections (6 or more episodes during the previous 12 months), allergy, number of siblings (>2 vs <=2), siblings with recurrent AOM (3 or more episodes during one year), smoking in the household, season, breastfeeding (> 6 months), bilateral disease, duration of symptoms of entry episode of AOM (>10 days vs <=10), treatment at entry. All these factors are described as determinants for recurrent AOM or persistent MEE in children of all ages. The associations between these factors and the outcome criteria (recurrent AOM, persistent MEE) were determined by applying multiple logistic regression analysis, using SPSS 9.0; analyses were performed separately for the two outcome parameters, and by including all potential prognostic determinants in the multivariate model. Results were expressed as adjusted odds ratio (OR) with 95% confidence interval (CI). Adjustment was made for all factors in the analyses.

All factors with a p-value equal or less than 0.1 in the multivariate analyses were included in the prognostic functions, which thus represented a multiple logistic regression model including a subset of the prognostic determinants. Goodness-of-fit of the models was tested by the Hosmer-Lemeshow statistics, which evaluate the correspondence between a model's predicted probabilities and the observed frequencies over groups spanning the entire range of probabilities.[21] The

discriminating ability of these prognostic functions was assessed by using receiver operating characteristics (ROC) analysis. The ROC curve is a plot of the true positive rate (sensitivity) versus the false positive rate (1 – specificity) evaluated at consecutive cut-off points of the predicted probability. The area under the ROC curve (AUC) provides a quantitative summary of the discriminative ability of a predictive model. A useless predictive model, such as a coin flip, would yield an AUC of 0.5. When the AUC is 1.0, the model discriminates perfectly between those with and without poor outcome.[21] In our analyses a value over 0.8 was considered as good with respect to discriminative ability.

5.4 Results

In total 240 patients were enrolled in the trial, 15 had an initial treatment failure during the first 10 days and were not followed further. [16] Another 15 were lost to follow-up. Thus 210 children were included in our prognostic study. Characteristics of these children are shown in table 5.1. The baseline characteristics of the 30 excluded children did not differ from those of the participating children.
Valid tympanograms on all possible occasions were obtained from 156 children, and their baseline characteristics were similar to those of the total group (table 5.2).

Clinical outcome

Recurrent AOM (n=210) - One hundred and five (50 per cent) children developed at least one recurrent episode of AOM within 6 months. Eighty per cent of all episodes reported by the parents were confirmed by their family doctor; the remainder were not seen by a doctor. Recurrent AOM was seen more often in males (adjusted OR 1.9 (95% CI 1.0 – 3.5)), children included in wintertime (Oct – March) (adjusted OR 2.4 (95%CI 1.3 – 4.6)), and children with symptoms lasting longer than 10 days after enrolment (adjusted OR 2.1 (95% 1.1 – 4.0)). Smoking in the household was associated with a lower risk of recurrence of AOM (adjusted OR 0.4 (95% CI 0.2 – 0.8)) (table 5.3). The factors season, sex, and persistent symptoms were included in the prognostic function. The goodness-of-fit test indicated an acceptable fit of the prognostic model (p=0.99). The AUC was 0.65; 95% CI 0.58 – 0.73.

Table 5.1 Characteristics of 210 children included in study.

	N	(%)
Age < 1year	89	42.4
Male	114	54.3
Breastfeeding >1/2 year	37	17.6
No of children in family >2	51	24.3
Season of inclusion (Oct – March)	136	64.8
Smoking in the household	75	35.7
Day-care attendance	42	20.1
Medical history		
Recurrent URTI	60	28.6
Positive family history recurrent AOM	53	25.2
History of allergy	20	9.5
Recurrent AOM	69	32.9
Clinical presentation		
Bilateral AOM	128	61.0
Persistent symptoms (>10days)	77	36.7
Treatment (amoxicillin)	107	51.0

AOM: acute otitis media
URTI: upper respiratory tract infection

Table 5.2 Characteristics of 156 children with a valid tympanogram.

	N	(%)
Age < 1year	63	40.4
Male	88	56.4
Breastfeeding >1/2 year	27	17.3
No of children in family >2	41	26.3
Season of inclusion (Oct – March)	101	64.7
Smoking in the household	54	34.6
Day-care attendance	29	18.6
Medical history		
Recurrent URTI	47	30.1
Positive family history recurrent AOM	41	26.3
History of allergy	14	9.0
Recurrent AOM	49	31.4
Clinical presentation		
Bilateral AOM	95	60.9
Persistent symptoms (>10days)	54	34.6
Treatment (amoxicillin)	79	50.6

AOM: acute otitis media
URTI: upper respiratory tract infection

Persistent MEE (n=156) - At 3 months 65 (42 per cent), and at 6 months 51 (33 per cent) children had persistent MEE. Twenty-six of the latter had had an ENT operation during those 6 months. Persistent MEE at 6 months was seen more often in children enrolled in winter (adjusted OR 3.3; (95% CI 1.4 – 8.1)) , in those who presented with bilateral AOM (adjusted OR 2.6; (95% CI 1.2 – 5.8)), and those who gave a history of a sibling with recurrent AOM (adjusted OR 1.1; (95% CI 1.0 – 1.3))(table 5.3).
The factors season, bilateral disease, day-care, and sibling with recurrent AOM were included in the prognostic function. The goodness-of-fit test indicated an acceptable fit of the prognostic model (p=0.66). The AUC was 0.70; 95% CI 0.61 – 0.78.

Table 5.3 Factors predicting recurrent AOM, persistent MEE at 6 months Presented are adjusted* OR with 95% confidence intervals.

	A: recurrent AOM (n = 210)	B: persistent MEE at 6 mths (n = 156)
Male	1.9 (1.0 - 3.5)	1.5 (0.7 – 3.3)
Breastfeeding	0.9 (0.4 - 1.9)	0.9 (0.3 – 2.3)
Children in fam.	1.2 (0.6 - 2.6)	1.0 (0.4 – 2.5)
Season (winter)	2.4 (1.3 - 4.6)	3.3 (1.4 – 8.1)
Smoking	0.4 (0.2 - 0.8)	0.8 (0.4 – 1.9)
Day care	1.1 (0.5 - 2.3)	2.5 (0.9 – 6.7)
Age <1 year	1.1 (0.6 – 2.0)	0.9 (0.4 – 2.0)
Medical history		
Sibling AOM	1.0 (0.9 - 1.1)	1.1 (1.0 – 1.3)
Previous AOM	1.3 (0.7 - 2.4)	1.7 (0.8 – 3.7)
Recurrent URTI	0.8 (0.4 - 1.6)	0.7 (0.3 – 1.7)
Allergy	1.7 (0.7 - 3.9)	0.5 (0.2 – 1.4)
Clinical symptoms		
Persistent sympt	2.1 (1.1 - 4.0)	1.5 (0.7 – 3.4)
Bilateral AOM	0.9 (0.5 - 1.6)	2.6 (1.2 – 5.8)
Treatm (amox)	1.2 (0.6 - 2.1)	0.8 (0.4 – 1.8)

* OR are adjusted for by logistic regression for all 14 factors discussed.

5.5 Discussion

Determinants for recurrence of AOM within 6 months in children aged under 2 were: winter season, persisting symptoms (> 10 days) of the entry episode, and being male. Winter season, bilateral disease at entry, and a sibling with recurrent AOM were independent predictors for persistent MEE at 6 months in these children. The performance of a prognostic model including these parameters in terms of the occurrence of poor outcome was rather poor.

Fifty per cent of the children in our study had at least one recurrence of AOM within 6 months. This rate of recurrent AOM after a previous episode of AOM is in accord with the findings in other studies.[11,13,22,23] Season and sex as determinants for such recurrence are frequently mentioned in studies of children of all ages.[1,3,9,11,12] Jero et al reported that primary clinical failure, defined as no improvement or worsening at 2

weeks, was a potential risk factor for recurrence of AOM on univariate analysis, but not on multivariate analysis.[11] We also found that persistent symptoms, defined as lasting longer than 10 days after entry, were a determinant for recurrence of AOM on multivariate analysis. Smoking was associated with a lower risk for recurrent AOM in our study, contrary to the often accepted idea that passive inhalation of smoke can cause ear disease, a view wich one review article concluded that there is no empirical evidence for.[24] A more recent paper also showed a lower risk of acute ear infections from passive smoking during early life.[25] They even suggested a biological explanation. The finding may also be attributable to lower reporting rates by parents who smoke.

Most studies looking at persistent MEE after an episode of AOM in children under 2 have included only a short follow-up period of 3 months or less. Persistent MEE at 3 months was found in 42 per cent of the children in our study. Shurin et al found persistent MEE at 3 months in 55 per cent of children aged under 2.[4] Iino et al found this condition in 50 per cent in this age group.[5] Studies with older children showed 0 to 10 per cent had persistent MEE at 6 months post AOM. [5,12,26] Bilateral disease as a determinant for persistent MEE has been mentioned before, [5,6,14] season is also a known determinant.[12,13] All these studies included children from roughly 6 months to about 12 years. Our finding that a positive sibling history of recurrent AOM increased the risk for peristent MEE after an episode of AOM by 10 per cent has not, to our knowledge, ever been reported before.

This study has a number of potential weaknesses. Recurrent AOM was based on parental reports, and although 80 per cent of all episodes were confirmed by a doctor, still 20 per cent were based on parental report only. A previous study has shown that parents can report fairly accurately whether their child suffers from AOM.[27] Thus, the dilution of the risk estimates this may have caused is likely to be quite limited. Diagnosis of MEE was based only on tympanometry, and thus a considerable number of children (25 per cent) had to be excluded from the analysis because we could not obtain a valid tympanogram on every occasion. Comparing the baseline characteristics of the remaining children with those of the total group, no real differences were found (table 5.2). Any selection bias resulting from this exclusion would be modest.

This study has shown that some of the known risk factors for recurrent AOM or persistent MEE for children of all ages also determine prognosis in children aged under 2, who are a risk group for recurrent AOM or persistent MEE as such.

Prediction of poor outcome in individual young children, on the basis of these determinants, as indicated by the area under the curve of the prognostic function, remains, however, poor.

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Chapter 6

Pneumococcal specific IgG antibody levels after AOM in infancy and the risk of recurrency

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Chapter 6

Pneumococcal specific IgG antibody levels after AOM in infancy and the risk of recurrency

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6.1 Abstract

Objective: To find out whether serum levels of specific IgG1 and IgG2 antibodies against selected pneumococcal serotypes can predict recurrent acute otitis media (AOM).

Study design: We performed a prospective study in family practice. Children between 6 months and 2 years presenting with AOM were included. Concentrations of specific IgG1 and IgG2 antibodies against pneumococcal capsular polysaccharides were determined. Children were followed for 6 months and recurrent episodes of AOM were registered.

Results: 114 children were enrolled. The immune status as determined by the level of pneumococcal specific IgG1 and IgG2 antibodies could not predict who would develop recurrent AOM.

Conclusions: Determination of specific pneumococcal antibody levels to predict recurrent AOM in primary care has limited clinical value.

6.2 Introduction

Early onset of AOM is related with a high rate of recurrence of AOM. If a child has its first episode of AOM before the age of 6 months, it has a chance of 62% of getting two or more additional episodes during the next two years.[1] This chance diminishes to 26% when the first episode occurs after the first year of life. In AOM, *Streptococcus pneumoniae, Moraxella catharalis,* and nontypeable *Haemophilus influenzae* are the microorganisms most often isolated .[2]

Apart from anatomical and other age-related factors, immunological factors do play a role in the etiopathogenesis of AOM. Protective immunity against infections with encapsulated bacteria, such as the species that cause otitis media, depends on the ability to produce specific antibodies against bacterial capsular polysaccharides. Physiologically, the antibody response to pneumococcal capsular polysaccharides is inadequate until the age of two years, which coincides with the peak incidence period of AOM.[3] Serum levels of antipneumoccocal antibodies in healthy children remain low up to 3-5 years.[4]

The relation between serum levels of antipneumococcal antibodies and AOM has been studied previously. In cord blood, low levels of IgG pneumococcal antibodies are a risk factor for early onset of AOM and recurrency.[5,6] Several studies of specific IgG

antibodies against AOM-associated pneumococcal serotypes revealed lower concentrations in children with recurrent AOM or a positive sibling history of recurrent AOM.[6,7,8,9,10] While hypogammaglobulinemia or IgG subclass deficiency predispose for recurrent bacterial infections, within the population of children with recurrent AOM, these conditions are rare.[11,12,13,14] All these studies were performed in children less than 3 years of age and largely on small numbers.

A study of 450 children aged 2-16 years, showed higher levels of antipneumococcal antibodies in the otitis prone group compared with a control group.[15] Previous studies revealed that recurrent AOM occurs in children with a delayed maturation of the immune response to pneumococci rather than with a persisting immunity disorder.[8,16]

In adults, IgG anti-polysaccharide antibodies are largely confined to the IgG2 subclass, while in children both IgG1 and IgG2 antibodies are generated after infection with encapsulated bacteria or vaccination with polysaccharide vaccines.[3] Functionally, IgG2 antibodies are superior over IgG1 in opsonophagocytosis of pneumococci.[17,18]

If we want to use IgG antibody levels as a clinical tool to identify children at risk for recurrent AOM, the primary target population is children less than 3 years because older children with recurrent AOM do not show lower antibody levels anymore. On the other hand, children who experience their first episode of AOM before the age of 6 months already are at risk for recurrence so that determination of antibody levels would not be of additional value. Because of differences in the functional activity of antibodies in the different IgG subclasses, specific IgG1 and IgG2 antibodies against AOM-associated pneumococcal subtypes should be determined, not total IgG antibodies.

This prospective study aims to determine whether serum levels of specific IgG1 and IgG2 antibodies against selected pneumococcal serotypes can predict recurrent AOM within six months, in primary care.

6.3 Methods

Patient population

The study was conducted between February 1996 and December 1998, in the Netherlands, within the framework of a placebo controlled, double blind, randomized clinical trial studying the effect of amoxicillin for AOM.[19] Children aged between 6

and 24 months were eligible if they presented with AOM at the office of their family doctor. Diagnosis was based on otoscopy and presence of acute signs of infection (fever, pain, irritability). Children with a known immunological disorder, craniofacial abnormality or Down's syndrome were excluded from this study. Almost all children in The Netherlands are being vaccinated against *Haemophilus influenzae* type b (Hib) at the age of 3, 4, 5 months with booster vaccination at 11-12 months. Pneumococcal vaccination is used only in children older than 2 years when based on clinical symptomatology a defect in specific humoral immunity is suspected.

The ethical committee of the Children's Hospital of the University Medical Center Utrecht approved the study protocol, and all parents of the children gave written informed consent before enrolment.

Capillary blood was obtained by heelpuncture 10 days after the start of the episode of AOM. All samples were frozen at –20°C and stored until analysis at the end of the study. Concentrations of specific IgG1 and IgG2 antibodies against the pneumococcal capsular polysaccharides 6B, 9V, 19F and 23F were determined. These pneumococcal serotypes are most prevalent in otitis media in Northwestern Europe.[20] Furthermore anti-Hib IgG antibodies were determined.

From all children the presence or absence of certain risk factors (table 6.1) for AOM was obtained.

Laboratory methods

IgG1- and IgG2-type serum antibody levels to pneumococcal polysaccharides 6B, 9V, 19F and 23F, and IgG antibodies to the *Haemophilus influenzae* type b polysaccharide polyribosylribitol phosphate (PRP) were measured by ELISA as described previously.[21] All serum samples were preincubated overnight with excess pneumococcal common cell wall polysaccharide (CPS), a procedure which neutralized anti-CPS antibodies. Peroxidase-labeled, subclass-specific murine anti-human IgG1 (MH161-1ME), or IgG2 (MH162-1ME) monoclonals (Central Laboratory of the Red Cross Blood Transfusion Service, Amsterdam, The Netherlands) were used as detecting antibodies. A standard serum from a normal non-vaccinated adult was included in every ELISA-run as a control.

Antibody concentrations of patient samples were expressed relative to a reference adult hyperimmune plasma pool.[22] This plasma pool contains 539 ng Ab N/ml for group 6; 927 ng Ab N/ml for group 9 and 440 ng Ab N/ml for group 19, as determined

by RIA.[22] Antibody concentrations in the plasma pool were assigned 100 U/ml (100%) for each serotype.

Follow up

The first author (RD) visited children at home at 6 weeks, 3 months and 6 months after their episode of AOM. The parents were asked whether the child suffered from another episode of AOM and whether this episode was verified by their family doctor.

Table 6.1 Baseline characteristics of 114 children.

Mean age	12.7 months
Male	46.5 %
Breastfeeding >1/2 year	17.5 %
No of children in family >2	27.2 %
Season of inclusion (Oct – March)	65.8 %
Smoking in the household	35.1 %
Day-care attendance	19.3 %
Medical history	
Recurrent URTI	24.6 %
Positive family history recurrent AOM	28.1 %
History of allergy	9.6 %
Recurrent AOM	32.5 %
Clinical presentation	
>3 days complaints	50.9 %
Earache	70.2 %
Fever	71.1 %
Perforation	12.3 %
Bilateral AOM	58.8 %
Bulging eardrum	16.7 %

AOM: AOM
URTI: upper respiratory tract infection

Statistical analysis

In view of the skewed distribution of antibody levels, results are expressed as median values with interquartile ranges.

Children were divided in good and low responders according to their antibody levels against pneumococcal capsular polysaccharides. These groups were defined as follows: Low IgG1+2 responders when at least 6 out of 8 specific anti-pneumococcal antibody levels were in the lowest quartile. Good IgG1+2 responders when at least 5 out of 8 specific antibody levels were in the highest quartile. Low IgG2 responders when at least 3 out of 4 were in the lowest quartile and good IgG2 responders when at least 3 out of 4 were in the highest quartile. Antibody levels against PRP were adjusted for age and good responders were those who had levels above the median within their age group.

The primary outcome variable was recurrent AOM defined as at least one episode of AOM within half a year after sampling. Responder status was the independent variables of interest. The frequencies of recurrent AOM in these groups and the remaining children were compared with a Chi square test. To adjust for possible confounding logistic regression analysis was performed with recurrent AOM as the dependent variable. We controlled for daycare attendance, age, history of at least one previous episode of AOM, number of siblings, siblings with recurrent AOM and recurrent upper respiratory tract infections (factors indicating possible exposure to pneumococci), duration of breastfeeding (>6 months), smoking in the household, gender, season, persistent symptoms of entry episode (factors known to be determinants for recurrent AOM).

6.4 Results

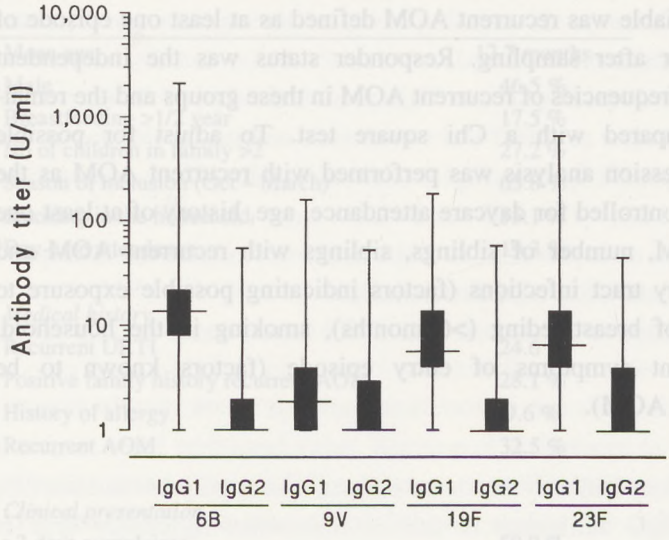
In this study 114 children were enrolled, one child was lost to follow up. Baseline characteristics of these children are shown in table 6.1. From the 113 children which were followed for half a year, 59 (52%) developed at least one recurrent episode of AOM. From all episodes mentioned by the parents, 80% were confirmed by the family doctor.

There was a wide variation in antibody levels against the four pneumococcal serotypes determined (figure 6.1).

Frequencies of recurrent AOM in the good and low responders are presented in table 6.2. No differences were seen between the groups defined and the remaining children concerning recurrent AOM. When these results were controlled for age, daycare attendance, duration of breastfeeding, smoking in the household, history of a previous

AOM, number of siblings, season, gender, recurrent urti, persistent symptoms and siblings with recurrent AOM, there was still no statistically significant effect of responder status on the incidence of recurrent AOM (table 6.2). Neither did we find differences concerning frequencies of recurrent AOM between children in the highest or lowest quartiles of the separate antipneumococcal IgG levels of the different pneumococcal serotypes and the remaining children (data not shown),

Figure 6.1 Pneumococcal polysaccharide antibodies.



IgG1 and IgG2 antibody levels against pneumococcal serotypes 6B, 9V, 19F, and 23F are determined by ELISA and expressed as units/ml (U/ml). Depicted are median values with interquartile ranges.

A trend was observed that good responders were seen more often in children above one year of age, children with 2 or more siblings, or with a history of a previous AOM before enrollment. The low responders were seen more often in the younger children, in children with only one or no siblings and children with no previous episode of AOM, these differences were not statistically significant either.

IgG antibody levels against PRP were adjusted for age, 49 (43%) children had levels above the median within their age group. In this group 25 (51%) had at least one episode of AOM within half a year against 53% in the low PRP responders (P=0.82). Good PRP responders were more often also good anti-pneumococcal IgG1+2

responders (P=0.01). The number of good IgG2 responders among good PRP responders was not statistically significant greater (P=0.64) than the number in low PRP responders.

Table 6.2 Occurence of at least one episode of AOM within half a year (n=114, and follow up complete for 113 children).

Responder status	N (%)	Recurrent AOM (%)	Rec.AOM in remaining (%)	OR (95%CI)	Adjusted OR (95%CI)*
Good IgG1+2	17 (15%)	9/17 (53%)	50/96 (52%)	1.04 (0.4-2.9)	0.98 (0.3-3.3)
Low IgG1+2	23 (20%)	13/23 (57%)	46/90 (51%)	1.24 (0.5-3.1)	1.60 (0.6-4.6)
Good IgG2	21 (19%)	11/21 (52%)	48/92 (52%)	1.00 (0.4-2.6)	0.91 (0.3-2.7)
Low IgG2	67 (59%)	35/67 (52%)	24/46 (52%)	1.00 (0.5-2.1)	1.17 (0.5-2.9)

*Adjusted for daycare, age, smoking in the household, duration of breastfeeding (>6 months), number of siblings, siblings with recurrent AOM, history of at least one previous AOM, season, gender, recurrent URTI, persistent symptoms of entry episode.
AOM: AOM
URTI: upper respiratory tract infection
OR: odds ratio

6.5 Discussion

In this study of 114 children with AOM in primary care, aged between six months and two years, the immune status as determined by the level of pneumococcal specific IgG1 and IgG2 antibodies could not predict recurrent AOM. A wide range in pneumococcal specific IgG antibody levels was seen, as is also reported in a previous study.[4] A trend was seen that a higher natural exposure to pneumococci (higher age, more siblings, more AOM episodes) resulted in higher numbers of good responders.
The number of children with a recurrent episode of AOM in this study is in accord with other studies.[1,23] Although we did not control for selection bias, the basic characteristics of these children suggest that results in our sample can be extrapolated to the general population of children seen in primary care in The Netherlands.[24]
Of all reported recurrent episodes of AOM, 80% was confirmed by the family doctor. In 20% diagnosis was based on parental report only. A previous study has shown that parents can report fairly accurate whether their child suffers from AOM.[25]

Previous studies concerning the relation between serum levels of pneumococcal antibodies and AOM, were mainly patient control studies. There are only a few prospective studies addressing the predictive value of pneumococcal antibody levels for acquiring recurrent AOM.[5,6,11] Salazar et al reported that children with low specific pneumococcal antibodies (type 14 and 19F) in cord blood had earlier onset of AOM.[5] Prellner et al reported that children with 6 or more episodes of AOM within a period of 12 months had lower antibody levels against S. pneumoniae 6A in cord blood compared with healthy controls, but due to a wide range recurrency could not be predicted.[6] The latter two studies are in fact dealing with the impact of maternal anti-pneumococcal polysaccharide antibody levels. Freijd et al determined total IgG2 levels and reported lower levels in highly otitis prone children (8 to 17 episodes in about two years).[11] In our study type specific antibody levels of the IgG1 and IgG2 subclasses against four most prevalent pneumococcal serotypes were determined. Pneumococci account for 40% of otitis media cases.[2] Forty-eight percent of pneumococci cultured from middle ear fluid are of serotype 6B, 9V, 19F, or 23F.[20] However, the design of our study precluded collection of middle ear fluid and therefore the microbiological cause of otitis media was not established. The fact that we did not find any differences in good or low responders concerning the risk of acquiring recurrent AOM could be explained by the fact that we studied a primary care population with at least one episode of AOM and for the outcome only one recurrent episode of AOM within six months was required. On the basis of our findings, we believe that determination of specific pneumococcal antibody levels to predict recurrency of AOM in this population, has limited clinical value. A study population of highly otitis prone patients may give rise to different results.

Our finding that good responders to the conjugated Hib vaccine mainly correlate with good IgG1 response to pneumococci and not with good IgG2 response is in line with earlier findings that a conjugated polysaccharide vaccine initially gives good IgG1 response but a booster with polysaccharide vaccine is needed to induce a IgG2 response.[26] The meaning of this finding for the effectiveness of pneumococcal conjugated vaccine needs further research.

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Chapter 7

Sibling history of recurrent acute otitis media correlates with low IgG2 anti-pneumococcal polysaccharide antibody levels

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STRUIKEL

NIET OVER

JE TWIJFELS

Loesje

A positive sibling history of recurrent acute otitis media (AOM) is a known risk factor for acute otitis media.[1] It is often suggested that because clusters of cases of AOM occur in families there must be a genetic predisposition to middle ear infection. Environmental and other factors within the household could also be the explanation for this family clustering.

Several studies have shown that otitis-prone children have lower pneumococcal specific IgG antibody levels than normal. One study reported that children with low pneumococcal IgG antibodies (against type 14 and 19F) in cord blood and a positive sibling AOM history have a higher risk of early AOM than those with low levels and a negative siblings AOM history.[2] Another study reported low levels of pneumococcal specific IgG antibodies in children with recurrent AOM but normal levels in those parents who had suffered from recurrent AOM in childhood.[3] We know that genetic factors influence the human antibody response to pneumococcal polysaccharides,[4] but so far there has been no proof that there is a genetic cause for clustering of AOM within families.

We determined levels of IgG2 antibody against pneumococci serotypes 6B, 9V, 19F and 23F (the serotypes most prevalent in otitis media in Northwestern Europe[5]) in 77 children aged six months to two years who had had at least one episode of AOM and who had at least one sibling. Antibodies of the IgG1 and IgG2 subclass to capsular polysaccharides of *S. pneumoniae* serotypes 6B, 9V, 19F, and 23F were measured by ELISA in serum samples obtained by heel puncture. In view of the skewed distribution of antibody levels, median levels with interquartile ranges were used as measurement. An adequate IgG2 antibody level was defined as having at least three out of the four serotype-specific IgG2 antibodies in the highest quartile.

Thirty-two children (42%) had a positive sibling history of recurrent acute otitis media (at least one sibling with three or more episodes of acute otitis media within one year). Two (7%) of these 32 children with a positive sibling history had adequate IgG2 antibody levels compared with 11 (25%) of 45 children with no sibling with a history of recurrent AOM. The rate difference was 18% (95% CI: 3% - 33%). The odds ratio adjusted for age, number of children in the family, recurrent upper respiratory tract infections, and attending a day-care group as possible confounding factors was 0.18 (95% CI: 0.04 – 0.93).

The fact that children with at least one episode of AOM and a positive sibling history of recurrent AOM had statistically significant lower IgG2 antipneumococcal polysaccharide antibody levels, even after adjusting for confounding factors indicating possible exposure to pneumococci, may indicate that genetic predisposition could be the explanation for liability to AOM. This observation warrants further research into the genetic control of regulation of antipneumococcal polysaccharide antibody production.

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Chapter 8

Reasons for non-guideline-based antibiotic prescriptions for acute otitis media in the Netherlands

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HOEZO
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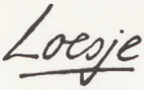

8.1 Abstract

Background: Appropriate use of antibiotics is a major issue in today's medicine. The increasing worldwide bacterial resistance to antimicrobial agents is forcing us to prescribe antibiotics more rationally. It is known that overuse of antibiotics for upper respiratory tract infections exists. Little is known about the reasons for actual prescribing of antibiotics. In order to be able to implement strategies to restrict inappropriate antibiotic prescriptions, insight into the reasons for the actual prescribing could be important.

Objective: We aimed to explore the reasons, other than those stated in the guideline of the Dutch College of General Practitioners, for prescribing antibiotics for acute otitis media.

Method: Seventy antibiotic prescriptions for acute otitis media, prescribed by 22 Dutch GPs, were evaluated to see whether they followed the guideline on acute otitis media of the Dutch College of General Practitioners. Non-guideline-based antibiotic prescriptions were discussed in stimulated recall interviews with the prescribing GPs regarding their prescribing behaviour of antibiotics for acute otitis media.

Results: In total, 77% of the antibiotic prescriptions did not follow the guideline of the Dutch College of General Practitioners. Medical reasons for prescribing antibiotics were mentioned most often for non-guideline-based antibiotic prescriptions; however, in a substantial number of cases doctors gave non-medical reasons as well.

Conclusions: Appropriate use of antibiotics might not be reached by focusing only on efficacy of these drugs. The impact of doctors' awareness of their non-medical motives for prescribing antibiotics on more rational antibiotic prescribing should be investigated further.

8.2 Introduction

The prescription of antibiotics and the reasons for it are major issues in medicine today.[1] The increasing worldwide bacterial resistance to antimicrobial agents is forcing us to prescribe antibiotics more rationally.[2,3] Nevertheless, what is rational prescribing? In 1995 Barber stated that good prescribing is more than just maximising effectiveness, minimising risks, and minimising costs. Respecting patients' choices should also be taken into account.[4]

It is known from studies with simulated cases that the decision to prescribe antibiotics is not based on biomedical factors alone. Social information about the patient also influences the decision to prescribe antibiotics.[5,6] Observational studies have shown relationships between antibiotic prescriptions and prescribers' characteristics.[7] To date, however, little is known about the reasons of actual prescribing of antibiotics.[8] Bradley performed a critical incident study on uncomfortable prescribing decisions that take place in general practice involving all kind of drugs. Reasons for uncomfortable prescribing decisions were medical, social, and logistic ones. The prescribing of antibiotics led most often to feelings of discomfort, but the reasons for the decision to prescribe antibiotics were not given separately.[9] In order to be able to improve the antibiotic prescribing behaviour of doctors in a more rational way, it may be important to know the reasons doctors have for prescribing antibiotics and to make the prescribers aware of them.

Dutch GPs are well acquainted with the guidelines for the treatment of acute otitis media (AOM) of the Dutch College of General Practitioners.[10] This study was aimed at finding reasons for the actual prescribing of antibiotics for AOM other than those provided by the guidelines of the Dutch College of General Practitioners on AOM (table 8.1).[11]

Table 8.1 Summary of the guideline of the Dutch College of General Practitioners on acute otitis media.

Age	Diagnosis	Management	Indication for antibiotics	Agent of first choice
a) < 1/2 years	History, Otoscopy	antibiotics		amoxicillin
b) 1/2-2 years	History, Otoscopy	Symptomatic with follow up after 24 hours	risk groups*, no improvement after one day or more than 14 days otorrhoea	amoxicillin
c) 2 years and older	History, Otoscopy	Symptomatic	risk groups*, abnormal course: earache or fever lasting more than 3 days or more than 14 days otorrhoea	amoxicillin

* Riskgroups:
- patients with recurrent otitis media
- patients with ENT malformations
- patients with immunodeficiencies

8.3 Methods

Setting

Data for this study were collected within the framework of a more extended international observational study on AOM. GPs were asked to include 13 consecutive patients with AOM in 3 different age categories (6-12 months, 13-24 months and 2-15 years). Children with chronic illness, congenital ear-nose-throat (ENT) malformations, or a complication which needed antibiotic treatment were excluded. All participating GPs were asked to give their standard treatment for AOM, and register the patients' clinical signs and resulting treatment on a registration form.

All Dutch GPs participating in the international study agreed to follow the guideline on AOM of the Dutch College of General Practitioners (table 8.1). It has to be mentioned that they were free to choose a different treatment if they considered that to be more appropriate for a specific patient.

Antibiotic prescriptions

Twenty-two Dutch GPs who each included more than 10 patients with AOM, between October 1994 and August 1995, were asked to participate in this study. All antibiotic prescriptions given to the included patients at the first encounter were evaluated to assess whether they followed the guideline on AOM of the Dutch College of General Practitioners. The prescriptions that did not follow the guideline were discussed with the prescribing general practitioner in an interview.

Nature of the interviews

The interviews were held from July 1995 until November 1995, using a stimulated recall procedure.[12] In order to enhance the recall, the general practitioner received the registration form from the international study before the interview. This form contained all clinical data, assessment of the severity of the illness, treatment given and possible reasons to deviate from the standard treatment. This form had been completed during the patient encounter by the same general practitioner. The general practitioner was also stimulated to use his own patient file. The nature of the interview was semi-structured, using a list with possible reasons that had been separated into three categories: medical reasons, patient- related reasons (e.g. request of patient), and doctor-related reasons (including logistical reasons) to elicit their perceptions during the encounter. The list was generated by the authors based on studies concerning

reasons for prescribing.[5,6,8,9] This list was merely used to facilitate the discussion and not as a prompt list.The doctors were allowed to give more than one reason.

8.4 Results

All 22 GPs agreed to participate in this study, which included in total 362 patients with an AOM episode. Antibiotics were prescribed during the first visit in 70 episodes (19%). Of all antibiotic prescriptions 54 (77%) did not follow the guideline of the Dutch College of General Practitioners. From these 54 antibiotic prescriptions, 42 (78%) were discussed with the prescribing general practitioner. Twelve cases could not be discussed due to lack of data.

Medical reasons were given in 40 (95%) non-conforming cases . Reasons from one category (medical,patient-, or doctor-related) were given in 16 cases(38%); from two categories in 18 cases(43%) and from three categories in 8 cases(19%) (table 8.2).

Table 8.2 Number of different categories with reasons given for antibiotic prescriptions other than those presented by the guideline (42 cases)

Medical reasons only	14
Patient-related reasons only	1
Doctor-related reasons only	1
Combination of medical and patient-related reasons	10
Combination of medical and doctor-related reasons	8
Combination of medical, patient-, and doctor-related reasons	8

Of the 81 listed medical reasons, 'Severity of illness at first contact' was mentioned 32 (40%) times (table 8.3). Of the 38 patient-related reasons 'the disease behaviour' of the specific patient was mentioned 23(60%) times (table 8.4), and finally of the 20 doctor-related reasons 'habit' was mentioned seven(35%) times (table 8.5).

Table 8.3 Medical reasons given for antibiotic prescriptions for AOM not according to the guideline of the Dutch College of General Practitioners.*

Reason for prescription	No. of cases
Severity of illness at first contact	32
Ear problems in history of patient	18
Co-morbidity	15
Young age (less than 2 years)	8
AOM resolves faster with antibiotics	3
Belongs to risk group	2
Other	3

* (more than one reason for one prescription is possible)

Table 8.4 Patient-related reasons for antibiotic prescriptions for AOM

Reasons for prescription	No. of cases
Disease behaviour of the patient	23
Request of patient	6
Expectation of doctor for request	4
Many other non-medical problems presented	3
Impact of disease on patient	2

Table 8.5 Doctor-related reasons for antibiotic prescriptions for AOM

Reasons for prescription	No. of cases
Habit	7
To ease the patient	4
Negative events in the past	3
To ease the doctor	2
Feeling how one should perform	2
Just before the weekend	1
Patient is about to go on holiday	1

8.5 Discussion

In this study about reasons for the actual prescribing of antibiotics, most of the reasons given were medical, although patient- and doctor-related reasons also played a substantial role. This qualitative study does not address the question about the relative importance of the different reasons.

The percentage of patients in our study receiving antibiotic therapy during the first encounter did not differ from that found in another Dutch observational study.[13]

The study of Hepler et al., on the reasons for the actual prescribing of antibiotics in 82 cases, revealed almost only medical pharmacological reasons; only twice was the request of the patient mentioned.[14]

Severity of illness at first contact was the reason most often given in our study. Efficacy studies will answer the question of when antibiotics are most effective. Howie has mentioned that the diagnosis may tend to be a justification for treatment rather than the reason for it.[15] Another reason for clinical reasoning when prescribing antibiotics might be the fact that doctors are led especially by their expectations of the effectiveness when choosing a therapy, rather than by their knowledge of possible side effects.[16]

In this study 'the disease behaviour' of the specific patient was mentioned most often as the non-medical reason. The Dutch general practitioner has enlisted patients and therefor he is familiar with the disease behaviour of most patients.

Our study might have been limited by the use of a selected group of GPs. They agreed to participate in an international study which dictated that they had to follow the Dutch guidelines on AOM. But since this was a qualitative study to gain insight in the matter of prescribing of antibiotics, systematic sampling was not necessarily a problem.[17] The results of this study could even be more meaningful considering that even doctors who say that they follow the guidelines use non-medical reasons as well to prescribe antibiotics. Another limitation could be the time delay between the prescribing incident and the interview. This may introduce recall bias. The use of a stimulated recall interview with extensive details of the prescribing incident on the form of the international study can bridge this distance in time.[12] A further limitation could be the fact that we used a list with possible reasons, which could suppress a spontaneous reaction. However, when asked directly about their rationale, doctors tend to give purely pharmacological reasons.[8] And our list, by containing medical as well as non-medical reasons, could have made it more acceptable for the doctors to mention non-medical reasons as well.

In order to change their prescribing behaviour, it might be important that doctors are aware of their motives for prescribing antibiotics when there is insufficient medical reason for it. This study does not say anything about the role of the patient in the process of prescribing. We obtained information only about the doctors' perception of the expectations of the patients. It is known that the doctors' perception does not always agree with patients' expectations of receiving a prescription.[18,19,20] If there is no medical reason for prescribing an antibiotic, the doctor should try to find out whether the patient really wants an antibiotic or merely desires the reassurance that there is nothing seriously wrong with them.

It is remarkable that despite the existing guidelines, which are well accepted by Dutch GPs,[10] 77% of the antibiotic prescriptions did not conform. The process of prescribing is an interaction between the doctor and the patient and many reasons for prescribing, objective as well as subjective, can be found. Because of the complexity of this process, guidelines will never be able to control this behaviour completely. In 1993 Kassirer asked, 'If guidelines do become rules, can they be sufficiently detailed to cover the myriad clinical variations among patients?'[21] Guidelines, instead, should be of help in choosing the best treatment, but each individual case needs to be judged as such. The value of guidelines in the process of rational antibiotic prescribing in general practice should not be overestimated.

The fight against the inappropriate use of antibiotics should not only be focused on the efficacy of these drugs. The impact of doctors' awareness of their non-medical motives for prescribing antibiotics on more rational antibiotic prescribing should be investigated further.

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Chapter 9

General discussion

ALS U ZE
ALLEMAAL OP
EEN RIJTJE HEBT

HOEDT U VOOR HET
DOMINO-EFFECT

Loesje

9.1 Introduction

Antibiotics are known to be of limited efficacy in acute otitis media (AOM) in terms of clinical improvement. The idea behind this study was that antibiotics might be more efficacious in children at increased risk of poor outcome or complications, particularly children under age 2. The current high prescription rates of antibiotics among these children with AOM were until now not sufficiently supported by evidence from published trials. This study has shown that children under 2 are indeed at risk of poor outcome: in 50 per cent of them their episode of AOM lasted for more than 8 days; 50 per cent had at least one recurrence of AOM within 6 months; and a third of them had persistent middle ear effusion (MEE) for 6 months.

This study of 240 children with AOM has shown also that antibiotics shortened the fever by one day and reduced the use of analgesics. Seven to eight children aged 6 to 24 months with AOM needed to be treated with amoxicillin to improve symptomatic outcome at day 4 in one child. This minor effect does not justify routine antibiotic treatment for these children. In view of this the doctor has to decide how to manage AOM in infancy in general practice, weighing the benefits of antibiotics against their risks. Is symptomatic treatment sufficient? And which children need special attention because of a higher risk of a poor outcome? These dilemmas will be discussed in this final chapter in the light of the results of this study and present knowledge.

9.2 Acute otitis media in infancy in general practice

Presentation

A Dutch general practitioner (with 2300 enlisted patients) sees 10 to 15 children under 2 with an episode of AOM each year.[1] Based on the findings of this study the following picture can be given of such children in general practice in the Netherlands. Half (46 per cent) of the children have already had symptoms lasting for more than 3 days when they present to the general practitioner. Fever is present in 66 per cent and earache in 68 per cent, vomiting in 26 per cent, diarrhoea in 27 per cent, crying in 85 per cent, irritability in 91 per cent, rhinitis in 84 per cent and cough in 71 per cent. In 23 per cent a bulging eardrum is seen and in 16 per cent it is perforated. Sixty-three per cent of the children have bilateral AOM at presentation. Fifty-four per cent of the children are boys, and 65 per cent are seen in winter. Only 20 per cent of the children attend day-care and a parent smokes in 35 per cent of their homes. Thirty-five per cent

of the children have a history of previous AOM, and 29 per cent a history of recurrent upper respiratory tract infections (six or more episodes during the previous 12 months). Only 10 per cent of the children are allergic, and 25 per cent have at least one sibling who has had three or more episodes of AOM in a year.

Duration of symptoms (short-term)

The median duration of fever is 2 days but after 10 days 5 per cent of the children are still febrile. The median duration of the combination of crying and/or earache is 8 days but in 31 per cent these symptoms last more than 10 days. Otorrhoea resolves within 4 days in 50 per cent of the children presenting with it, but is still present after 10 days in 19 per cent. The median duration of otorrhoea developing during 'treatment' is only one day.

Long-term outcome

Recurrent AOM, defined as at least one episode of AOM within the 6 months after the end of the initial treatment period, occurs in 50 per cent of the children. Three months after the end of treatment 42 per cent still have persistent MEE and after 6 months this figure is 33 per cent.

Presenting symptoms in our study were the same as reported elsewhere in the literature on children under 2.[2,3,4,5,6,7] Until now, however, little was known in detail about the course of symptoms in an episode of AOM in such children. The fact that these younger children have prolonged symptoms was known before.[8,9,10] Our rate of recurrent AOM after a previous episode of AOM is in accord with other studies.[11,12,13] MEE persisting for up to 3 months in this age group has been studied before and the results were the same as ours,[14,15] but to our knowledge there have been no studies based on MEE persisiting up to 6 months after an episode of AOM so far in this age group.

In conclusion it can be said that children under 2 are indeed a group more at risk of prolonged symptoms, recurrent AOM, and persistent MEE than are older children.

9.3 Antibiotic treatment of an episode of acute otitis media in infancy

In most countries it is recommended that episodes of AOM should be treated with antibiotics,[16,17] although there is an increasing call for restriction of their use for it.[18,19,20] The restriction is meant mainly for children over 2, since the effectiveness of antibiotics for these children with AOM is moderate. For children under 2 antibiotics are still strongly recommended by these authors, mainly because of the increased risk of poor outcome in these young children, although there is no proper evidence of the effectiveness of antibiotics at this age; this is also shown by our systematic literature review (chapter 2).[21] The recently revised guidelines of the Dutch College of General Practitioners now recommend also withholding antibiotics in children aged 6 to 24 months, but to start them if symptoms persist for more than 3 days.[22]

In order to answer the question whether children under 2 with AOM need to be treated with antibiotics, we should first consider the reasons we want to give antibiotics for and how efficacious they are. We should also take into account their potential adverse effects.

Reduction of symptoms could be a reason to give antibiotics but until now little evidence has been available that they achieve this in this age group. Our study showed only a modest effect of antibiotics on symptoms. Seven to eight children needed to be treated to improve symptomatic outcome in one at day 4 and the duration of fever was reduced by only one day (chapter 3).[23] Antibiotics can thus not be recommended routinely for relief of symptoms.

A second reason to prescribe antibiotics is the eradication of micro-organisms. Howie and Ploussard showed already in the early 1970s that antibiotics were highly effective in eradicating bacteria.[24] The correlation between bacteriological outcome (based on demonstration of the eradication of a pathogen on repeat tympanocentesis) and clinical outcome based on the resolution of symptoms and signs in general is poor.[25,26]

A recent study in children aged 3 to 24 months with a positive middle ear fluid culture, reported that those in whom the bacteria were eradicated had a better clinical outcome, and the conclusion was that a subset of patients with AOM clearly benefits from antibiotic treatment.[27] But all children received antibiotics at entry and effective eradication of the pathogens could not be predicted. Furthermore, it is still impossible to identify bacteria in middle ear fluid at the first visit since a culture result will take at least some days. And even if, in the near future, it becomes possible to identify bacteria at such an early stage it is doubtful whether all children in primary care

should be subjected to tympanocentesis. Finally it should be mentioned that in this latter study most patients improved regardless of the bacteriological outcome.

Rosenfeld and Bluestone said that preventing complications is the primary purpose of antimicrobial therapy for AOM.[28] They attribute the decline of acute mastoiditis since the 1940s (from 20 per cent to a current rate of less than 0.1 per cent) to the introduction of antibiotics. Rudberg showed in 1954 a reduction of 17 per cent in clinical mastoiditis in a group treated with penicillin compared with controls,[29] but in the Netherlands, where most episodes of AOM were not treated with antibiotics a similar drastic decline of the incidence of acute mastoiditis has been seen. There must be other causes. One can consider the overall improvement in physical health and environmental conditions and the variation in the pathogenicity and epidemiology of the causative bacteria.[30] Since the incidence of acute mastoiditis in the Netherlands is very low in spite of the restricted use of antibiotics for AOM, prevention of mastoiditis can-not be an argument for routine use of antibiotics for AOM. Another very rare complication of AOM is meningitis. In our study we saw one case of meningitis in the placebo group, but when meningitis was diagnosed on the third day, the child was already on oral antibiotics, and a recent review showed that oral antibiotics do not prevent meningitis.[31] Close monitoring for deterioration, and proper treatment is probably more effective.[32]

Another reason to prescribe antibiotics is to prevent recurrent AOM or persistent MEE. In our study antibiotics had no effect on these sequalae, as has been the case in other placebo controlled studies.[10,33,34]

In conclusion, the effectiveness of antibiotics for AOM in children aged 6 to 24 months is but moderate as far as all the outcomes discussed are concerned. If we also take into account the adverse effects of antibiotics (diarrhoea, vomiting, allergic reactions) and the increasing problem of resistance of microbes world-wide, then watchful waiting at the first visit of these children is recommended, as now in the revised guidelines of the College of General Practitioners.[22] Although complications such as mastoiditis or meningitis are rare, close monitoring for deterioration should be discussed with the parents.

What if symptoms persist? We showed that 50 per cent of the children had symptoms lasting for more than 8 days, and this was not influenced by the use of antibiotics. Therefore persistence of symptoms beyond 3 days is not a good criterion for starting antibiotic therapy in this age group, as is recommended by the College guidelines. Maybe children with AOM who are 'toxic', severely ill, or who have high fever benefit more from antibiotics, as Kaleida et al. have shown in their study in older

children with severe infection (severity was based on fever and otalgia score).[33] Subgroup analysis in our study was inconclusive (Appendix, chapter 3). But in clinical practice we have found that severity of illness at the first contact was a frequent reason to prescribe antibiotics in children of all ages (chapter 8).[35] A good definition of severity, with clinical and perhaps laboratory findings at the first visit that predicts outcome is needed to identify a subgroup that may benefit much more from antibiotics.

9.4 Prognosis

Until now we only have discussed single episodes of AOM. For the clinician the greatest problem is the frequent recurrent AOM. This condition is distinct from isolated AOM and different management strategies are suggested.[28] Howie et al. introduced the 'otitis prone' condition for children suffering 6 or more episodes of AOM before the age of 6.[36] Nowadays recurrent AOM is best defined as three or more well documented and separate AOM episodes in the preceding 6 months or four or more episodes in the preceding 12 months.[28] Most often when we discuss the term 'otitis prone', we refer to numbers of episodes of AOM. Faden et al. stated that the total time spent with middle ear disease could also be used to define the 'otitis prone' child.[37] They defined otitis prone as 8 months or more of middle ear disease in the first year of life. They also mentioned the importance of identifying the otitis prone child early in life in order to prevent further suffering. The question whether a child is otitis prone arises when a child has one or two episodes of AOM early in life. These children are known to have an increased risk of recurrent AOM and persistent MEE. Despite intensive study of the risk factors for recurrent AOM, little is known about the clinical factors which may predict the development of recurrence of AOM after an initial episode of AOM in children aged 6 to 24 months.[11] In our study we found that season (Oct – March), male sex, and persistence of symptoms for more than 10 days in the index episode were predictors for recurrent AOM in this age group after an initial episode of AOM (chapter 5). But it has to be said that our definition of recurrent AOM was based on only one recurrent episode of AOM within 6 months. We certainly can not claim that these children were otitis prone according to the internationally accepted definition. The group of children with persistent MEE for 6 months after the initial episode of AOM in our study is, according to the definition of Faden et al., much more likely to be called otitis prone.[37] Winter season, bilateral

disease, and a positive sibling history of recurrent AOM were independent predictors of persistent MEE for 6 months in our study (chapter 5). Two of these factors were already known for children in general but are now also demonstrated in the age group most at risk, from 6 to 24 months. Prediction of poor outcome in individual young children, on the basis of these determinants, as indicated by the area under the curve of the prognostic function remains, however, poor.

Besides these clinical factors, others such as vitamin status, microbiological markers, and immunological markers have been investigated as to whether they can predict recurrent AOM. Serum vitamin A concentrations could not do so.[38] Nasopharyngeal colonisation with noncapsulated Haemophilus influenzae in children under 1 year old seems to be a possible candidate microbiological marker.[39,40,41,42] An in vitro adherence test of Streptococcus pneumoniae also proved to have a predictive value for recurrent AOM,[43] but the value of these investigations in primary care still needs to be established. In cord blood, low levels of IgG pneumococcal antibodies are a risk factor for early onset and recurrence of AOM.[44,45] Several studies of specific IgG antibodies against AOM-associated pneumococcal serotypes have revealed lower concentrations in children with recurrent AOM.[45,46,47,48] In our study we found that determination of specific pneumococcal antibody levels to predict recurrent AOM in primary care has limited clinical value (chapter 6).

Twin studies have shown that there must be a strong genetic component to the amount of time with middle ear effusion and episodes of AOM.[49,50] In our study we found an association between low IgG2 anti-pneumococcal polysaccharide antibody levels and a positive sibling history of recurrent AOM, possibly indicating a genetic predisposition as the explanation for liability to AOM (chapter 7).[51] The frequency of HLA-A2 antigens was significantly higher in children with recurrent AOM than in healthy children and that of HLA-A3 lower.[52] With the unravelling of the human genome in the near future it should be possible to find genetic markers to predict recurrent AOM.

In conclusion we can say that, with the present knowledge, in primary care it is very difficult to predict recurrent AOM or persistent MEE after an initial episode of AOM in children aged 6 to 24 months. Most promising are probably microbiological markers and genetic markers, but more research also in primary care has to be done. For the moment we can only identify children with recurrent AOM after they have had three or more episodes in 6 months or four or more in a year. Children with persistent MEE can only be identified in primary care by tympanometry.[53]

9.5 Limitations of this study

Patients

Diagnosis was based on symptoms and the appearance of the tympanic membrane, as proposed by the Dutch College guidelines. Internationally this is felt not to be sufficient, because middle ear effusion has to be present and therefore pneumatic otoscopy is regarded as the diagnostic tool to measure middle ear status. In the Netherlands pneumatic otoscopy is seldom performed. Even in countries where the use of pneumatic otoscopy is a diagnostic criterion it is used infrequently in daily practice.[54] We chose a study based on daily practice in primary care in the Netherlands, so that the results should be generalisable to all patients seen in primary care in the Netherlands. Furthermore, two studies on AOM in primary care in the Netherlands have shown very good concordance between diagnoses made by general practitioners and by ENT-specialists.[55,56] The general practitioners participating in our study were trained to classify ear drums by using a standard set of slides depicting a range of common eardrum pictures with the emphasis on discriminating between acute otitis media and otitis media with effusion. Therefore we think that the diagnosis of AOM in our study is sufficiently solid for our findings to be applicable to all children with AOM aged 6 to 24 months seen in primary care.

A second item is selection bias. Among the children who were eligible for the study 122 (34 per cent) could not be randomised; 27 (7 per cent) of them because their general practitioner judged it necessary to prescribe antibiotics and these children might have had more severe AOM. Furthermore, it is unlikely that all episodes of AOM seen by the participating general practitioners were recorded, when we compare the number of recorded episodes with the results of registration studies.[1] Whether this jeopardises the generalisability of the results remains unanswered. But according to the baseline characteristics of the study children we feel that our results can be generalised to the population seen in primary care in the Netherlands.[1]

Intervention

Amoxicillin is still regarded as the drug of first choice for AOM. Because of the increasing concern about drug resistant bacteria there has been a call for use of higher dosages (up to 80 mg/kg/day).[57] Since incidences of resistant Streptococcus pneumonia and Haemophilus influenzae in the Netherlands remain low, the dosage used in this study (40mg/kg/day) was deemed sufficient, certainly taking into account the good compliance achieved in the study. Internationally there is much discussion as

to for how long antibiotics should be given. A recent review on shorter courses of antibiotics for AOM showed that 5 days of a short acting antibiotic had almost the same effect as a long course of 7 days or more at all ages,[58] though subgroup sample sizes were too small for any conclusion about children under 2. Already one year before it had been reported that short courses are not best for infants and young children, but this study did not meet the standards for a proper systematic review.[59] Because of these controversies we chose to give antibiotic therapy for 10 days. Therefore we can say that the treatment (dosage and duration) chosen was adequate by international standards.

Outcome measures

In the trial we chose resolution of symptoms as the clinical outcome. In primary care this outcome is nearest to what we expect from treatment in daily practice. We did not look at bacterial eradication since it would be considered unethical in the Netherlands to perform myringotomy in every child with AOM in primary care. This would also have led to a high refusal rate and thus hampered the generalisability of our results.

For long-term follow up we looked at recurrent AOM, defined as at least one further episode of AOM within 6 months after the index episode. We do realise that this group of children is not the otitis prone population. According to Faden et al. 5 per cent of children are regarded as otitis prone, so this group would be very small in a sample our size.[37] Research for determinants of disease should be done in large cohort studies or case-control studies. Nevertheless studies with smaller sample sizes can be used to identify determinants which can be checked later in cohort or case-control studies. Therefore we have looked at determinants of recurrent AOM and persistent MEE, knowing that we have to regard these findings with caution.

9.6 Recommendations

The implication of this thesis for clinical practice is that it supports only part of the revised guidelines on AOM of the Dutch College of General Practitioners. Children aged 6 to 24 months with AOM can initially be managed by watchful waiting. But from the results of this study we should abandon the College's recommendation that antibiotics should be given when symptoms persist for more than 3 days. Parents can be told how long symptoms are likely to persist and that this duration is not influenced

by antibiotics. More emphasis should be laid on proper relief of symptoms, mainly by analgesics.

The question arises whether antibiotics are completely obsolete for AOM. In daily practice we found that severity of the disease was a reason to prescribe antibiotics in children of all ages. This thesis does not answer the question whether children who are 'toxic', have high fever and are severely ill benefit significantly more from antibiotics. A doctor faced with such a case should weigh the benefits of antibiotics against the adverse effects, and when such a child has to be managed he may choose to play safe. This can-not be regarded as malpractice. In spite of all the evidence from clinical trials, doctors treat individuals and not populations. But we found also that non-medical reasons underlie doctors' prescribing of antibiotics, and this is confirmed by others.[60] Doctors should be made aware of this phenomenon and discuss their thoughts with parents and then take the decision whether to prescribe an antibiotic.

Furthermore, children should be watched carefully for deterioration of their condition or development of complications. When complications (mastoiditis, meningitis) arise, the child should be referred to a paediatrician or an ENT-specialist. This study has also shown that children under 2 are at risk for recurrent AOM and persistent MEE after an episode of AOM. The Dutch guidelines advise that patients should be referred to an ENT-specialist when the child has had three or more recurrent episodes of AOM in a year. Since we did not find proper determinants to identify these children at an earlier stage, there is certainly no valid reason to refer before three episodes in a year have occurred. When referring, it has to be borne in mind that the results of the available management options are modest. The parents must be told that the natural history of the condition is favourable and primary prevention measures could be advised.

9.7 Future research

Future research related on AOM in primary care should be focused on the host, and eradication of the causative pathogen should no longer be the primary objective. First of all we should try to find determinants for the otitis prone population. Clinical determinants have been investigated extensively and it is not likely that useful new ones will be found. Research should be directed towards microbiological and genetic markers. A well-designed case-control study should be the first step. When these otitis prone children can be identified at an early stage then intervention strategies should be

developed and tested. Vaccination strategies are most promising but until now effects are still modest.[61,62,63] But not all episodes of AOM can be prevented and future research should also be directed to find a subgroup of patients who might benefit much more from antibiotics. We have to think of the young child with AOM that is 'toxic', severely ill, has high fever or has other determinants for severity of disease. Efficacy trials of antibiotics for AOM should be focused on these subgroups.
And for all the children who suffer from an episode of AOM and for whom it is expected that antibiotics will not alter the course of the episode, the best methods of management and relief of symptoms should be studied.

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Summary

Chapter 1: Introduction and aims of the study.

Two recent meta-analyses of published reports on the effectiveness of antibiotics for acute otitis media (AOM) have shown that they have only a modest effect on symptom resolution in this common childhood infection. Internationally there is a call to restrict the use of antibiotics for it and antibiotics should be restricted to children under 2 years, because they are regarded as at risk of a poor outcome. In this first chapter we describe why such children should be regarded as a special group: they have an increased susceptibility to AOM, because of the immaturity of their immunological system and because of the differences from older in their nasopharyngeal anatomy. They present differently from older children and diagnostic certainty is lowest in this age group. Their symptoms are known to persist longer during episodes of AOM than in older children, although little is known about the exact duration of symptoms. In addition they have an increased risk of recurrent AOM or persistent middle ear effusion (MEE) after an episode of AOM, but little is known about possible other determinants for this poor long-term outcome. Many expect antibiotics to be more effective in this group mainly because it is regarded as at risk of poor outcome. But the effectiveness of antibiotics for AOM in children aged under 2 still needs to be established and the first aim of this study was to determine their effectiveness for AOM in this risk group. The second was to determine the duration of clinical symptoms during an episode of AOM in these infants, and the third to look for factors predisposing to recurrent AOM and persistent MEE after an episode of AOM under age 2.

Chapter 2: Antibiotic treatment of AOM in children under two years of age: evidence based?

This chapter presents a systematic literature review and a quantitative analysis with an assessment of the methodological quality of published trials, comparing antibiotic treatment with non-antibiotic treatment for AOM in infants. The aim of this study was to assess whether the current high prescription rates of antibiotics for AOM in such children at risk of poor outcome are based on any established evidence of increased efficacy. Six trials were included. Trials from before 1981 had a poor methodological quality. Four were suitable for the quantitative analysis. Only two of them were truly placebo-controlled. Of these two, one included only recurrent AOM and the other

included only non-severe episodes. With these restricted data, no statistically significant difference was found between antibiotic treated children and controls under two years of age with AOM, judged on the basis of clinical improvement within seven days (common odds ratio = 1.31; 95% confidence interval = 0.83 – 2.08). The conclusion was that the current high prescription rates of antibiotics among children under two years of age with AOM were not sufficiently supported by evidence from published trials. And it is suggested that new randomised placebo-controlled trials using reliable methodology are needed in this young age group.

Chapter 3: Primary care based randomised, double blind trial of amoxicillin versus placebo for AOM in children aged under two years.

To determine the effectiveness of antibiotic treatment for AOM in children aged between 6 months and 2 years we conducted a practice based, double blind, randomised, placebo controlled trial involving 240 children aged 6-24 months with the diagnosis AOM from 53 general practices in the Netherlands. The antibiotic used was amoxicillin, 40 mg/kg/day in three doses. All children used decongestant nose drops and paracetamol was allowed for pain.

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 vs 2.3 doses, P=0.004). In addition, no otoscopic differences were observed at days 4 and 11, and tympanometric findings at 6 weeks were similar in both groups. Our conclusion was that seven to eight children aged 6 to 24 months with AOM needed to be treated with antibiotics to improve symptomatic outcome at day four in one child. This modest effect does not justify prescription of antibiotics at the first visit, provided close surveillance can be guaranteed.

Chapter 4: Duration of clinical symptoms in children under two years of age with AOM.

The objective of this study was to describe the course of symptoms from day to day during the first 10 days of an episode of AOM in children under 2. Within the framework of the placebo controlled, double blind, randomised trial studying the

effect of amoxicillin on AOM in such children, symptoms were recorded in a diary by the parents. Durations of symptoms were plotted by means of Kaplan-Meier curves. Possible factors influencing the duration of symptoms were included in a Cox regression. Data from 230 children were used in the analyses. The median duration of fever was two days. Placebo treatment and the use of more than 2 doses of analgesics were associated with a prolongation of fever. More than 3 days' symptoms before entry in the study resulted in a shorter duration of fever. The median duration of earache/crying was 8 days and this was not influenced by any factor analysed. It was concluded that 50 per cent of infants with an episode of AOM had symptoms for more than 8 days. Treatment with antibiotics did not influence this period. Therefore persistence of symptoms should not be a reason for changing antibiotic therapy. More research is needed on optimal relief of symptoms in these children.

Chapter 5: Long-term prognosis of AOM in infancy: determinants for poor outcome.

This prospective study examined factors associated with recurrences of AOM and/or with persistent MEE after an acute episode in children under 2,who are at special risk of such sequelae. Known determinants for recurrent AOM and persistent MEE in children of all ages were included in multivariate analyses. From the data from 210 children, recurrent AOM was found to be associated with season of the year, sex of the child and persistence of symptoms for more than 10 days in the entry episode. Persistent MEE (data from 156 children and diagnosis based on tympanometry, failures excluded) was associated with season, bilateral disease at entry, and a sibling history of recurrent. No sufficiently discriminatory prognostic model could be constructed for either recurrent AOM or persistent MEE.

Chapter 6: Pneumococcal specific IgG antibody levels after AOM in infancy and the risk of recurrence.

In order to find factors that could predict recurrence of AOM after an initial episode of AOM serum levels of specific IgG1 and IgG2 antibodies against selected pneumococcal serotypes, most prevalent in otitis media in north-western Europe were measured in a prospective study in primary care after an episode of AOM in 114 children followed for 6 months, any recurrent episodes of AOM being recorded. In view of the skewed distribution of antibody levels, the results were expressed as

median values with interquartile ranges. Good responders and low responders were defined. The immune status as determined by the level of pneumococcal specific IgG1 and IgG2 antibodies could not predict recurrent AOM. It was concluded that determination of specific pneumococcal antibody levels to predict recurrent AOM has limited clinical value in primary care.

Chapter 7: Sibling history of recurrent AOM correlates with low IgG2 anti-pneumococcal polysaccharide antibody levels.

In this cross-sectional study an association between lower IgG2 anti-pneumococcal polysaccharide antibody levels and a positive sibling history of recurrent AOM was observed, even after adjusting for confounding factors indicating possible exposure to pneumococci. This may indicate that liability to AOM is genetically determined.

Chapter 8: Reasons for non-guideline-based antibiotic prescriptions for AOM in the Netherlands.

In this qualitative study we aimed to explore the reasons, other than those stated in the guidelines of the Dutch College of General Practitioners on AOM, for prescribing antibiotics for this common childhood disease. Seventy antibiotic prescriptions for AOM, prescribed by 22 Dutch general practitioners, were evaluated to see whether they followed the guidelines on AOM of the Dutch College of General Practitioners. In total 77% of these prescriptions did not follow the guidelines on AOM. Forty-two of them were discussed in stimulated recall interviews with the prescribing general practitioners regarding their prescribing behaviour of antibiotics for AOM. Medical reasons for prescribing antibiotics were mentioned most often for non-guideline-based antibiotic prescriptions; however, in a substantial number of cases doctors gave non-medical reasons as well. Our conclusion was that appropriate use of antibiotics might not be reached by focussing only on efficacy of these drugs. The impact of doctors' awareness of their non-medical motives for prescribing antibiotics on more rational antibiotic prescribing should be investigated further.

Chapter 9: General discussion.

The main results of this thesis are discussed in the light of present knowledge. Patient characteristics, management of episodes of AOM in infancy, and prognosis are summarised. The limitations of this work as regards the patients included, the interventions, and the outcome measures chosen are then discussed. The implications of this thesis are: first, that watchful waiting for children under 2 is justified.

Secondly, there is no point, however, in specifying a particular duration for a watchful waiting period, as in the revised College guidelines: symptoms should be actively and adequately treated and the child carefully monitored for signs of severe illness or complications. Thirdly, that doctors should tell parents how long symptoms may last and that antibiotics do not shorten this period. Fourthly, that doctors should be made aware of non medical motives that may lead them to prescribe antibiotics, in order to find ways to make the prescribing of antibiotics in such cases more rational. And last, and perhaps least, the fact that no proper prognostic model could be developed to predict recurrence of AOM or persistent MEE.

Future research should be directed towards the otitis prone population. Determinants other than clinical should be sought to identify these children at an early stage. Then intervention strategies (vaccinations) should be tested. In addition we could try to define severity of an episode of AOM and find out whether antibiotics are more effective in severe episodes. And the best management of symptoms in children with AOM for whom it is expected that antibiotics will not alter the duration of symptoms, should be further studied.

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Samenvatting

Hoofdstuk 1: Inleiding en doelstellingen van het onderzoek.

Twee recente meta-analyses over de effectiviteit van antibiotica bij acute middenoorontsteking lieten zien dat er slechts een gering effect is aangaande de vermindering van symptomen bij deze veel voorkomende kinderinfectie. In de meeste landen, Nederland uitgezonderd, wordt echter nog steeds bij bijna elke episode van acute middenoorontsteking een antibioticum voorgeschreven. Internationaal wordt gepleit voor een beperking in het gebruik van antibiotica voor acute middenoorontsteking. Antibiotica zouden beperkt moeten worden tot kinderen onder de 2 jaar vanwege het feit dat deze groep gezien wordt als een risico groep wat het beloop betreft. In dit eerste hoofdstuk beschrijf ik waarom deze kinderen onder de 2 jaar als een aparte groep beschouwd moeten worden. Kinderen in deze leeftijd groep hebben een grotere kans op acute middenoorontsteking in vergelijking met de oudere kinderen vanwege een onrijpheid van het immuun systeem en ongunstigere anatomische verhoudingen in de nasopharynx. Deze kinderen hebben een andere symptomatologie in vergelijking met de oudere kinderen en diagnostische zekerheid is het laagste in deze leeftijd groep. Het is bekend dat ze een geprolongeerd beloop hebben tijdens een episode van acute middenoorontsteking in vergelijking met de oudere kinderen, echter er is weinig beschreven over de exacte duur van symptomen. Verder hebben ze een verhoogd risico op recidiverende acute middenoorontsteking of persisterende middenooreffusie na een acute middenoorontsteking, maar er is weinig bekend over eventuele andere determinanten voor dit ongunstige beloop op de langere termijn. Het idee leeft onder velen dat antibiotica in deze groep effectiever zijn vooral vanwege het ongunstigere beloop. Maar de effectiviteit van antibiotica voor acute middenoorontsteking bij kinderen onder de 2 jaar moet nog bepaald worden. De belangrijkste doelstelling van dit onderzoek was om de effectiviteit van antibiotica voor acute middenoorontsteking in deze leeftijd groep vast te stellen. Een tweede doelstelling was de bepaling van de duur van symptomen gedurende een episode van acute middenoorontsteking en een derde doelstelling was het zoeken naar factoren die recidiverende acute middenoorontsteking of persisterende middenooreffusie na een acute middenoorontsteking voor het tweede levensjaar, kunnen voorspellen.

Hoofdstuk 2: Antibiotica voor otitis media acuta bij kinderen onder de 2 jaar: effectiviteit bewezen?

Hier presenteren we een systematisch literatuuronderzoek en een kwantitatieve analyse met een beoordeling van de methodologische kwaliteit van de gepubliceerde trials die behandeling met antibiotica vergelijken met behandeling zonder antibiotica bij kinderen onder de 2 jaar. Het doel van dit onderzoek was het bepalen of de huidige hogere voorschrijfpercentages van antibiotica voor otitis media acuta bij kinderen onder de 2 jaar die een risicogroep vormen voor een abnormaal beloop, gebaseerd zijn op een bewezen betere effectiviteit. Zes onderzoeken werden ingesloten. Trials van voor 1981 hadden een matige methodologische kwaliteit. Vier onderzoeken waren geschikt voor de kwantitatieve analyse; hiervan waren er slechts twee echt placebogecontroleerd. Van deze twee had de ene alleen recidiverende otitis media acuta ingesloten en de andere alleen niet-ernstige gevallen. Met deze beperkte data werd geen statistisch significant verschil gevonden tussen beide groepen kinderen ten aanzien van de klinische verbetering binnen zeven dagen (common odds ratio 1,31; 95%-BI 0,83 – 2,08). De conclusie was dat het relatief vaak voorschrijven van antibiotica voor otitis media acuta bij kinderen onder de twee jaar onvoldoende onderbouwd werd door gepubliceerde trials. Nieuwe gerandomiseerde placebogecontroleerde trials van voldoende methodologische kwaliteit zijn nodig in deze leeftijdsgroep.

Hoofdstuk 3: Een gerandomiseerd, dubbel blind onderzoek van amoxicilline, vergeleken met placebo, voor otitis media acuta bij kinderen onder de 2 jaar in de huisartsenpraktijk.

Om de effectiviteit van antibiotica voor otitis media acuta bij kinderen tussen 6 maanden en 2 jaar te bepalen werd in de huisartsenpraktijk een dubbel blind, gerandomiseerd, placebogecontroleerde onderzoek verricht. Uit 53 huisartsenpraktijken in Nederland werden 240 kinderen met een diagnose otitis media acuta ingesloten. Het gebruikte antibioticum was amoxicilline, 40 mg/kg/dag in drie giften. Alle kinderen gebruikten decongestieve neusdruppels en het gebruik van paracetamol was toegestaan als het kind pijn had.

Persisterende symptomen op dag 4 kwamen minder voor in de amoxicilline groep (risico verschil 13%: 95% betrouwbaarheids interval 1% tot 25%). De mediane duur van koorts was 2 dagen in de amoxicilline groep tegen 3 dagen in de placebo groep (P=0,004). Er werd geen statistisch significant verschil gevonden betreffende de duur

van pijn of huilen, maar het gebruik van pijnstillers was hoger in de placebo groep gedurende de eerste 10 dagen (4,1 versus 2,3 doseringen, P=0,004). Verder werden er geen otoscopische verschillen gevonden op dag 4 of dag 11. Tympanometrische bevindingen na 6 weken waren gelijk in beide groepen.
Onze conclusie was dat 7 tot 8 kinderen in de leeftijd van 6 tot 24 maanden met otitis media acuta met antibiotica behandeld zouden moeten worden om 1 kind extra op dag 4 zonder symptomen te hebben. Dit bescheiden effect rechtvaardigt niet om al bij het eerste bezoek een antibioticum voor te schrijven, mits het kind goed vervolgd kan worden.

Hoofdstuk 4: De duur van klinische symptomen bij kinderen onder de 2 jaar met otitis media acuta.
Het doel van dit onderzoek was het beschrijven van het beloop van de symptomen van dag tot dag gedurende de eerste 10 dagen van een episode van otitis media acuta bij kinderen onder de 2 jaar. Binnen het kader van de placebo gecontroleerde, dubbel blinde, gerandomiseerde trial naar het effect van amoxicilline op otitis media acuta bij kinderen in deze leeftijdsgroep werden symptomen in een dagboek geregistreerd door de ouders. De duur van de symptomen werden uitgezet middels Kaplan-Meier curven. Factoren met een mogelijke invloed op de duur van de symptomen werden gebruikt in een Cox regressie. De gegevens van 230 kinderen werden gebruikt in de analyse. De mediane duur van de koorts was 2 dagen. Placebo behandeling en het gebruik van meer dan 2 doseringen pijnstillers was geassocieerd met een langere duur van de koorts. In het geval dat er meer dan 3 dagen voor insluiting al klachten waren dan was de duur van de koorts korter. De mediane duur van oorpijn/huilen was 8 dagen en dit werd niet beïnvloed door enige factor in de analyse. De conclusie was dat 50% van de kinderen onder de 2 jaar met een episode van otitis media acuta langer dan 8 dagen klachten hadden. Behandeling met antibiotica had hier geen invloed op. Daarom zou het persisteren van symptomen geen reden moeten zijn om antibiotische therapie te veranderen. Meer onderzoek moet verricht worden naar een optimale symptoom bestrijding bij deze kinderen.

Hoofdstuk 5: Lange termijn prognose van otitis media acuta bij kinderen onder de 2: determinanten voor een ongunstig beloop.
In dit prospectief onderzoek hebben we determinanten voor recidiverende otitis media acuta en persisterende middenoor effusie na een episode van otitis media acuta onderzocht bij kinderen onder de 2 jaar, die op zich al een verhoogd risico hebben voor deze gevolgen. Reeds bekende determinanten voor recidiverende otitis media acuta en persisterende middenoor effusie betreffende kinderen van alle leeftijden werden gebruikt in een multivariate analyse. Wat recidiverende otitis media acuta betreft werden de gegevens van 210 kinderen gebruikt en winterseizoen, geslacht en persisterende symptomen langer dan 10 dagen bij de episode van insluiting waren voorspellers voor deze uitkomst. Wat persisterende middenoor effusie betreft werden de gegevens van 156 kinderen (diagnose middenoor effusie was gebaseerd op tympanometrie en 'failures' werden uitgesloten) gebruikt en winterseizoen, dubbelzijdige otitis media acuta bij insluiting, en het hebben van broertjes of zusjes met recidiverende oorontstekingen waren voorspellers voor deze uitkomst. Er kon echter geen prognostisch model, met voldoende discriminatoire waarde, samengesteld worden voor recidiverende otitis media acuta, noch voor persisterende middenoor effusie.

Hoofdstuk 6: Pneumococ specifieke IgG antilichamen titers na een acute middenoorontsteking bij kinderen onder de 2 jaar en de kans op een recidief.
Om mogelijke factoren te vinden die recidivering van otitis media acuta na een initiële episode kunnen voorspellen, hebben we serum titers van IgG1 en IgG2 antilichamen gericht tegen een aantal geselecteerde pneumococcen serotypen, die het meest voorkomen bij otitis media in Noordwest Europa, bepaald. In een prospectief onderzoek binnen de eerste lijn zijn deze antilichaam titers bepaald bij 114 kinderen na een episode van otitis media acuta. Deze kinderen werden 6 maanden vervolgd en recidieven van otitis media acuta werden geregistreerd. Gezien de asymmetrische verdeling van de antilichaam titers zijn de resultaten gepresenteerd als de mediaan waarde met de quartielen. Kinderen met goede reacties en kinderen met slechte reacties werden gedefinieerd. De immuun status, bepaald door pneumococ specifieke IgG1 en IgG2 antilichaam titers kon een recidief van otitis media acuta niet voorspellen. Onze conclusie was dat het bepalen van deze antilichamen weinig klinische waarde heeft binnen de eerste lijn om recidiverende otitis media acuta te voorspellen.

Hoofdstuk 7: Het hebben van een broertje of zusje met recidiverende otitis media acuta correleert met lage IgG2 anti pneumococcen polysaccharide antilichaam titers.

In dit transversaal onderzoek observeerden wij een associatie tussen lagere IgG2 anti pneumococcen polysacchariden antilichaam titers en het hebben van een broertje of zusje met recidiverende otitis media acuta, ook na correctie voor verstorende factoren die een aanwijzing waren voor mogelijke blootstelling aan pneumococcen. Deze bevinding kan een aanwijzing zijn dat een genetische predispositie een verklarende factor is voor de vatbaarheid van recidiverende otitis media acuta.

Hoofdstuk 8: Redenen voor antibiotica recepten voor otitis media acuta in Nederland, die niet onderbouwd zijn door de standaard.

In dit kwalitatief onderzoek wilden we redenen, anders dan die in de standaard van het Nederlands Huisartsen Genootschap genoemd, voor het voorschrijven van antibiotica bij otitis media acuta onderzoeken. Zeventig antibiotica recepten voor otitis media acuta, voorgeschreven door 22 Nederlandse huisartsen werden beoordeeld of ze conform de eerder genoemde standaard waren. Van deze recepten was 77% niet conform de standaard. Hiervan werden er 42 besproken middels 'stimulated recall interviews' met de voorschrijvende huisarts betreffende zijn voorschrijf gedrag van antibiotica bij otitis media acuta. Medische redenen werden het meest genoemd om een antibioticum voor te schrijven zonder onderbouwing door de standaard. Echter in een aanzienlijk aantal werden ook niet medische redenen genoemd. Onze conclusie was dat het adequaat voorschrijven van antibiotica mogelijk niet bereikt wordt door alleen aandacht te besteden aan de effectiviteit van deze middelen. De invloed van het bewust zijn van artsen dat ze ook niet medische redenen hebben om antibiotica voor te schrijven op een meer rationele antibiotica prescriptie zou verder onderzocht moeten worden.

Hoofdstuk 9: Discussie.

De voornaamste resultaten van dit proefschrift worden hier besproken in het licht van de huidige kennis. Patiënten kenmerken, behandeling van een episode van acute middenoorontsteking bij kleine kinderen en de prognose hiervan worden besproken. Vervolgens worden de beperkingen van dit proefschrift benoemd, betreffende de ingesloten patiënten, de interventie en de gekozen uitkomstmaten.

De betekenis van dit proefschrift is: ten eerste, dat ook voor kinderen jonger dan 2 jaar een afwachtend beleid gerechtvaardigd is, zoals ook door de hernieuwde NHG

standaard geadviseerd wordt. Ten tweede, dat na een afwachtende periode van 3 dagen bij het persisteren van klachten een antibioticum voorgeschreven zou moeten worden niet door dit proefschrift onderbouwd wordt. Meer aandacht zou gegeven moeten worden aan voldoende symptoom bestrijding en voldoende controle op tekenen van complicaties. Ten derde, dat huisartsen ouders nu kunnen vertellen hoe lang symptomen kunnen blijven bestaan en dat antibiotica deze periode niet verkorten. Ten vierde, dat huisartsen zich bewust moeten zijn van hun niet medische redenen om een antibioticum voor te schrijven met het oog op het optimaliseren van het voorschrijfbeleid van antibiotica. En als laatste het feit dat geen goed prognostisch model ontwikkeld kon worden betreffende de prognose voor recidiverende otitis media acuta of persisterende middenoor effusie.

Toekomstig onderzoek zou gericht moeten worden op de 'otitis prone' populatie. Er zou gekeken moeten worden of er factoren zijn die deze groep in een vroeg stadium kunnen identificeren. Vervolgens kunnen dan interventies (vaccinaties) binnen deze groep onderzocht worden. Verder zou er getracht moeten worden om een ernstige episode van acute middenoorontsteking te definiëren en vervolgens te onderzoeken of deze groep meer baat heeft van een behandeling met antibiotica. Tot slot zou er onderzoek verricht moeten worden naar een optimale symptomatische behandeling voor al die kinderen met een acute middenoorontsteking voor wie verwacht mag worden dat antibiotica geen invloed hebben op de duur van de symptomen.

Dankwoord

Het is natuurlijk een cliché om hier te vertellen dat ik het niet alleen gedaan heb. Het zij zo. Ook dit proefschrift is tot stand gekomen doordat velen hand en spandiensten verricht hebben. Met wie ik zou moeten beginnen is vaak door mijn hoofd gegaan, wie heeft nu echt aan de basis van dit werk gestaan?

Professor Ruut de Melker, beste Ruut, dit was jouw laatste orenkindje. Voor jou was dit werk een logisch vervolg op al je eerdere werk. Over de kleine kinderen was nog onvoldoende bekend en dat moest uitgezocht worden. Dat je mij daarvoor kon gebruiken heeft mij 5 goede jaren opgeleverd. Je had steeds alle aandacht voor dit project en dat is voor een promovendus maar wat gemakkelijk. Ook na je emeritaat stond je altijd klaar met je kennis en een schat aan ervaring. Het grote voordeel van een promotor op leeftijd is het historisch perspectief dat altijd een belangrijk deel uit maakte van onze beschouwingen. Dit heeft zeker mijn enthousiasme voor het onderwerp vergroot en ook in de toekomst zullen orenkinderen mijn belangstelling houden.

Beste Frank, jij had net je eigen project met succes afgerond en wist dus goed wat er bij een niet meer zo jonge promovendus, die ook in de tropen gezeten had, allemaal meespeelt. Het eigenwijze in mij wist jij uitzonderlijk goed te bespelen met jou geduld en absoluut niet drammerige overredingskracht. Jouw ervaring met jouw eigen trial heeft ons geen windeieren gelegd. De kunst om jouw kennis over te dragen en mij het gevoel te geven dat ik het zelf ontdekt had beheers je geweldig. Dit werkte voor mij erg motiverend en was zeer plezierig. We hebben het niet alleen over oortjes gehad, de tropen, het terugkomen, de huisartsgeneeskunde waren ook onderwerpen die ik graag met jou besprak. Hopelijk is Wapenveld niet te ver!

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enkele namen verbonden, maar zonder de collegae in het veld, zou het huisartsgeneeskundig onderzoek niet mogelijk zijn.
Terug bij de vakgroep wil ik toch enkele mensen noemen met het gevaar iemand te vergeten, en als dat teveel onrecht doet dan maken we dat goed met een fles wijn!
Aan de volgorde moeten verder ook geen rechten ontleend worden, hoewel die natuurlijk niet willekeurig is, zal de ratio hiervan altijd verborgen blijven. Peter Zuithoff, dit dankwoord is niet zonder jouw broers computer gemaakt. Jouw belangrijkste bijdrage is jouw kennis van SPSS en de analyse. Jouw wiskundig inzicht in allerlei modellen wist je prima uit te leggen aan een huisarts, die dat wel leuk vond. Hoe jij je dit hebt eigen gemaakt via de psychologie en de seksuologie in het bijzonder blijft voor mij altijd een raadsel. Fred, je monitoring programma's waren te goed om te vergeten (helaas geen fles wijn). Diana, als Marianne op vakantie was nam jij met plezier haar taak over. Carla, van jouw ervaring met vragenlijsten hebben we bij de analyse veel profijt gehad. Luc, jij hebt mijn wetenschappelijke interesse aangewakkerd tijdens mijn opleiding tot huisarts en tijdens mijn promotie bleef je geïnteresseerd in je pupil. In den beginne was er Marcel, mijn eerste kamergenoot, jij hebt me bijgebracht dat wetenschappers gewone mensen zijn, die zeker ook hun onzekerheden hebben. En op het laatst was er Sjoerd, Boston was misschien wat ver weg, maar Londen hebben we bereikt!
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tropenverleden heeft een levenslange band gesmeed. Jan, als jij niet als jongere broer gepromoveerd was, had ik misschien wel nooit overwogen om die titel te gaan halen. Dat er dan ook nog enige immunologie in zit zal dan ook wel geen toeval wezen.
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Curriculum vitae

Roger Damoiseaux is op 17 augustus 1961 geboren in Schinnen. In 1979 behaalde hij het diploma Gymnasium β aan het St. Odulphus lyceum in Tilburg. In dat zelfde jaar begon hij zijn studie geneeskunde aan de Katholieke Universiteit Nijmegen. Het artsexamen werd behaald in 1987. Als voorbereiding op uitzending naar de tropen werkte hij gedurende een jaar als arts-assistent op de afdeling chirurgie van het Elizabethgasthuis in Arnhem en een half jaar op de afdeling gynaecologie van het Groot Zieken Gasthuis in 's-Hertogenbosch. De tropencursus werd gevolgd op het Koninklijk Instituut voor de Tropen. In november 1989 werd hij door Memisa uitgezonden naar Malawi, waar hij 4 jaar als medical officer in het Trinity Hospital in Muona werkte. Na terugkeer in Nederland begon hij in september 1993 aan de tweejarige huisartsenopleiding in Utrecht. In september 1995 volgde een aanstelling via NWO bij de vakgroep huisartsgeneeskunde Utrecht waar dit proefschrift verslag van doet. Daarnaast werkte hij vanaf februari 1996 als huisarts in dienstverband in Terwolde.

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