RECURRENT ACUTE OTITIS MEDIA

a contribution to answering the question
how to treat acute otitis media

lman

J.Q.P.J. Claessen

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C.L.M. Appelman J.Q.P.J. Claessen

Study drugs:

amoxicillin-clavulanate (Augmentin®)
supplied by SmithKline Beecham Farma

oxymethazoline HCl (Nasivin®)
supplied by E. Merck Nederland B.V.

paracetamol (Sinaspril®Paracetamol)
supplied by Nicholas-Mepros B.V.

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RECIDIVERENDE OTITIS MEDIA ACUTA

een bijdrage tot het beantwoorden van
de vraag naar de behandeling van otitis media acuta
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor van de Rijksuniversiteit te Utrecht op gezag van de Rector Magnificus, prof. dr. J.A. van Ginkel, ingevolge het besluit van het College van Dekanen in het openbaar te verdedigen op dinsdag 26 mei 1992 des namiddags te 1.45 uur

door

CORNELIUS LAURENTIUS MARIA APPELMAN

geboren op 27 september 1946 te Midden-Beemster

en

JOHANNES QUIRINUS PETRUS JACOBUS CLAESSEN

geboren op 30 maart 1960 te Amsterdam

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Prof. Dr. G.J. Hordijk
Prof. Dr. F.W.M.M. Touw-Otten

The success of the study, performed on behalf of this thesis, is the result of a close collaboration between the Department of General Practice of the University of Utrecht and the Department of Otorhinolaryngology of the Utrecht University Hospital.

AUTHORS

Conducting a research project and writing a thesis about it together is a shared effort. Both of us have been intensively involved in all of the aspects of this study and the end product represents the input of each of the authors.
However, each of us concentrated on specific parts of the project. As a consequence, one of us carries the final responsibility for different sections. The division is as follows:

C.L.M. APPELMAN:
Chapter II
Chapter V
Chapter VI
Chapter VIII

J.Q.P.J. CLAESSEN:
Chapter III
Chapter IV
Chapter VII
Chapter IX

Joint responsibility:
Chapters I and X

CONTENTS

CONTENTS

Chapter I

GENERAL INTRODUCTION

C.L.M. Appelman J.Q.P.J. Claessen

GENERAL INTRODUCTION

Acute otitis media is a common disease in children, with reported cumulative incidences ranging from 65% to 95% before the age of seven [1,2]. Most of the episodes will heal without complications. Due to a greater number of recurrent bouts of the disease, a subpopulation of these children must be considered 'otitis-prone' [3]. Howie, who introduced this concept, defined the 'otitis-prone' condition as the occurrence of six or more episodes of acute otitis media before the age of six [3]. The most important predictive risk factor was a first episode of acute otitis media at very young age [3]. Though defined by strict criteria by Howie, a recent report showed considerable differences between other authors with respect to the criteria for the 'otitis-prone' condition [4]. Paleopathological research has revealed that acute otitis media and its sequelae have occurred since man's early development [5-8]. In the developed countries the morbidity of acute otitis media and frequency of occurrence of its sequelae has changed over time and, as every clinician must assent, during the past three to four decades in particular. The incidence of mastoiditis, once one of the most feared complications, has declined dramatically [9-11]. In the Netherlands the incidence of mastoiditis fell from 10-40% of all acute otitis media episodes before the Second World War, to 0.25% at present [12]. Above all, the advent of antibiotics is considered to have contributed greatly to this phenomenon. Myringotomy was for long the treatment of choice in the Netherlands and antibiotic therapy was reserved for cases not responding to it. Yet the same decline in sequelae could be noted as in countries where antibiotic treatment was given more freely. Fry was one of the first to question openly the necessity of unconditional antibiotic treatment in every episode of acute otitis media [13]. Since then many investigators from the fields of otorhinolaryngology, paediatrics, family medicine, epidemiology, microbiology and immunology

have studied fundamental and clinical aspects related to aetiology, pathophysiology and treatment of acute otitis media. Notwithstanding this, many questions and differences of opinion remain.

In the Netherlands general practitioners propagate an attitude of watchful waiting for three days in children of two years and older, followed by reevaluation [14]. When otalgia and/or fever persist treatment with amoxicillin is advised [14]. In children of six months to two years old a similar attitude is advocated, though with reevaluation after 24 hours [14]. In children with multiple recurrences (≥3 episodes within a year), severe general disease conditions, or those younger than six months, immediate antibiotic treatment is advised [14]. In the 1990 Dutch Consensus Conference on Acute Otitis Media, participating general practitioners, paediatricians and otolaryngologists agreed on an attitude of watchful waiting in children older than one year, with the restriction that this age-related threshold may well lie at two years, and that conclusive evidence resolving this dilemma is still lacking [15]. This attitude has been influenced strongly by one of the very scarce placebo-controlled studies in acute otitis media [16]. This Dutch study in children aged two years and older showed no significant difference in clinical course between treatment groups.

In the United States opinion is strongly in favour of antibiotic treatment for every episode of acute otitis media, preferably with broad-spectrum antibiotics [17]. In Scandinavia a recent consensus conference recommended primary antibiotic treatment with penicillin-V [18]. A survey by Froom et al. illustrates these differences in management [19]. In the United States antibiotics are prescribed in 97.9% of the cases, compared to 31.2% in the Netherlands. When prescribing antibiotics, Dutch physicians prefer ampicillin or amoxicillin in 91.1% of the episodes, whereas in Switzerland this antibiotic is used in only 47.1% of the cases receiving antibiotic treatment. In spite of these differences, there is little

variation in the overall clinical course of the disease in the respective countries. As research and clinical experience seem to favour an attitude of watchful waiting in many patients, a sharper definition is required to identify those at risk for an irregular course of the disease warranting active treatment. A doctor treating a child with a recurrent episode of acute otitis media within weeks to a few months from the previous episode may often by nature be inclined to give a more active treatment, perhaps even more so in patients younger than two years.

It is still unclear whether the characteristics of an 'otitis-prone' subpopulation with respect to the clinical course of the episode itself and possible sequelae justify this attitude. In other words, are patients who are considered 'otitis-prone' on the basis of previously documented episodes of acute otitis media truly at greater risk? Are they at risk not only for an irregular course of the episode itself, but also for sequelae such as persistence of middle ear dysfunction? The controversies and unanswered questions on management of acute otitis media are apparent and illustrate the incessant need for more well-conducted clinical trials. Therefore, a double-blind placebo controlled clinical trial was carried out to address the objectives of this thesis, as stated below.

OBJECTIVES OF THIS THESIS

1. To determine the natural course of recurrent acute otitis media and the efficacy of amoxicillin-clavulanate in a population of children from six months to 12 years of age.
2. To assess inter-observer reliability between general practitioners and otolaryngologists in diagnosis and otoscopic classification of acute otitis media.
3. To establish the value of otoscopic findings as a predictor of the clinical course.
4. To establish the persistence of middle ear dysfunction one month after an episode of recurrent acute otitis media and determine the possible predictive factors defining those at risk for this sequela.
5. To establish the long-term clinical course with respect to renewed recurrences of acute otitis media, persistence of middle ear dysfunction and upper respiratory tract infections, as well as their possible therapy during a one-year follow-up.
6. To search for possible predictive factors determining those at risk for recurrences and persisting middle ear dysfunction requiring referral to a specialist for further therapy.

In Chapter II the study methods of the clinical trial are motivated and described. To elucidate the design of the study, epidemiology and the criteria for diagnosis of acute otitis media are reviewed.

In Chapter III the current state of knowledge on microbiological aspects of acute otitis media is reviewed, with special reference to clinical implications.

In Chapter IV a critical review of 50 clinical trials is given concerning treatment in acute otitis media. These trials conducted between 1965 and 1989 illustrate how current controversies in management can exist in spite of the apparent multitude of studies.

In Chapter V the results of our clinical trial are presented and discussed.

In Chapter VI the inter-observer reliability of otoscopic examination as diagnostic procedure is estimated. Furthermore, the prognostic value of otoscopic subclassification in acute otitis media is assessed.

In Chapter VII the persistence of middle ear dysfunction one month after a recurrent acute otitis media and its predictive factors are studied.

In Chapter VIII data of a one-year follow-up study in family practice are given, analysed and discussed. Special attention is paid to identification of children at high risk and the long-term effects of antibiotic therapy.

In Chapter IX pathophysiology of recurrent acute otitis media and otitis media with effusion and treatment options currently advocated are reviewed. In the second part, data of one year follow-up with respect to possible referral and specialist therapy are given, analysed and discussed.

In Chapter X conclusions are drawn and recommendations are given based on the findings in the preceding chapters.

REFERENCES

1. Ingvarsson L, Lundgren K, Olofsson B. Incidence and risk factors of acute otitis media in children: longitudinal cohort studies in an urban population. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988, 6-8.
2. Klein JO, Teele DW, Bernard A et al. Epidemiology of acute otitis media in Boston children from birth to seven years of age. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988, 14-15.
3. Howie VM, Ploussard JH, Sloyer J. The 'Otitis-prone' condition. Am J Dis Child 1975; 1239: 676-678.
4. Alho OP, Koivu M, Sorri M. What is an 'otitis-prone' child? Int J Ped Otorhinolaryngol 1991; 21: 201-209.
5. Gregg JB, Steele JP, Holzhueter A. Roentgenographic evaluation of temporal bones from South Dakota Indian burials. Am J Phys Anthrop 1965; 23: 51-61.
6. Schultz M. Zeichen akuter und chronischer Entzündungen des Mittelohres an frühgeschichtlichem Skelettmaterial. HNO 1979; 27: 77-85.
7. Loveland CJ, Collins Pierce L, Gregg JB. Ancient temporal bone osteopathology. Ann Otol Rhinol Laryngol 1990; 99: 146-154.
8. Bruintjes Tj D. The auditory ossicles in human skeletal remains from a leper cemetery in Chichester, England. J Arch Science 1990; 17: 627-633.
9. Ginsburg CM, Rudoy R, Nelson JD. Acute mastoiditis in infants and children. Clin Pediatr 1980; 19: 549-553.
10. Herwig SR. Acute pediatric otomastoiditis: a review. Milit Med 1984; 149: 216-218.

11. Hawkins DB, Dru D, House JW, Clark RW. Acute mastoiditis in children: a review of fifty-four cases. Laryngoscope 1983; 93: 568-572.
12. Van den Hoogen HJM, Huygen FJA, Schellekens JWG et al. Morbidity figures from general practice. Nijmegen: University Department, Nijmegen, 1985.
13. Fry J. Antibiotics in acute tonsillitis and acute otitis media. Br Med J 1958; 2: 883-886.
14. Otitis media acuta, standaard M09. Huisarts Wet 1990; 33(6): 242-245.
15. Hordijk GJ. Consensus over therapie bij otitis media acuta. Ned Tijdschr Geneeskd 1992; 136: 85-88.
16. Buchem FL van, Dunk JH, Hof MA van 't. Therapy of acute otitis media: myringotomy, antibiotics or neither. Lancet 1981; ii: 883-887.
17. Bluestone CD, Klein JO. Management. In: Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: WB Saunders Company, 1988.
18. Karma P, Palva T, Kouvalainen K et al. Finnish approach to the treatment of acute otitis media. Report of the Finnish Consensus Conference. Ann Otol Rhinol Laryngol 1987; 96 Suppl 129: 1-19.
19. Froom J, Culpepper L, Grob P et al. Diagnosis and antibiotic treatment of acute otitis media: Report from international Primary Care Network. Br Med J 1990; 300: 582-586.

Chapter II

METHODS

C.L.M. Appelman, J.Q.P.J. Claessen, G.J. Hordijk, R.A. de Melker, F.W.M.M. Touw-Otten.

INTRODUCTION

In this chapter the methods will be described that were used to develop the study protocol and to find the answers to the study questions. To set up the protocol and the calculations, several assumptions were made with regard to the number of patients and the duration of the research project. These assumptions were derived from a survey of the literature and are discussed below. First, we discuss the assumptions concerning the epidemiology of acute otitis media, especially of recurrences. Next, we consider the definition and diagnosis of recurrent acute otitis media. Tympanometry, a tool to assess the presence of low pressure or effusion in the middle ear cavity, is explained. Against this background, we then describe the methods we employed in our clinical trials.

EPIDEMIOLOGY OF ACUTE OTITIS MEDIA

In order to draw up the study protocol, we needed accurate morbidity figures on acute otitis media for the population in which we intended to conduct our research. The city of Utrecht was chosen as the investigation area. It has 230,000 inhabitants and about 100 general practitioners. The city has a university hospital with a department of otorhinolaryngology to which the patients would be referred for further investigation on behalf of the study. Dutch morbidity figures were a prime concern, since they could be applied to our research population.

Acute otitis media is a disease with a high incidence, not only in the Netherlands but also in most parts of the world [1]. Despite this frequent occurrence, relatively few reliable epidemiologic studies of otitis media have been reported. The interpretation of the results of morbidity studies must take several factors into account.

Illness behaviour: Depending on the severity of the symptoms as perceived by an afflicted person and/or the parents, the

decision is taken either to consult a physician or not. Not all those suffering from acute otitis media (or their parents) do so. Hence, disease behaviour, health information and education might be highly influential, but quantitatively unknown factors in the frequency of patient-doctor contacts. Thus, the morbidity figures registered during patient-doctor contacts are not necessarily equal to the real incidence of acute otitis media in the population. The patient selection for our study took place during patient consultations with a general practitioner. Since the Dutch health care system demands a referral by the general practitioner for a patient-specialist contact, the Dutch morbidity figures for primary health care were applicable in our study protocol. On the other hand, fluctuations of reported incidence through time cannot be interpreted exclusively as a change in the occurrence of acute otitis media in the population. They might be due to alterations in the illness behaviour of patients as well.
Uniformity of registration and classification: To obtain comparable morbidity figures the various registrations must use similar criteria for diagnosing the disease. In the Netherlands, diagnosis is always based on patient's history, physical examination and more specifically, otoscopic examination. Up to now the mobility of the eardrum as judged by pneumatic otoscopy, has never been a criterion for diagnosing acute otitis media in the Netherlands. This criterion is used for incidence studies conducted elsewhere such as Scandinavia, Finland, the U.S.A. and Canada. Furthermore, various definitions used for acute otitis media differ from one another. It is not always clear what is meant by a diagnosis of otitis media, acute otitis media, otitis media with effusion and acute otitis media with a non-suppurative effusion. A description of an episode is hardly ever given. Vague conceptions about relapses and re-infections within a short time interval imply that these might or might not be considered as a new episode of acute otitis media. Finally, figures on incidence have been calculated based on the basis of episodes

as well as on persons. Thus these figures do not take into account the possibility that one patient can have several episodes during the time of observation.
Population base: Many reports from other countries concern selected populations or consider specific risk factors. Rarely is the total population denominator known. And no study was found with standardized measures for the frequency of disease. This makes it difficult to compare results. In the Netherlands, we can take advantage of the fact that every inhabitant has his/her own general practitioner. This enables investigators to register morbidity continuously on a known population denominator.

For the years 1945 to 1965 Huygen reported an average yearly incidence of 99 and 73 acute otitis medias per thousand for boys and girls respectively, in children aged zero to four. For the years 1971 to 1975, the corresponding incidences increased to 252 and 258 acute otitis medias per thousand [2]. From then on a decrease in incidence has been observed. The Continuous Registration of Morbidity (CMR) from Nijmegen over the period 1978-1982 reports an average yearly incidence of 218 acute otitis medias per thousand in children aged zero to four [3]. A recent national survey registered a corresponding incidence of 205 acute otitis medias per thousand [4]. Lamberts reports an incidence of 172 acute otitis medias per thousand in 1991 in the same the age category [5].
Non-age-specific incidences from Dutch epidemiologic studies show a similar trend through time. The CMR reported 25.4 acute otitis medias per thousand for the period 1978-1982 [4]. In 1982 Lamberts found an incidence of 29 acute otitis medias per thousand [6]. Five years later the same author reported 19 acute otitis medias per thousand per year [7]. Of these, 17 diagnoses were certain and two were uncertain. The NIVEL project of registration in 1987 describes 14.2 acute otitis medias per thousand [8]. Finally, in his latest report, Lamberts records a yearly incidence of 17 acute otitis medias

per thousand [5]. These morbidity figures are summarized in Table 1.

Table 1: Incidences of episodes of acute otitis media per 1000 persons

Author:	registration period:	age category	episodes per 1000
Huygen, 1978	'45 - '65	0 - 4	♂ 99 ♀ 73
Huygen, 1978	'71 - '75	0 - 4	254
Hoogen, 1985	'78 - '82	0 - 4	218
Velden, 1991		0 - 4	205
Lamberts, 1991		0 - 4	172
Hoogen, 1985	'78 - '82	all	25.4
Lamberts, 1982		all	29
Lamberts, 1987		all	19
NIVEL, 1987	'86	all	14.2
Lamberts, 1991		all	17

All these epidemiologic studies were conducted in the Dutch population. They suggest a decrease since the early eighties. We can only speculate whether this diminishing incidence reflects the real occurrence of acute otitis media in the course of the time or not. Another explanation might be development in medical management of acute otitis media in the Netherlands. Myringotomy is now hardly ever performed as of the past 10 to 15 years. After publication of the results of studies by Van Buchem et al. [9,10], most patients are advised to use analgesics and decongestive nose drops only [11]. If the clinical features have not improved after three days, antibiotics are prescribed. This might be a reason why parents, once they are acquainted with the current medical management strategy, postpone consultation for their child and ultimately refrain from it. This way leads to a decrease in registered acute otitis media. Finally, the possibility remains that alterations in pathogenesis have occurred. These might be caused by fluctuations in bacterial spectra or their virulence in the population. They could also result from changes in the average resistance of individuals due to

improvement of social circumstances.
Acute otitis media is a strongly age-related disease. Eighty per cent of the episodes develop in persons of 12 years old or younger [12,13,14].
As suggested before, studies in other countries are of limited value for comparison, due to loosely applied definitions or by the fact that they regarded selected populations.
We consider it highly desirable that epidemiologic studies provide insight into the person-based occurrence of disease. It is relevant to know about the proportion of persons with recurrences, because medical management might be different for this category of patients. Only two, not very recent, reports of Dutch studies give some information on recurrences. In a population of 329 children surveyed during their first six years of life, Huygen found that 41% had not had any acute otitis media, 20% had had only one acute otitis media, and 39% had experienced more than one acute otitis media [2]. He concluded that an acute otitis media during the first years of life increased the risk of recurrence. Van Buchem monitored 171 children aged 2 to 12 years with an acute otitis media over a period of six months [15]. Ten per cent had a recurrence during this half year. In the category that never had had an acute otitis media before this figure was six per cent. In the category that had already had four acute otitis medias or more, this figure was 16%. However, due to the small number of patients the difference between these percentages was not statistically significant.
A number of international studies pay more attention to the epidemiology of recurrence. Pukander et al. report the results of a large epidemiologic study performed in Finland in 1978/79 in 146,822 persons [13,14]. A total annual incidence was found of 4.08% for episodes of acute otitis media. The percentage of persons with one or more attacks of acute otitis media was 3.12%. In children under 15 years old these figures are 16.6% and 11.5% respectively. The second year of life appeared to be the age at which the risk of recurrence was the highest. The

mean number of recurrences was 1.55 in the subsequent year, decreasing to 0.26 for the age category 10-15 years. On the whole, among index attack children younger than 16 years, 72% experienced only one attack of acute otitis media, 18% two attacks, seven per cent three attacks and three percent four or more attacks during the study year. Hence, 28% had at least one recurrence during the subsequent year. Biles et al. reported in Texas that of children 0-8 years old with otitis, 34% experienced recurrent attacks during a one-year period [16]. Onion et al. observed one or more recurrences in 76 out of 161 (47%) children during one year of follow-up [17]. We did not find a satisfactory reason for this high proportion in contrast with the results of other studies. Onion et al. did not observe rising incidence of recurrences with age as reported by others [18,19].

Another way to report recurrence is the incidence rate among children with an acute otitis media for the subsequent year. This incidence rate appeared to be 0.7-0.9 in several studies [11,20,21].

Many authors take initial onset in the first year of life as a predictor for frequent recurrences. Yet a recently and properly designed study finds a predictive value for frequent recurrences ($\geq$ 6 per year) of 0.60 and 0.32 when initial onset is before six and 12 months of life, respectively [22]. The corresponding predictive values for negative outcome are 0.88 and 0.90 respectively. Ahlo et al. found that early onset of acute otitis media was only a weak predictor of susceptibility, both for the individual child and the whole population. They concluded that the sensitivity levels and predictive values are too low to permit accurate prediction [23].

Conclusions

* We assumed an incidence of acute otitis media of 20 patients per 1000 persons per year, of which 80% is 12 years old or younger. The percentage of recurrences within one year is expected to be 25%.

* The incidence of acute otitis media is decreasing. We do not know to what extent the validity of the measurement and factors related to patient's illness behaviour influence the observed frequency of disease.
* There is a need in the Netherlands for appropriate estimation of frequency of recurrences, i.e. recurrence rates, implying observed person-time units measuring subsequent recurrences.
* The assessment of the incidence of subsequent recurrences should take number of recurrences in account. It should be made on levels that are stratified for age as well.
* Besides early onset in life of acute otitis media, there is a need for the detection of stronger predictors for recurrent acute otitis media and the 'otitis-prone' condition.

DIAGNOSIS OF ACUTE OTITIS MEDIA

Definition and classification

Otitis media is defined as inflammation of the middle ear, without reference to etiology or pathogenesis [24]. Acute otitis media is regarded as a specific feature in the classification of otitis media and refers to a clinically identifiable infection of the middle ear with sudden onset and short duration. These definitions often result in confusion among clinicians who provide health care to infants and children with ear disease. This confusion impedes appropriate evaluation of studies reported in the literature, since interpretation of results of these investigations depends upon precise definition of the disease studied. In daily practice clinical signs and symptoms are used to diagnose an acute otitis media. Criteria for diagnosis in general practice were formulated in 1983 at the WONCA conference [25].

With regard to acute (suppurative) otitis media (ICHPPC code 3820) the criteria are described as follows:

* any of the following:
    * recent perforation of tympanic membrane, discharging pus
    * inflamed and bulging tympanic membrane
    * one eardrum redder than the other
    * red tympanic membrane with ear pain
    * bullae on tympanic membrane

After the beginning of our study a consensus was reached in the Netherlands with regard to the definition of acute otitis media. This definition is practical and unambiguous [11,26]. Acute otitis media is defined as an infection of the mucous membrane of the middle ear with an acute onset and a duration of less than three weeks. It is characterized by changes of the tympanic membrane, with or without earache, fever, and or general illness.

Thus, acute otitis media refers to a constellation of symptoms and signs rather than a pathological entity [27]. The disadvantage of such a broad concept is that the impression might develop that acute otitis media is a separate disease. It might seem to have no relation to the other types of otitis media (myringitis, otitis media with effusion, and chronic otitis media). Clinicians might be tempted to pay less attention to the mutual connections.

For our study, we defined acute otitis media as follows: a condition of acute or subacute otalgia in which the general practitioner as well as the otolaryngologist finds characteristic changes in the eardrum.

Reasons for encounter

Some parents tell the physician that their child has an acute otitis media. Notwithstanding, several complaints make the doctor decide to take this as a serious hypothesis.

Lamberts reports various reasons for encounter [28]:

44%	earache
12%	fever
7%	initiative of general practitioner
6%	request for general physical examination
6%	otorrhoea
4%	acute otitis media
2%	coughing
2%	tiredness, feeling of illness

Another recent study also investigated the initial reasons for encounter of acute otitis media [4]:

63%	earache
7%	fever
5%	otorrhoea
3%	hearing disorders

Other complaints of a local nature include rubbing or tugging at the ears and impaired hearing function; less frequent complaints are vertigo, nystagmus, tinnitus, swelling about the ear and, very rarely, facial paralysis. Other non-specific complaints might include: irritability, headache, apathy, anorexia, and, especially in very young children vomiting and diarrhoea [29]. In our study protocol, the reason for encounter was not one of the criteria for enrolment of the patient in the study.

Signs and symptoms

The reason for encounter is hardly ever sufficient to assess the diagnosis with certainty. Symptoms may be helpful in directing clinical attention to the ear, but they are often vague, subtle, or absent. Under most circumstances, the diagnosis of otitis media depends exclusively or mainly on otoscopic findings [30].

Bain summarized the presenting symptoms of 100 children under the age of 12 years with acute otitis media in general practice [31].

He registered 266 complaints, subsumed under eight symptoms:

86%	ear pain
44%	recent upper respiratory tract infection
35%	previous history otitis media
33%	cough
23%	fever
21%	nasal discharge
13%	vomiting/diarrhoea
10%	sore throat

Discharge from a perforated drum is indicative of an active infection. The normal shape of the eardrum is somewhat concave. Loss of concavity, or in a more extreme case, the development of fullness or bulging, is indicative of increased hydrostatic pressure within the tympanic cavity. The normal colour of the eardrum is pearly grey. Of course, mild and diffuse redness may be imparted by crying. But it can also be a sign of inflammation, just as intense or localized redness is. Abnormal whiteness can result from the presence of pus in the tympanic cavity. The lustre of the eardrum is normally evident, with a well-defined light reflex. However, in young infants even the normal drum may appear dull, with a diminished, diffused, or absent light reflex. The latter findings may also develop in older children as an aftermath of inflammation, and do not necessarily indicate concurrent disease. On the other hand, a normal lustre and light reflex may often persist despite underlying middle ear inflammation. Thus, the presence or absence of lustre and light reflex are not highly sensitive and specific in discriminating the normal from the diseased middle ear. The normal translucency of the eardrum can alter into opacity caused by underlying effusion of the tympanic cavity. The assessment of impaired mobility of the eardrum is the most helpful diagnostic for effusion in the middle ear [32].

In the Netherlands the assessment of the mobility of the tympanic membrane is not a common way to diagnose acute otitis media. Nevertheless, practitioners in other countries feel it is necessary to check for impairment of the mobility of the drum [32].

Feenstra distinguishes three grades of inflammation of the middle ear. These are reflected in the otoscopic appearance of the tympanic membrane [33]:

Stage I: hyperaemia at the malleus handle and the annulus of the tympanic membrane; opacification of the drum; and light reflex still visible

Stage II: thickening of the eardrum with complete redness; absence of the light reflex

Stage III: bulging or perforated eardrum

The author claims that this classification has practical relevance beyond other classifications, which pertain to the clinical course of the episode and the medical management.
Karma et al. performed a study to assess the diagnostic value of otoscopic signs in acute otitis media [34]. The posterior odds were calculated in two populations with an incidence of acute otitis media of 56.6% and 37.5%, respectively.

	group 1	group 2
prior odds	1.3	0.6
posterior odds for:		
distinctly red	2.3	1.2
slightly red	0.6	0.2
cloudy	22.3	4.0
normal colour	0.01	0.05
bulging	24.6	8.4
retracted	0.9	1.0
normal position	0.5	0.3
mobility:		
distinctly impaired	15.5	3.7
slightly impaired	1.4	0.5
normal	0.03	0.05

It appears that cloudiness, distinctly impaired mobility, and bulging of the tympanic membrane, if present, indicated the middle ear effusion of acute otitis media rather reliably. Redness, retraction, and slightly impaired mobility of the tympanic membrane were not of much use in detecting acute otitis media.
In other countries, physicians agree upon the fact that to

diagnose acute otitis media, signs of middle ear effusion must be present, together with acute ear-related symptoms [35,36]. The most reliable non-surgical method to assess effusion in the middle ear is tympanometry. A Danish study in general practice showed a reduction in diagnosis of acute otitis media from 8.4% to 2.6% in children under 15 years of age by making use of tympanometry [37].
The various signs and symptoms make it possible to diagnose acute otitis media with a high degree of certainty. Needle aspiration and bacterial culture are, except in rare cases, not necessary to supply more information before starting the treatment.

Diagnostic criteria

In order to be sure that only patients with an acute otitis media were enrolled, we formulated the following diagnostic criteria:

1. acute or subacute developed earache,
2. partial or total redness of the tympanic membrane or perforation with purulent otorrhoea, and
3. confirmation of the diagnosis of the general practitioner by the otolaryngologist.

Conclusions

* In this study acute otitis media is an acute or subacute developed condition of earache, with otoscopically partial or complete redness of the eardrum, diagnosed by the general practitioner and confirmed by the otolaryngologist. Assessment of the mobility of the tympanic membrane is not necessary for diagnosis, mainly for practical reasons.
* It would be useful to assess the validity of diagnoses of acute otitis media, based on history and otoscopic examination but not on the mobility of the tympanic membrane.
* It would be useful to estimate the clinical relevance of a classification in grade of inflammation of the middle ear based on otoscopic examination.

TYMPANOMETRY

Part of this study was concerned with the detection of persistent middle ear dysfunction one month following a recurrent episode of acute otitis media. Since the detection of middle ear effusion by otoscopy is subjective and highly dependent on the clinician's experience [38], we used tympanometry to detect middle ear dysfunction. Tympanometry was developed in search of a more objective assessment of the middle ear status, employing an electro-acoustic impedance bridge. A schematic drawing of this instrument is shown in Figure 1.

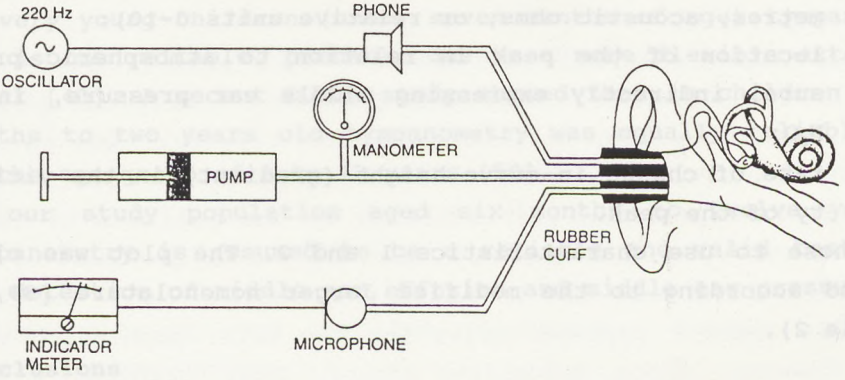

Figure 1: Schematic drawing of tympanometer.
Derived from: Bluestone CD, Klein JO, eds. Otitis media in infants and children. 1988.

To perform the test a probe tip with a rubber flange is introduced in the patient's external meatus, tightly sealing it and thus forming a closed cavity between the tip, the walls of the external canal and the tympanic membrane. The tip contains three tubes: one transmitting a 220 Hz tone, another monitoring the sound pressure level in the external canal; and one

connected to an air pump, varying the air pressure from +200 mm H_2O to -400 mm H_2O.

In essence, tympanometry measures eardrum compliance as the air pressure in the external canal is varied. In this way, the mobility of the tympanic membrane and ossicular chain can be assessed [39]. The flow of the acoustic energy is affected by mechanical factors encountered at the eardrum [40]. Space-occupying tumours, ossicular fixation, or interruption may also result in changes of the mechanical transmission. Nonetheless, the presence of fluid in the middle ear is of paramount importance as a cause for impaired transmission in children. The instrument generates a graph plotting pressure variation against compliance. On this graph three major characteristics are defined [41]:

1. height of the peak, or maximal compliance (cubic centimetres, acoustic ohms, or relative units 0-10);
2. location of the peak in relation to atmospheric pressure, indirectly expressing middle ear pressure, in mm H_2O;
3. rate of change in curve height (gradient) in the vicinity of the peak.

We chose to use characteristics 1 and 2. The plot was classified according to the modified Jerger nomenclature [39,42] (Table 2).

Table 2: Tympanometry classification

Type A	: compliance: ≥ 0.2 ml	pressure: ≥ -100 mm H_2O
Type C_1	: compliance: ≥ 0.2 ml	pressure: -100 - -199 mm H_2O
Type C_2	: compliance: ≥ 0.2 ml	pressure: -200 - -400 mm H_2O
Type B	: compliance: < 0.2 ml	absence of peak

Tympanometer: Tympanometer type 85 AR, probe tone frequency 220 Hz, American Electromedics Co.

The use of the gradient has been propagated by several authors to make prediction of the presence of effusion more reliable [43,44]. Nevertheless, these authors do not seem to agree on

the value of the gradient for which prediction of effusion could be more accurately done. That value is given as ≤0.1 ml in Fiellau-Nikolajsen's study and ≤0.15 ml in Paradise's report. Moreover, the gradient is not employed by all investigators [38,45,46,47] and its establishment is relatively time-consuming.

To establish the value of tympanometry for the identification of middle ear effusion, myringotomy was used in many studies to assess the presence or absence of fluid in the middle ear [38,42,44,47,48,49].

All these studies showed that tympanometry is a valid tool in the detection of middle ear effusion. They also demonstrate that a type B tympanogram is highly predictive for the presence of middle ear effusion. Overall, sensitivity of tympanometry ranged from 83% to 89% and specificity from 75% to 100%. In very young children (under seven months of age) tympanometry is not reliable, probably due to a more flexible external canal [43]. A recent Dutch study showed that in children five months to two years old tympanometry was equally reliable as in the age group of 2 to 12 years [50].

In our study population aged six months to twelve years, tympanometry is assumed to be a reliable and valid test for the detection of middle ear effusion and middle ear pressure.

Conclusions

* Tympanometry is a valid tool for the detection of middle ear effusion.
* A type B tympanogram is highly predictive for the presence of middle ear effusion.
* In the study population, tympanometry is assumed to be a reliable and valid test for the detection of middle ear effusion and measurement of middle ear pressure.

METHODS

The most appropriate method to estimate the effect of an intervention on the natural course of a disease is the clinical trial. In this study design a number of patients with a clearly circumscribed disease have to be selected in a specific way. They must be representative of all patients with this particular disease. If this is not feasible, then at least the characteristics of the study sample must be known, as far as they may influence the course of the disease. These include age, gender, race, etc. In this way the results of the study can be generalized to all patients with the disease who have these characteristics.

Study population

In the Netherlands all patients who seek medical assistance have to contact their own general practitioner. If the general practitioner observes an indication for referral, the patient is sent to a specialist. Most episodes of acute otitis media for which medical care is requested by the patients or their parents are treated in primary care. Only four per cent of the patients referred to an otolaryngologist [5]. Referred patients are not representative for the total population with the disease, since selection occurs. Most clinical trials regarding therapy for acute otitis media have been conducted with select populations. Thus the results cannot be generalized to the larger population with an acute otitis media, who are attended by the general practitioner. We decided to select the patients for our clinical trial from a primary care setting, in order to maximize the possibility to generalize from the results.

Entry criteria

In our study we selected patients with a recurrent acute otitis media.

Acute otitis media was defined as follows:

* an episode with an acute or subacute onset of otalgia, or signs of otalgia such as rubbing or tugging at the ears, in children who are too young to express their earache in a verbal way;
* otoscopic signs, seen at the eardrum, of an inflammation of the tympanic cavity (red or bulging eardrum), assessed by the general practitioner and confirmed by the otolaryngologist. These symptoms were described as follows:

  Stage I: hyperaemia at the malleus handle and the annuals of the tympanic membrane; opacification of the drum; and light reflex still visible

  Stage II: thickening of the eardrum with complete redness; absence of the light reflex

  Stage III: bulging or perforated eardrum.

If an acute otitis media is suspected as a rule the mobility of the tympanic membrane is not assessed by the physician, neither by pneumotoscopy nor by tympanometry. Accordingly, we did not adopt this characteristic as a condition for diagnosis. Our reason was to permit generalization of the results to the patients in whom the general practitioner ascertains the diagnosis acute otitis media. To certify that a correct diagnosis is made, the patient was seen immediately by the otolaryngologist, who repeated the history taking and the otoscopic examination.

We did not obtain material from the tympanic cavity by needle aspiration for a bacterial culture. The diagnosis acute otitis media is never affirmed by bacterial investigation in general practice. The therapy is prescribed without knowledge of the presence of specific microbes in an individual patient. Yet we wanted to be able to apply the study results to the general population with an acute otitis media in primary care. Therefore, confirmation of the diagnosis by bacterial culture was not adopted as an inclusion criterion for the study.

Recurrence was defined as an episode of acute otitis media following a preceding episode of acute otitis media with an

interval between the two distinct episodes of at least four weeks and a maximum of one year. An episode was considered to be cured if the general practitioner felt that was the case on the basis of clinical signs and symptoms.
In view of the results of epidemiological studies, we selected patients aged from ½ to 12 years. In the first half year of life an acute otitis media is seldom seen. Only when the balance between defense (natural resistance) and offence (virulence of micro-organism) is disturbed does an infection of the middle ear occur. This might be an expression of underlying pathology, such as an immune system disorder or local anatomical abnormalities, or a microbe with strong virulence. After the age of seven years the incidence of acute otitis media decreases. The occurrence of an acute otitis media in patients older than 12 years requires a different medical approach, as well as an investigation, because of the probability of other pathology.
The selection did not include patients at high risk of complications or an abnormal clinical course because of the presence of a congenital disorder or a systemic disease, which usually requires treatment with an antibiotic. If for any reason the patient had already used an antimicrobial therapy during the preceding four weeks, we assumed that this could have influenced the bacterial flora in a way that would interfere with the medical management of the current episode. Nor was the child selected for the study if signs of an allergy to penicillin were present in the history of the patient. To obtain independent subjects, no patient was enrolled who was already participating in the study.
In summary, patient selection was performed according to the following criteria:

Inclusion criteria:
* (sub)acute onset of otalgia
* red or bulging eardrum
* previous acute otitis media between four weeks and one year
* age from ½ to 12 years

Exclusion criteria:
* severe concurrent or existing disorder
* use of antibiotic in the past four weeks
* allergy to penicillin
* already participating in the study.

Informed consent

The protocol was approved by the ethics committee of the University Hospital of Utrecht. Informed consent was obtained by the general practitioner from the parent(s). This was accomplished after the general practitioner explained the aim and the procedures of the study to the parents. Furthermore, the parents received a written explanation. The general practitioner certified in writing on the study form the receipt of parental consent.

Randomization

To assess the effect of intervention on the course of the disease, specified outcome parameters pertinent to the clinical course are measured in the group of patients participating in this study. This group of selected patients is called the intervention group. The course of the disease is compared with that in a group of similar patients, who receive either a placebo or another therapy. Assignment to one of the treatment groups should be performed independent of a preconceived opinion of the physician or investigator and independent of the preference of the patient. The goal of this procedure is to obtain two treatment groups that are comparable in all respects except for the therapy. This random assignment to treatment groups was executed by the otolaryngologist immedi-

ately after confirmation that the child met the entry criteria. The codes for the treatment groups were kept in consecutively numbered envelopes. By opening the next envelope the otolaryngologist would find out which therapy to randomly prescribe to the patient. The codes in the envelopes were linked to the numbers by computer.
In order to avoid any subjective measurement of the effect of the medical intervention, the investigator was not allowed to know which treatment was prescribed to the patient. In our study the outcome parameters of the course of the disease were assessed by the general practitioner, who was not told which medication the patient had received. To make sure the patient did not tell him about the nature of the medication, the patient did not know either whether he was taken the drug under study or the placebo. Another reason for not telling the patient which medication he was taking is that this knowledge might have psychobiological influence on the course of the disease. In this way the clinical trial was double-blind.

Therapy

Immediately after enrolment and randomization the patient received the medication from the otolaryngologist according to the treatment code. All patients in both treatment groups were given paracetamol as an analgesic. This drug provides a symptomatic therapy and does not influence the course of the disease. It was to be taken three times a day as long as necessary, meaning as long as otalgia was present. The dosage was dependent on age (Table 3). Furthermore, all patients were given oxymethazoline nose drops as a local decongestant. The concentration was age-dependent (Table 3). The nose drops were to be applied three times a day for five days. No reliable research has been done to assess the efficacy of decongestant nose drops in acute otitis media. It is generally believed that application of decongestant nose drops by the right technique shrinks the swollen mucosa around the orificium of the eustachian tube and thus might restore the functioning of

the tube in an early stage. The drainage of mucus from the tympanic cavity to the nasopharynx and the admittance of air into the middle ear would thus be possible again.
The patients in the intervention group received amoxicillin-clavulanate, to be used three times a day for seven days in an age-related dosage (Table 3). The children in the placebo group received a placebo, not to be distinguished from the drug under study with regard to packing, volume, colour, taste or smell.
The choice of amoxicillin-clavulanate on bacteriological grounds is justified in Chapter III. Here we point out another reason for using this antibiotic in this study. Amoxicillin is still the drug of choice in the Netherlands. Therefore we wanted to avoid the possibility that failure of the antibiotic in those patients with an irregular clinical course could be attributed to ß-lactamase-producing strains of Haemophilus influenzae or Branhamella (Moraxella) catarrhalis.

Table 3: Daily dosage schedules for drugs used in study (in mg)

1. analgesic:		
paracetamol	½-1 yr.:	3 dd 60
(as long as pain	1-2 yr.:	4 dd 60
is present)	2-4 yr.:	3 dd 120
Sinaspril® Paracetamol	4-7 yr.:	4 dd 120
	7-12 yr.:	3 dd 240
2. decongestant nose drops:		
oxymetazoline HCl	<6 yr.:	3 dd gtt 2 0.025%
Nasivin®	6-12 yr.:	3 dd gtt 2 0.05 %
3. antibiotic:		
amoxicillin-	<3 kg.:	3 dd 25/ 6.25
clavulanate	4-6 kg.:	3 dd 50/12.5
(for 7 days)	7-10 kg.:	3 dd 75/18.75
Augmentin®	11-13 kg.:	3 dd 100/25.0
	14-25 kg.:	3 dd 125/31.25
	26-35 kg.:	3 dd 250/62.5

The compliance of the patient with the medication was checked by the general practitioner at the second and third visit,

after three and 14 days, respectively. Upon specific inquiry, the general practitioner recorded whether the medication was taken in the advised way and for how many days. Because of the ongoing relationship between the patient and the general practitioner, we felt it was unnecessary, even offensive, to assess the patient's compliance by weighing bottles or counting tablets. Mutual trust is an important characteristic in doctor-patient relationship in the Netherlands.
At the second and third visit the general practitioner inquired about side effects. In the event of allergic reactions, the physician had to take immediate measures. In case of gastro-intestinal side effects, the continuation of the medication would depend on the severity of the disturbance.

Assessments

After having checked the entry criteria and having obtained the consent the physician recorded the baseline data during the first visit (T_1). These are earache - in young infants signs of earache such as rubbing or tugging at the ears - and body temperature, measured rectally by the general practitioner. The following data were recorded to provide a description of the population: date of birth, gender, type of health insurance (as an indicator of socio-economic class), and date of onset. Furthermore, the following variables were registered during the first visit:

* case history: reason for encounter, duration of this episode, hearing impairment, prior common cold, use of analgesics, and habitual mouth breathing;
* medical history: dates of previous episodes of acute otitis media, adenoidectomy, tonsillectomy, tympanostomy tubes, specialist care and chronic diseases;
* total number of siblings; number of siblings, known with history of acute otitis media or respiratory disease;
* physical examination: general impression, body temperature, results of otoscopy, examination of nose, throat, tonsils and lymph nodes.

After this assessment by the general practitioner the patient was referred to the otolaryngologist. The specialist checked the entry criteria, repeated the history-taking and the examination, allocated the child at random to one of the treatment groups, and supplied the medication. The data were recorded on a special study form. It was decided not to make a bacterial culture from the middle ear. This is not customary in primary care in the Netherlands. Making a middle ear culture and stratifying the analysis on this level would be of no use, since any positive results could not have been applied in primary care without the unrealistic recommendation to make a culture routinely. Also for this reason the choice was made to provide an antibiotic with a broad spectrum in the study.
Three days after enrolment (T_2) the patient was seen once more by the general practitioner. The following data were recorded:

* case history: presence or signs of otalgia, presence of otorrhoea, hearing impairment, presence of common cold, and evaluation of compliance with therapy;
* physical examination: general impression, body temperature, results of otoscopy, examination of nose, throat, tonsils and lymph nodes.

If otalgia and/or fever (elevated body temperature: ≥38° C was present, the general practitioner contacted the otolaryngologist and the randomization code was broken. The course of the disease was classified as irregular. In that case appropriate medical management was started by the physician. If the course appeared to be regular - that is, no otalgia or signs of otalgia and no fever present - the patient was told to continue the medication.
Fourteen days after enrolment (T_3) the third visit took place to the general practitioner. The general practitioner repeated the activities of the second visit. In case of an otorrhoea the general practitioner informed the otolaryngologist, who broke the randomization code. Therapy was given. The findings of this visit were recorded on the same study form that was sent to the investigators.

Four weeks after enrolment (T_4) the presence of effusion in the middle ear was assessed by the otolaryngologist by means of tympanometry. In children of four years or older also an audiogram was also made. The results were recorded on the study form. In case of an abnormal result the examination was repeated after two months.
One year after enrolment (T_5) a tympanogram was made once more by the otolaryngologist. In children aged four years or older an audiogram was also made.
In the period between T_4 and T_5 the general practitioner registered the occurrence of the following events on a special study form:

* the number and dates of next acute otitis media and/or otitis media with effusion;
* the occurrence of other upper respiratory tract infections and the dates;
* the occurrence of other upper respiratory tract infections and the dates in siblings of the trial patient;
* the prescribed therapy, the course of the episode of the registered infections, and referral to a specialist, if this took place.

Outcome measures

The short-term goals of medical management for an episode of acute otitis media should be to cure the disease within an acceptable time period, to prevent sequelae, and to keep the patient and his relatives from suffering and discomfort. Especially after the investigations by Van Buchem et al. in the early eighties, most patients in the Netherlands have been treated without antibiotics. Antibiotics are only prescribed if the course of the disease is irregular after three days. This strategy, called 'watchful waiting', is generally accepted by patients. Apparently, three days is an acceptable time span. For this reason, and in order to compare the results of our study with those of Van Buchem et al., we agreed to a waiting time of three days to test the null hypo-

thesis of no difference between antibiotic and placebo. Moreover, it is justified to estimate the efficacy of an antibiotic after three days, since the discomfort of the patient can be treated in a symptomatic way. Otalgia, fever, and general illness are the most common complaints of a patient with an acute otitis media. In the majority of the cases, however, these complaints, especially earache, can be effectively treated with an adequate dose of an analgesic.
The incidence of complications is very low. Therefore a prospective study that aims to find out whether an antibiotic prevents the occurrence of sequelae, other than persistence of effusion and otorrhoea, requires a large number of patients. Consequently, the occurrence of sequelae will not be an outcome measure. Persistent effusion in the middle ear is not really a complication. It is a physical disorder that happens after an episode of acute otitis media. Since it may cause hearing impairment, it would be useful to have a therapy that can prevent or shorten the duration of effusion after an attack of acute otitis media.
The long-term goals of medical management of an episode of acute otitis media should be to prevent or postpone the occurrence of subsequent recurrences.

The following outcome measures were formulated:

* the course of the acute otitis media, as assessed after three days; an irregular clinical course is defined as the persistence or presence of otalgia and/or fever;
* the presence or absence of persistent otorrhoea after 14 days;
* the presence or absence of persistent middle ear effusion after four weeks, as assessed by tympanometry;
* the occurrence of subsequent episodes of acute otitis media, especially the number of episodes during the year of follow-up and the time elapsed between the index episode and the next one.

Statistics and interpretation

Our main outcome measure is an irregular clinical course three days after enrolment. Therefore we decided to test the null hypothesis that there is no difference between the proportion of irregular clinical course at T_2 in the two treatment groups. This hypothesis was also tested on stratified levels. Our preference is to show the differences with the calculated 95% confidence intervals whenever possible. This method of analysis immediately gives more insight into the range that includes the true difference in the general population, from which the study population is a sample. However, we used the chi-square statistic with Yates's correction for small numbers when necessary, as well as the Fisher exact statistic for comparison between two proportions. Logistic regression analysis was conducted to estimate the weight of risk factors. The results are expressed in odds ratios with 95% confidence intervals. The use of other methods of analysis, when appropriate, is mentioned and described in the chapters where the results are presented.

If in the antibiotic treatment group the proportion of patients with an irregular clinical course is 0.05 or less, and the corresponding proportion is 0.15 or more in the placebo treatment group, there will be a preference for antibiotics over analgesics and decongestant nose drops. If on the contrary, the proportion of irregular clinical courses in the placebo treatment group is less then 0.07, a preference will be demonstrated for analgesics and decongestant nose drops. Even if in this situation the difference between the proportions of irregular clinical courses in the two treatment groups is statistically significant, this difference is not regarded to be of clinical relevance.

REFERENCES

1. Melker RA de, Burke PD. Epidemiology of Otitis Media and the Role of the General Practitioner in Management. Family Practice 1988; 5 No 4: 307-313.
2. Huygen FJA. De epidemiologie van otitis media in de huisartspraktijk. Huisarts Wet 1978; 21: 208-211.
3. Hoogen HJM van den, Huygen FJA, Schellekens JWG et al. Morbidity figures from general practice. Nijmegen: University Department, Nijmegen, 1985.
4. Velden J van der. Basisrapport Morbiditeit in de Huisartspraktijk. Nationale studie naar ziekten en verrichtingen in de huisartspraktijk. 1991.
5. Lamberts H. In het huis van de huisarts. Verslag van het transitieproject. Lelystad: Meditekst; 1991: 175.
6. Lamberts H. Incidentie en prevalentie van gezondheidsproblemen in de huisartspraktijk. Huisarts Wet 1982; 25: 401-414.
7. Lamberts H. Transitionproject. Department of General Practice, University of Amsterdam, 1987.
8. NIVEL. 1987. Personal communication.
9. Buchem FL van, Dunk JHM, Hof MA van 't. Therapy of acute otitis media: myringotomy, antibiotics or neither? The Lancet 1981; ii: 883-887.
10. Buchem FL van, Peeters MF, Hof MA van 't. Acute otitis media: a new treatment strategy. Br Med J 1985; 290: 1033-1037.
11. Appelman CLM, Bossen PC, Dunk JHM, Lisdonk EH van de, Melker RA de, Weert HCPM. Otitis media acuta. Huisarts Wet 1990; 33: 242-245.
12. Medical Research Council. Acute otitis media in general practice - report of a survey by the Medical Research Council's working party for research in general practice. Lancet 1957; ii: 510-514.

13. Pukander J, Luotonen J, Sipilä M, Timonen M, Karma P. Incidence of acute otitis media. Acta Otolaryngol 1982; 93: 447-453.

14. Pukander J, Karma P, Sipilä M. Occurrence and recurrence of acute otitis media among children. Acta Otolaryngol 1982; 94: 479-486.

15. Buchem FL van, Dunk JHM, Hof MA van 't. Acute otitis media: paracentese, antibiotica of geen van beide? Ned Tijdschr Geneeskd 1982; 126: 462-467.

16. Biles RW, Buffler PA, O'Donell AA. Epidemiology of otitis media: A community study. Am J Public Health 1980; 70: 593.

17. Onion DK, Taylor C. The epidemiology of recurrent otitis media. Am J Public Health, 1977; 67: 472-474.

18. Perrin JM, Charney E, MacWhinney JB Jr. Sulfisoxazole as chemoprophylaxis for recurrent otitis media: a double-blind cross-over study in pediatric practice. N Engl J Med 1974; 291: 664-667.

19. Reed D, Dunn W. Epidemiologic studies of otitis media among eskimo children. Pub Hlth Report 1970; 85: 699-706.

20. Lowe JF, Bamforth JS, Pracy R. Acute otitis media. One year in general practice. Lancet 1963; ii, 1129.

21. Bäckström-Järvinen L, Tiisala R, Kantero RL, Hallman N. Illness among normal Finnish children during the first five years of life. Ann Paediatr Fenn 1966; 12:13.

22. Harsten G, Prellner K, Heldrup J, Kalm O, Kornfält R. Recurrent Acute Otitis Media. Acta Otolaryngol 1989; 107: 111-119.

23. Ahlo OP, Koivu M, Sorri M. What is an 'otitis-prone' child? Int J Ped Otorhinolaryngol 1991; 21: 201-209.

24. Lim DJ, editor. Recent advances in otitis media. Report of the fourth research conference. Ann Otol Rhinol Laryngol 1989; 98 (suppl 139): 10.

25. WONCA (World Organisation of National Colleges and Academies, Academic Associations of General Practitioners/-Family Physicians) Classification Committee. ICHPPC - 2 - defined. Oxford, Oxford University Press. 1983; 3rd ed.: 59.

26. Hordijk GJ. Consensus over therapie bij otitis media acuta. Ned Tijdschr Geneeskd 1992; 136: 85-88.

27. Bain J. Otitis media: diagnostic and therapeutic dilemmas. Update 1986; 34: 136-141.

28. Lamberts H. In het huis van de huisarts. Verslag van het transitieproject. Lelystad: Meditekst 1991; 178.

29. Bluestone CD, Klein JO. Diagnosis. In: Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: W.B. Saunders company, 1988; 69.

30. Paradise JL. Otitis media in infants and children. Paediatrics 1980; 65: 917-943.

31. Bain JG. Acute otitis media in children: diagnostic and therapeutic dilemmas. The Journal of Family Practice. 1978; 6: 259-265.

32. Whelmed J. Otitis media in general practice. The Practitioner. 1987; 231: 1101-1107.

33. Feenstra L. Acute ontsteking van het middenoor. Ned Tijdschr Geneeskd 1985; 129: 532-536.

34. Karma PH, Pentilla MA, Sipilä MM, Timonen MS. Diagnostic value of otoscopic signs in acute otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media. Proceedings of the fourth international symposium. Toronto: BC Decker, 1988: 44-47.

35. Bluestone C. State of the art: definitions and classifications. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the Third International Symposium. Toronto: BC Decker, 1984: 1-4.

36. Karma P, Palva T, Kouvalainen K,et al. Finnish approach to the treatment of acute otitis media. Report of the Finnish consensus conference. Ann Otol Rhinol Laryngol 1987; 96 (Suppl 129):1-19.

37. Lildholdt T, Feldong JU. Tympanometry in general practice: a controlled study of its influence on diagnosis and treatment of otitis media. In: Abstracts of the Fifth International Symposium Recent Advances in Otitis Media. Ft. Lauderdale, Florida; May 20-24, 1991.

38. Bluestone CD, Beery QC, Paradise JL. Audiometry and tympanometry in relation to middle ear effusion in children. Laryngoscope 1973; 83: 594-604.

39. Jerger J. Clinical experience with impedance audiometry. Arch Otolaryngol 1970; 92: 311-324.

40. Feldman AS. Eardrum abnormality and the measurement of middle ear function. Arch Otolaryngol 1974; 99: 211-217.

41. Brooks DN. An objective method of determining fluid in the middle ear. J Int Audiol. 1968; 7(2): 280-286.

42. Fiellau Nikolajsen M. Tympanometry and secretory otitis media. Acta Otolaryngol 1983; Suppl. 394: 1-73.

43. Fiellau-Nikolajsen M, Falbe-Hansen J, Knudstrup P. Tympanometry in three-year-old children (III). Scand Audiol 1980; 9: 49.

44. Paradise JL, Smith CG, Bluestone CD. Tympanometric detection of middle ear effusion in infants and young children. Pediatrics 1976; 58: 198-210.

45. Jerger S, Jerger J, Mauldin L, Segal P. Studies in impedance audiometry II. Children less than 6 years old. Arch Otolaryngol 1974; 99: 1-9.

46. Jerger J, Anthony L, Jerger S, Mauldin L. Studies in impedance audiometry III. Middle ear disorders. Arch Otolaryngol 1974; 99: 165-171.

47. Orchik DJ, Dunn JW, McNutt L. Tympanometry as a predictor of middle ear effusion. Arch Otolaryngol 1978; 104:

4-6.

48. Cantekin EI, Bluestone CD, Fria TJ, Stool SE, Beery QC, Sabo DL. Identification of otitis media with effusion in children. Ann Otol Rhinol Laryngol 1981; suppl 68: 190-195.

49. Gates GA, Avery C, Cooper JC, Hearne EM, Richard Holt G. Predictive value of tympanometry in middle ear effusion. Ann Otol Rhinol Laryngol 1986; 95: 46-50.

50. Sassen ML, Van Aarem A, Hulshof JH, Grote JJ, Bouwhuis ML. Validiteitsonderzoek tympanometrie bij otitis media met effusie. Ned Tijdschr Geneeskd 1989; 133 (48): 2418.

Chapter III

MICROBIOLOGY OF ACUTE OTITIS MEDIA

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INTRODUCTION

The purpose of this chapter is to review current knowledge on the microbiology of acute otitis media, with special reference to its relevancy for clinical management. In studying acute otitis media a proper understanding of its microbiological aspects is essential.
In our clinical trial on the efficacy of amoxicillin-clavulanate in recurrent acute otitis media no cultures from the middle ear or nasopharynx were made. This decision was not taken before ample study of the microbiological aspects of acute otitis media justified this attitude.

Role of bacteria

Bacteria play an important role in the pathogenesis of acute otitis media. A compilation of 13 studies conducted between 1970 and 1986, in which 4157 cases of acute otitis media were bacteriologically evaluated, showed positive cultures in approximately 70% of the cases [1-15] (Table 1, page 60). Similar findings were reported from 12 different studies conducted in the United States, Finland and Sweden between 1952 and 1981 [2,8,16-26]. More recent reports showed even higher percentages of positive cultures in acute otitis media, ranging from 84% to 93% [27,28].

Role of viruses

A direct role of viruses in the etiology of acute otitis media does not seem to be present at the level of the middle ear [29]. Directly isolated from middle ear effusions, viruses were reported in only 4.4% and 4.5% of acute otitis media cases [30-31]. However, as clinical experience shows, acute otitis media almost invariably occurs during the course of an upper respiratory tract infection or is preceded by it. Viral involvement of the upper respiratory tract mucosa, including eustachian tube and middle ear cavity, may facilitate the concurrent development of a middle ear infection.

Henderson and co-workers showed a clear correlation between isolation of viruses in the upper respiratory tract and the presence of otitis media. In this longitudinal study a concurrent or recent viral infection was found in 26.3% of the cases [32].
Isolation of viral antigens is another way to detect a possible role of viruses in patients suffering from acute otitis media. This yields virus antigens from ±25% of the cases [33]. Various studies showed that particularly respiratory syncytial virus (RSV) is associated with acute otitis media [33-35].

Sterile cultures

Negative culture results, reported in around 30% of the cultures, do not necessarily imply that pathogenic micro-organisms are not associated with the infectious process [36]. The bacterial organism, such as an anaerobic bacterium, may not have been isolated by usual laboratory techniques [36]. Also, the presence of antimicrobial enzymes such as lysozymes, alone or in combination with immunoglobulins, or recent administration of antibiotics may already have suppressed bacterial growth [36]. Non-bacterial organisms as viruses, Chlamydia, or Mycoplasma may be involved [36].
In this respect the use of the Gram stain is of value in identifying fastidious bacterial organisms. This technique may demonstrate their presence in cases where antibiotics or antimicrobial substances may have inactivated bacterial growth [36].
Another way to determine bacterial involvement in acute otitis media is by detecting antibodies to specific micro-organisms during the course of an episode of acute otitis media. Using this technique Karjalainen et al. clearly demonstrated that in culture-negative acute otitis media, bacteria-specific secretory antibodies were found in 21% of the ears with 'culture-negative' acute otitis media at the initial visit, compared to 36% of the ears with 'culture-positive' acute otitis media.

Also, they found that the appearance of secretory antibodies did not correlate with the number of preceding acute otitis media attacks, a percentage increasing during the course of the infection [37,38].

Predominant bacterial pathogens

Streptococcus pneumoniae is consistently reported to be the most frequently occurring pathogen, followed by Haemophilus influenzae. In earlier years the third most frequent micro-organism was Streptococcus Group A [16]. However, studies conducted in the eighties showed an increasing number of Branhamella catarrhalis [14]. Culture results from the Pittsburgh Otitis Media Research Center between 1980 and 1989 clearly showed Branhamella catarrhalis to be the third most frequent pathogen in acute otitis media [27]. In one recent report this micro-organism emerged as the second most frequent pathogen in acute otitis media, found in 26% of the cultures [28]. For the specific Dutch situation little is known about the flora in acute otitis media. An early study showed Streptococcus pneumoniae to be the most predominant micro-organism in middle ear aspirates, followed respectively by Haemophilus influenzae and Streptococcus Group A [39].

In a later study the most predominant micro-organism was Streptococcus Group A [40]. Thus far this isolated finding cannot be confirmed by other studies. This anomalous finding cannot be explained. Even when the fact is taken into account that the study population consisted of children whose acute otitis media episode took an unsatisfactory course; all patients suffered from persistent earache and/or fever three days from onset of an untreated acute otitis media episode. Recently, a study from Denmark reported the reappearance of Streptococcus Group A in acute otitis media, with an increasing percentage of this micro-organism in cultures made in the period of January through March from 1986 to 1989 [41]. The decrease in Streptococcus pneumoniae was not statistically significant, with unchanged percentages of Haemophilus influ-

enzae and Branhamella catarrhalis. Latter findings suggest a transient epidemic of Streptococci Group A, rather than a consistent rise and reappearance of Streptococcus Group A as an important micro-organism in acute otitis media [41].
Although in children younger than three months a more predominant role is found for gram-negative enteric bacteria, such as Escherichia Coli, Klebsiella and Enterobacter species, even in this group the most common pathogens in acute otitis media are Streptococcus pneumoniae and Haemophilus influenzae [42-45].

Origin of bacterial pathogens in acute otitis media

By now, it is well understood that the source of the most common middle ear pathogens is in the nasopharynx and that they belong to the normal flora of both healthy and otitis-prone persons [46-50]. A study on antibiotic sensitivities of nasopharyngeal pathogens in a relapse of acute otitis media again demonstrated the nasopharynx as the source of microbial invasion of the middle ear [51]. The study by Faden et al. showed that otitis-prone children were more frequently colonized with middle ear pathogens than a comparable group of non-otitis-prone children [50]. The mechanisms that lead to colonization of the middle ear cavity, normally devoid of bacteria, and subsequently to the development of middle ear infection during the course of an upper respiratory tract infection still are poorly understood.
The lower frequency of acute otitis media in older children may be explained by the finding that middle ear pathogens in the nasopharynx diminish in number with advancing age [49].
Because of their clear predominance only the three most important pathogenic micro-organisms are discussed seperately below.

Streptococcus pneumoniae

This micro-organism is consistently reported to be the sole pathogen in 30% to 40% of the cultures. This proportion does not seem to vary much with age [9]. Pneumococci, isolated from

otitis media, are invariably encapsulated with polysaccharides, pneumococci without capsular polysaccharides may be considered non-pathogenic [52]. Currently, 85 capsular polysaccharide types are recognized. Of these, relatively few types are associated with acute otitis media; 10 to 15 types account for over 90% of the isolates [53,54]. Most predominant are types 1, 3, 6A, 7F, 14, 18C, 19F, 23 F. Less commonly associated are types 2, 4, 5, 8, 9N, 12F, 25F [55]. The capsular type does not have direct implications for possible antibiotic therapy, but it determines the pneumococcal vaccine composition. Because immunoprophylactic therapy is beyond the scope of this chapter, it will not be discussed further.

Haemophilus influenzae

This micro-organism is consistently reported to be the sole pathogen in about 20% of the cultures. Non-typable or unencapsulated types account for 85% to 90% of the cases of acute otitis media caused by Haemophilus influenzae, whereby Haemophilus influenzae Type b is responsible for the remaining 10% to 15% [56]. Typable Haemophilus influenzae strains are found in six different capsular types, a through f [56]. The earlier notion that Haemophilus influenzae otitis media is predominantly a disease of children in the pre-school age is not entirely accurate. The micro-organism is comparably frequent in acute otitis media at older age [57]. The first reports of ß-lactamase producing strains of Haemophilus influenzae, causing resistance to aminopenicillins, emerged in 1974 [58,59]. In the United States, the prevalence of ß-lactamase-producing strains of Haemophilus influenzae isolates in acute otitis media is reported to range from 17% to 36%, with this percentage steadily increasing from 1981 to 1986 [60]. In a Finnish report the overall proportion of ß-lactamase producing strains in otitis media appeared to be around 15% [61]. Here too, the percentages were found to increase in time. In acute otitis media the same investigators reported approximately 5% of the strains to be ß-lactamase-producing. In this study the

micro-organism was cultured somewhat more frequently (17%) in recurrent or prolonged episodes of acute otitis media than in primary attacks (8%) [61]. In a large European multicenter study Haemophilus influenzae strains from different specimen sources were compared in a standardized way with respect to ß-lactamase- production, capsular types and resistance to different antibiotics [62]. This revealed an overall mean percentage of 11% ß-lactamase-producing strains, more often (17%) in type b than in non-b strains (10%). Overall resistance percentages ranged from 1.6% in West Germany to 30.6% in Spain. For type b strains resistance ranged from 0% in West Germany to 63.6% in Spain; for non-b strains, from 1.8% in West Germany to 25.6% in Spain [62]. In the Netherlands cultures from head (ear, eye) and upper respiratory tract (nasopharynx, sinus) showed 90% and 85% non-b types respectively. The non-b types showed in 4.7% ß-lactamase-producing strains, the b type in 12% and the total of Haemophilus influenzae cultures in 6.8% [62].

Branhamella catarrhalis (Moraxella catarrhalis)

This micro-organism has emerged during the past two decades as an increasingly important pathogen in acute otitis media. A Finnish study found it in 10.2% of the middle ear fluids in acute otitis media [63]. In the United States higher frequencies are consistently reported. In some studies it is detected in up to 26% of the children suffering from acute otitis media [10,28]. A predilection for the younger children has been reported [12], though others could not confirm this finding within the first four years of life [63]. A majority of the strains are ß-lactamase producing. In Finland this is true of 40% to 60% of the strains [63,64]. In the United States these percentages are still higher, ranging from 75% to 91% in a recently reported study [10,12,28]. In a Finnish article no difference between the prevalence in primary or recurrent attacks was reported [63].

Indirect pathogenicity of ß-lactamase producing micro-organisms

Apart from playing a direct role in the infectious process, ß-lactamase-producing strains of Haemophilus influenzae or Branhamella catarrhalis may also act as indirect pathogens by protecting penicillin-susceptible organisms from this drug. This concept of indirect pathogenicity by ß-lactamase-producing micro-organisms has been illustrated by Brook [65].

CONCLUSIONS

In view of current knowledge on the microbiology of acute otitis media, the following conclusions can be drawn.

Firstly, considerable stability over time exists in the frequency of acute otitis media caused by Streptococcus pneumoniae and Haemophilus influenzae as the most important pathogens. Up to now, Streptococcus pneumoniae shows excellent susceptibility to (amino)penicillins. Although ß-lactamase-production is reported for Haemophilus influenzae, the great majority of strains indicated in acute otitis media maintain aminopenicillin susceptability.

Secondly, Branhamella catarrhalis must now be considered as the third most important pathogen. The majority of strains from this micro-organism are reported to be ß-lactamase-producing. Thirdly, so far the literature gives no evidence of essential differences between the micro-organisms cultured in primary acute otitis media compared to those isolated recurrent acute otitis media.

Fourthly, in view of current knowledge of the most likely pathogens involved in acute otitis media, cultures from middle ear aspirates are not necessary in otherwise healthy children of six months and older. Amoxicillin-clavulanate (Augmentin®) shows good antimicrobial activity against all major pathogens responsible for acute otitis media, including ß-lactamase-producing strains of Haemophilus influenzae and Branhamella catarrhalis. This drug also shows good penetration of middle

ear fluids in therapeutic concentrations [66].
In our study, where no cultures of middle ear aspirates were made and the population consisted of otherwise healthy children, it was safe to assume good activity of the study drug Augmentin®, with its maximally broad spectrum for an orally administered drug, in acute otitis media.

Table 1: Distribution of middle ear pathogens. Culture studies, 1970-1986

Year	Str. Pneum.	Haem. Infl.	Branh. Catar.	Strept Gr. A	Staph. aureus	Others	No growth	ref. nr.
	%	%	%	%	%	%	%	
1970	34	20	8	3	0	2	30	2
1971	36	23	0	1	0	0	38	3
1974	35	31	0	2	0	4	28	4
1979	24	18	0	5	3	32	14	5
1980	37	20	6	2	2	1	29	6
1981	28	31	0	2	2	5	31	7
1981	27	6	5	1	3	8	41	8
1983	25	17	16	1	1	0	34	9
1983	24	18	2	5	11	2	26	10
1983	32	25	19	0	0	0	0	11
1984	25	19	13	1	0	0	33	12
1984	26	15	6	3	3	3	26	13
1986	20	20	5	0	4	21	15	14

Derived from: Giebink GS. The microbiology of otitis media.
Ped Infect Dis J. 1989; 8: S18-S20.

REFERENCES

1. Giebink GS. The microbiology of otitis media. Ped Infect Dis J 1989; 8: S18-S20.
2. Howie VM, Ploussard JH, Lester R. Otitis media: a clinical and bacteriological correlation. Pediatrics 1970; 45: 29-35.
3. Howie VM, Ploussard JH. Bacterial etiology and antimicrobial treatment of exudative otitis media: relation of antibiotic therapy to relapses. South Med J 1971; 64: 233-239.
4. Howie VM, Ploussard JH, Sloyer J. Comparison of ampicillin and amoxicillin in the treatment of otitis media in children. J Infect Dis 1974; 129(Suppl): 181-184.
5. Brook I. Otitis media in infants and children: a prospective study of aerobic and anaerobic bacteriology. Laryngoscope 1979; 89: 992-997.
6. Shurin PA, Pelton SI, Donner A, Finkelstein JM, Klein JO. Thrimethoprim-sulfamethoxazole compared with ampicillin in the treatment of acute otitis media. J Pediatr 1980; 96: 1081-1087.
7. Pelton SI, Teele DW, Shurin PA, Klein JO. Disparate cultures of middle ear fluids. Am J Dis Child 1980; 134: 951-953.
8. Schwartz AR: Bacteriology of otitis media: a review. Otolaryngol Head Neck Surg 1981; 89: 444-450.
9. Luotonen J, Herva E, Karma P, Timonen M, Leionen M, Mäkelä PH. The bacteriology of acute otitis media in children with special reference to Streptococcus pneumoniae as studied by bacteriological and antigen detection methods. Scand J Infect Dis 1981; 113: 177-183.
10. Shurin PA, Marchant CD, Kim CH et al. Emergence of beta-lactamase producing strains of Branhamella catarrhalis as important agents of acute otitis media. Pediatr Infect Dis J 1983; 2: 34-38.

11. Fujita K, Iseki K, Yoshioka H, Sasaki T, Ando T, Nakamura M. Bacteriology of acute otitis media in Japanese children. Am J Dis Child 1983; 137: 152-154.
12. Kovatch AL, Wald ER, Michaels RH. Beta-lactamase-producing Branhamella catarrhalis causing otitis media in children. J Pediatr 1983; 102: 261-264.
13. Marchant CD, Shurin PA, Turcyzk VA et al. A randomised controlled trial of cefaclor compared with trimethoprim-sulfamethoxazole for treatment of otitis media. J Pediatr 1984; 105: 633-638.
14. Giebink GS, Batalden PB, Russ JN, Le CT. Cefaclor versus amoxicillin in the treatment of acute otitis media. Am J Dis Child 1984; 138: 287-292.
15. Chonmaitree T, Howie VM, Truant AL. Presence of respiratory viruses in middle ear fluids and nasal wash specimens from children with acute otitis media. Pediatrics 1986; 77: 698-702.
16. Bluestone CD, Klein JO. Microbiology. In: Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: W.B. Saunders Company, 1988: 45-58.
17. Bjuggren G, Tunevall G. Otitis in childhood: a clinical and serobacteriological study with special reference to the significance of Haemophilus influenzae in relapses. Acta Otolaryngol 1952; 42: 311-328.
18. Lahikainen EA. Clinico-bacteriologic studies on acute otitis media: aspiration of tympanum as diagnostic and therapeutic method. Acta Otolaryngol 1953: 107: 1-82.
19. Mortimer Jr EA, Watterson Jr RL. A bacteriologic investigation of otitis media in infancy. Pediatrics 1956; 17: 359-366.
20. Grönroos JA, Kortekangas AE, Ojala L, Vuori M. The aetiology of acute middle ear infection. Acta Otolaryngol 1964; 58: 149-158.
21. Coffey Jr JD. Otitis media in the practice of pediatrics: bacteriological and clinical observations. Pediatrics 1966; 38: 25-32.

22. Feingold M, Klein JO, Haslan GE, Tilles JG, Finland M, Gelles SS. Acute otitis media in children: bacteriological findings in middle ear fluid obtained by needle aspiration. Am J Dis Child 1966; 111: 361-365.
23. Halsted C, Lepow ML, Balassanian N et al. Otitis media. Clinical observations, microbiology, and evaluation of therapy. Am J Dis Child 1968; 115, 542-551.
24. Nilson BW, Poland RL, Thompson, RS, Morehead D, Baghdassarian A, Carver DH. Acute otitis media: treatment results in relation to bacterial etiology. Pediatrics 1969; 43: 351-358.
25. Kamme C, Ageberg M, Lundgren K. Distribution of diplococcus pneumoniae types in acute otitis media in children and influence of the types on the clinical course in penicillin V therapy. Scand J Infect Dis 1970; 2: 183-190.
26. Howard JE, Nelson JD, Clahsen J, Jackson LH. Otitis media of infancy and early childhood: A double-blind study of four treatment regimens. Am J Dis Child 1976; 130: 965-970.
27. Stephenson JS, Martin D, Kardatzke D, Bluestone CD. Prevalence of bacteria in middle ear effusion for the 80's. In: Abstracts of the Fifth International Symposium Recent Advances in Otitis Media. Ft. Lauderdale, Florida; May 20-24, 1991; 123.
28. DelBeccaro MA, Mendelman PM, Inglis AF, Richardson MA, Clausen C. Bacteriology of acute otitis media (AOM): a new perspective. In: Abstracts of the Fifth International Symposium Recent Advances in Otitis Media. Ft. Lauderdale, Florida; May 20-24, 1991; 27.
29. Klein JO. Microbiology and antimicrobial treatment of otitis media. Ann Otol Rhinol Laryngol 1981; 90 (Suppl 84): 30-36.
30. Klein JO, Teele DW. Isolation of viruses and mycoplasmas from middle ear effusions: a review. Ann Otol Rhinol Laryngol 1976; 85 (Suppl. 25): 140-144.

31. Howie VM, Pollard RB, Kleyn K, Lawrence B, Peskuric T, Paucker K, Baron S. Presence of interferon during bacterial otitis media. J Infect Dis 1982; 145: 811-814.
32. Henderson FW, Collier Am, Sanyal MA et al. A longitudinal study of respiratory viruses and bacteria in the etiology of acute otitis media with effusion. N Engl J Med 1982; 306: 1377-1383.
33. Klein BS, Dolette FR, Yolken RH. The role of respiratory syncytial virus and other viral pathogens in acute otitis media. J Pediatr 1982; 101: 16-20.
34. Sarkkinen H, Ruuskanen O, Meurman O, Puhakka H, Virolainen E, Eskola J. Identification of respiratory virus antigens in middle ear fluids of children with acute otitis media. J Infect Dis 1985; 151: 444-448.
35. Ruuskanen O, Arola M, Putto-Laurila A et al. Acute otitis media and respiratory virus infection. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 307-309.
36. Bluestone CD, Klein JO. Microbiology. In: Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: W.B. Saunders Company, 1988: 49-50.
37. Karjalainen H, Koskela M, Luotonen J, Sipilä P. Secretory antibodies specific to Streptococcus pneumoniae, Haemophilus influenzae and Branhamella catarrhalis in middle ear effusion during acute otitis media. Acta Otolaryngol 1991; 111: 524-529.
38. Karjalainen H, Koskela M, Luotonen J, Herva E, Sipilä P. Occurrences of antibodies against Streptococcus pneumoniae, Haemophilus influenzae and Branhamella catarrhalis in middle ear effusion and serum during the course of acute otitis media. Acta Otolaryngol 1991; 111: 112-119.
39. Dishoeck HAE van, Derks ACW, Voorhorst R. Bacteriology and treatment of acute otitis media in children. Acta Otolaryngol 1959; 50: 250-261.

40. Buchem FL van, Peeters MF, Hof MA van 't. Acute otitis media: a new treatment strategy. Br Med J 1985; 290: 1033-1037.

41. Jensen IP, Ejlertsen T. Reappearance of Group A streptococci in acute otitis media. Scand J Infect Dis 1990; 22: 431-435.

42. Berman SA, Balkany TJ, Simons MA. Otitis media in infants less than 12 weeks of age. J Pediatr 1978; 93: 453-454.

43. Bland RD. Otitis media in the first weeks of life: Diagnosis, bacteriology and management. Pediatrics 1972; 49: 187-197.

44. Shurin PA, Howie VM, Pelton SI, Ploussard JH, Klein JO. Bacteriological etiology of otitis media during the first six weeks of life. J Pediatr 1978; 92: 893-896.

45. Tetzlaff TR, Ashworth C, Nelson JD. Otitis media in children less than 12 weeks of age. Pediatrics 1977; 59: 827-832.

46. Ingvarsson L, Lundgren K, Ursing J. The bacterial flora in the nasopharynx in healthy children. Acta Otolaryngol 1982; Suppl 386: 94-96.

47. Freijd A, Bygdeman S, Rynnel-Dagöö B. The nasopharyngeal microflora of otitis-prone children with emphasis on H. influenzae. Acta Otolaryngol 1984; 97: 117-126.

48. Prellner K, Christensen P, Hovelius B, Rosén C. Nasopharyngeal carriage of bacteria in otitis-prone and non-otitis-prone children in day-care centres. Acta Otolaryngol 1984; 98: 343-350.

49. Stenfors LE, Räisänen S. Occurence of middle ear pathogens in the nasopharynx of young individuals. A quantative study in four age groups. Acta Otolaryngol 1990; 109: 142-148.

50. Faden H, Waz MJ, Bernstein JM, Brodsky L, Stanievich J, Ogra PJ. Nasopharyngeal flora in the first three years of life in normal and otitis-prone children. Ann Otol Rhinol Laryngol 1991; 100: 612-615.

51. Thore M, Lidén M. Relapse of acute purulent otitis media: antibiotic sensitivities of nasopharyngeal pathogens. Scand J Infect Dis 1987; 19: 315-323.
52. Robbins JB, Schneerson R, Szu SC. Special lecture: Recent developments of bacterial vaccines related to the prevention of otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 211-214.
53. Austrian R, Howie VM, Ploussard JH. The bacteriology of pneumococcal otitis media. Johns Hopkins Med J 1977; 141: 104-111.
54. Robbins JB, Austrian R, Lee CJ et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. J Infect Dis 1983; 148: 1136-1159.
55. Sloyer JL, Ploussard JH, Howie VM. Efficacy of pneumococcal polysaccharide vaccine in preventing acute otitis media in infants in Huntsville, Alabama. Rev Infect Dis 1981; 3 (Suppl): 119-123.
56. Wald ER. Haemophilus influenzae as a cause of acute otitis media. Pediatr Infect Dis J 1989; 8: S28-S30.
57. Klein JO. Microbiology of otitis media. Ann Otol Rhinol Laryngol 1980; 89 (Suppl 68): 98-101.
58. Gunn BA, Woodall JB, Jones JF, Thornsberry C. Ampicillin-resistant Haemophilus influenzae. Lancet 1974; ii: 845.
59. Tomeh M, Starr SE, McGowan JE, Terry PM, Nahmias AJ. Ampicillin-resistant Haemophilus influenzae type b infection. JAMA 1974; 229: 295-297.
60. Krenke CF, Stephenson JS, Wald ER. Incidence of organisms in otitis media. Ann Otol Rhinol Laryngol 1988; 97 (Suppl 133): 20.

61. Karma P, Luotonen J, Pukander J, Sipilä M, Herva E, Grönroos P. Haemophilus influenzae in acute otitis media. Acta Otolaryngol 1983; 95: 105-110.

62. Machka K, Braveny I, Dabernat H et al. Distribution and resistance patterns of Haemophilus influenzae: a European cooperative study. Eur J Clin Microbiol Infect Dis 1988; 7: 14-24.

63. Karma P, Virtanen T, Pukander et al. Branhamella catarrhalis in acute otitis media. Acta Otolaryngol 1985; 99: 285-290.

64. Forsgren A, Walder M. Activity of common antibiotics against Branhamella catarrhalis, Haemophilus influenzae, Pneumococci, group A streptocci and Staphylococcus aureus in 1983. Acta Otolaryngol 1984; Suppl. 407: 43-49.

65. Brook I. The concept of indirect pathogenicity by ß-lactamase-production, especially in ear, nose and throat infection. J. Antimicr. Chemoth. 1989; 24 (Suppl. B): 63-72.

66. McCracken GH Jr. Selection of antimicrobial agents for treatment of acute otitis media with effusion. Pediatr Infect Dis J 1987; 6: 985-988.

Chapter IV

A CRITICAL REVIEW OF CLINICAL TRIALS REGARDING TREATMENT IN ACUTE OTITIS MEDIA

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ABSTRACT

A survey was made of the literature in English on clinical trials of therapy in acute otitis media. The articles were analysed systematically on 24 parameters related to study design and the acute otitis media condition. We retrieved 50 studies published from 1965 to 1989. Surprisingly, the combination of a double-blind method, clearly defined inclusion criteria, and criteria for outcome representative for the acute otitis media condition was found in only 13 studies. Most of these 13 compared different antibiotic regimens and only four were placebo-controlled. A condensed recommendation based on the conclusions reached can, even in these 13 studies, hardly be obtained. This is due to failure to show an overall difference in favour of a specific treatment regimen. Our study shows that many trials are methodologically flawed, which makes it difficult to adopt their results unconditionally. In view of current controversy on management of acute otitis media, well-conducted placebo-controlled clinical trials on therapy in acute otitis media are still needed.

INTRODUCTION

Acute otitis media is a common disease in children. Before the age of seven, 65% - 95% of all children will have suffered from one or more attacks [1,2]. However, treatment strategies show important differences. In the United States, antibiotics are prescribed in 97.9% of the cases. On the other hand, in the Netherlands, where myringotomy was the preferred therapy for many years, antibiotics are prescribed in only 31.2% of cases. Also, the antibiotics of choice differ. When antibiotics are prescribed in the Netherlands, ampicillin or amoxycillin is preferred in 91.1% of the episodes, whereas in Switzerland, this is the chosen antibiotic in only 47.1% of the cases [3]. The Finnish Consensus Conference recommended

penicillin-V as the antibiotic of first choice for Scandinavia [4].

Treatment strategies are based on clinical experience as well as on results of studies on therapy in acute otitis media. We presumed that the apparent controversy on management may be the result of failure of clinical trials to provide convincing evidence on which to build consensus on therapy. We therefore reviewed clinical trials on therapy in acute otitis media reported in English since 1965. All studies were analysed in a systematic way on items relevant to the study design and the acute otitis media condition. The aim of this review was to assess their scientific merit in providing answers to therapeutic dilemmas in acute otitis media. At the same time this literature study was part of the research for our recently concluded randomized double-blind placebo-controlled trial on the efficacy of an antibiotic in the treatment of a recurrent acute otitis media.

METHODS

To ensure that our survey would include a maximum of reports on clinical trials available in English, the literature was reviewed by several methods. Studies were retrieved by computer research in MEDLINE, complemented by a manual search in the INDEX MEDICUS. Reference lists of important reviews on otitis media in general, Bluestone's textbook on otitis media, as well as the reference lists of several consensus conferences were consulted [4-8]. All retrieved reports were read thoroughly by the first two authors and evaluated on 24 different parameters relevant to the study design and the acute otitis media condition. The parameters concerning methodology were based mainly on Pocock's textbook on clinical trials [9]. All items were scored independently by J.C. and C.A.. Of the evaluated parameters, 22 are listed and shown with overall results in Table 1.

Table 1: Parameters of study design and of study population.

PARAMETERS OF STUDY DESIGN	NUMBER OF STUDIES N=50
Randomization	41
Placebo control group	9
Double-blind	26
single-blind, objective outcome	2
Compliance control	20
≥2 investigators confirming diagnosis	11
Validation of investigators	7
Outcome at fixed time	43
clinical history	25
physical dianostic signs	43
Statistical significance	41
Statistical methods used	27
Intended size of population	0
statistical power (α,β)	3
PARAMETERS OF STUDY POPULATION	
Inclusion criteria	40
clinical history	23
physical diagnostic signs	39
Age group 0 - 12 years	28
Exclusion criteria	43
Antibiotic-free episode ≥ 2 weeks	12
Allergy to antibiotics used	35
Baseline characteristics	37

Because long-term follow-up is not directly related to the initial outcome of therapy in the acute phase of the disease we omitted the data on the two parameters concerning followup.

RESULTS

A total of 50 studies published from 1965 to 1989 were retrieved. Of these, 34 were reported since 1980 and another 11 between 1970 and 1980. Out of 1200 items to be scored, only 20 were initially judged differently by the investigators, mostly due to interpretation of the text. In all of these cases consensus was reached by meticulously rereading the passage.

Sort of studies and primary reported results

A comparison between various antibiotics was made in 31 studies that were uncontrolled for therapy, with a total of 20 different antibiotics. Two different antibiotics were compared in 24 out of these 31 studies [12,18-20,25,26,28,32,33,36-38, 40,41,44,47-50,52,53,56,57,59]. Only three of these 24 reported a difference in clinical outcome [32,40,44]. In one study cyclacillin showed quicker recovery compared to amoxicillin [32]. Amoxicillin-clavulanate was superior to cefaclor in two of five studies comparing these therapies [40,44]. The other three could not detect a difference [47,52,53]. Seven uncontrolled studies compared three or more antibiotics [10,13,17, 21,39,46,51]. Slightly better results of amoxicillin and erythromycin-trisulfapyrimidine over penicillin-V and erythromycin were reported in one study [21].

Three uncontrolled studies compared long and short courses of an antibiotic [34,42,51]. In two of these studies a two-day course of amoxicillin was propagated [42,51]. One study reported that a five-days course of penicillin-V was equally effective as a 10-day course [34]. One study advocated early start of therapy with penicillin-V [54]. Furthermore, a study comparing two dosage schedules of cefaclor advised 60 mg/kg/day

as the best regimen [23]. Only nine studies out of the 50 were placebo-controlled. Two studies investigated duration of therapy, demonstrating equal efficacy of a short course of antibiotics (two respectively three days) compared to a seven day course [35,45]. In four studies the controlled group was inferior on outcome [14-16,58]. Three studies showed no significant difference between placebo and antibiotic therapy [29,30,43]. Finally, in nine studies the effect of myringotomy was also investigated [11,22,24,27,29,31,43,55,58]. Only two reported a beneficial effect of myringotomy [24,27].

Scores on rated parameters:

Parameters of study design

Randomization of treatment allocation. Of a total of 50 studies, 46 described allocation of treatment as randomized. We excluded studies that allocated treatment by date of birth or sequence of presentation [11,23,24,33,54]. A total of 41 randomized studies remained[10,12-22,25-29,32,34,36-53,55-58].

Presence of placebo-control group. As mentioned earlier, a placebo-controlled group was included in nine studies [14-16, 29,30,35,43,45,58]. In two of these, the duration of treatment was subject to investigation [35,45].

Double-blind treatment allocation. Double-blind treatment allocation was used in 26 studies [13,14,16,17,19,21,25,28-30, 32,35-41,43-47,56-58]. Treatment allocation was single blinded in two studies where culture results were used as objective outcome criteria [26,48].

Patient compliance control. Of the 50 studies reviewed, 20 reported patient compliance control [17,21,25,26,30,32,35,37-41,44,46-50,56,58]. Various methods were used to check compliance; for instance, weighing of the bottles to determine the amount of medication consumed, a questionnaire, or urine analysis.

Diagnosis by more than one investigator,validation of investigators. One of these procedures or a combination of both was

performed in 17 studies [11,13,17,18,20,21,25,26,29,30,37,40, 43,44,47,49,56]. In 11 of these, the diagnosis acute otitis media had to be confirmed by a second investigator before the patient was included in the study [11,13,17,18,20,21,25,26,29, 30,43]. In one study, the validity of the diagnosis acute otitis media made by these investigators was established before starting the trial [11]. In six the reliability of the diagnosis acute otitis media made by the one doctor seeing the patient was validated prior to the start of the trial [37,40, 44,47,49,56].

Outcome assessment. We found 43 studies to have a predefined fixed outcome assessment moment [11,13-20,22-32,34-38,40-42, 44-53,55-59]. All used otoscopy as physical sign; 25 studies used clinical and physical diagnostic signs [11,14,18,20,25-27-30,32,35-38,40,42,44,45,47,49-51,56-58].

Statistics, methods used for statistical analysis. In our survey, 41 studies stated that the results were statistically significant [10-12,14-16,18-22,24-28,30,32,34,35,37-47,49, 51-59]. Of these, 27 described the statistical methods used [14,16,21,26-28,30,32,35,37,39-47,49,51,53,55-59]. None reported confidence intervals.

Intended size of trial, statistical power calculations (α,β). Three of the 50 studies in our survey identified the statistical power calculation used [35,56,59]. None of the studies defined the intended trial size.

Parameters of study population

Inclusion criteria. A total of 40 studies lucidly described inclusion criteria [10-15,17,20,22,24,25,27-38,40,41,43,44,46, 47,49-59]. In 22 studies, a combination of clinical and physical diagnostic criteria related to the acute otitis media condition was used [10,12,24,27-30,35-38,40,43,44,46,47,49-51, 56-58]. In 39 studies, only otoscopic signs were considered [10-15,17,20,22,24,25,27-38,40,41,43,44,46,47,49-53,55-59].

Age group 0 - 12 years. In 34 studies, age group prerequisites were clearly stated. In 28 of these age group boundaries were

set between 0 and 12 years [11,13,14,16,19,21,23,25,26,29,30, 33-37,40,42-45,47,49-51,53,58,59]. In six studies different age boundaries were used, the oldest patients being between 14 and 17 years [12,28,31,32,41,56]. In the remaining 16 studies age requirements were unclear.

Exclusion criteria. In 43 trials, exclusion criteria were clearly stated [10-14,16-25,27-30,32-35,37-47,49-51,53,55-59]. In 15 studies, it was unclear if allergy to the antibiotic used was an exclusion criterion [11,15,16,20,26,27,31,34,36, 39,41,48,52,54,55]. We checked if recent antibiotic treatment was considered as an exclusion criterion. In two studies, recent antibiotic treatment was an essential prerequisite, so these were left out of this assessment [53,55]. In 22 of the remaining 48 trials, an antibiotic-free period was obligatory. Two weeks were mandatory in 12 [18,27,29,30,34,35,39,42, 43,45,51,58]. In another five this period was one week [21,40, 41,49,59]. Three studies demanded 72 hours [25,46,50]. In a remaining two, 48 hours were required [32,57].

Baseline characteristics. In 37 studies the treatment groups were similar. In the remaining 13 this was unclear [10,14-16, 21,22,24,31,34,39,46,48,54]. Most reports showed the baseline characteristics in table form, though for some a simple statement sufficed.

DISCUSSION

Review methods in general

Computer search alone can miss important papers because of trouble finding the correct key words [60]. Therefore we combined a computer search with a manual search and consultation of reference lists of important reviews on the subject. The problem of selection bias caused by personal preference was thus minimized. To assess the merit of a study, it is essential to know which methods are used. Since we could only score parameters that were explicitly described, some studies will have scored negatively on items that were actually con-

sidered by the investigators but could not be retrieved from the article. The absence of items in an article was found to be only partly based on underreporting. It was mostly due to failure to carry out the procedure [61]. Therefore, it is justified to give a negative score to parameters considered but not described in a paper.

Studies and primary reported results

When making an inventory of all treatments subject to investigation and the conclusions reached in the studies, a condensed overall recommendation can hardly be obtained. The fact that a total of 20 uncontrolled studies comparing two different antibiotics failed to show a real difference in efficacy, is revealing. Studies that do claim differences in clinical efficacy are often refuted by a similar number of studies reaching opposite conclusions. This showed us that only taking the conclusions into account does not suffice; a systematic evaluation of study reports is imperative.

Randomisation of treatment allocation

Treatment allocation by date of birth or sequence of presentation is not true randomization. As such methods can lead to bias in treatment assignment and evaluation [9], they should not be classified as randomization. Even with this exclusion, a large number of studies (41) were randomised. Exact information about the method of randomization is lacking in most cases. Details were presented in only six of those 41 studies (15%). This percentage is lower than two figures given by other investigators, who found precise information on the randomization methods used in 40% of studies [62].

Presence of placebo-control group

The therapeutic dilemma of the advantage of antibiotic therapy in acute otitis media over a therapy of watchful waiting still has not been resolved satisfactorily. To evaluate the respec-

tive advantages, we consider a placebo-controlled treatment group essential. We are aware that placebo-controlled studies are difficult to perform in some countries because of the prevailing attitudes on the ethical problems involved. Yet this does not alter the fact that only placebo-controlled studies can resolve this dilemma. Only seven studies were placebo-controlled from the start of therapy. The question whether initial treatment with antibiotics is justified in acute otitis media can therefore not be answered by the vast majority of the present studies.

Double-blind treatment allocation

To avoid any possible bias in assessment of treatment outcome, a double-blind procedure is essential [9]. A single-blind design is only sufficient when the outcome is based on objective criteria not influenced by knowledge of the treatment received. Culture results can be considered objective criteria. A total of 22 studies met neither of these prerequisites.

Patient compliance control

Non-compliance of patients on drug therapy is an important factor that negatively influences the beneficial effect of the treatment. Nevertheless, in 30 studies no assessment of compliance was made. Thus, the effects of non-compliance cannot be ruled out.

Diagnosis by more than one clinician; validation of diagnostic ability of investigators

All studies were conducted by clinicians experienced in the field of acute otitis media (general practitioners, paediatricians, otorhinolaryngologists). Notwithstanding, the above-mentioned procedures enhance the reliability of a diagnosis of acute otitis media, based on clinical and physical signs. This fact was considered in only 17 out of 50 studies.

Outcome assessment

In cases of acute otitis media, the clinical course over time is an essential factor in evaluating the efficacy of therapy. We checked if the outcome assessment was performed at a predefined point in time after diagnosis and start of therapy. This would make the results comparable among patients. We also determined whether clinical as well as physical diagnostic criteria were used. A fixed time of outcome assessment was retrieved for a large number of studies. Yet only 25 remained after checking if outcome criteria were related to the acute otitis media condition in terms of both clinical and physical diagnostic signs.

Statistics; methods of statistical analysis

In 41 studies, the statistical significance of results was indicated. However, we could only assess the appropriateness of the methods used in 65% of the studies; the remainder did not specify which tests were applied. None mentioned confidence intervals. The use of confidence intervals permits a wider clinical application of the conclusions reached [9,63].

Intended size of trial, statistical power calculations (α,ß)

The intended number of patients in a clinical trial should be determined in advance. Statistical power calculations are valuable aids in doing this [9]. Another survey of reported clinical trials revealed that only 11% of the papers described intended trial size based on statistical power calculations [63]. In studies concerning therapy in acute otitis media, we find that only three out of 50 mention statistical power calculations.

Inclusion criteria

It is of vital importance to know whether the patients investigated are representative of the disease studied. Only then can the findings of a study be generalized. Detailed criteria in the study protocol are thus required [9]. To diagnose acute

otitis media, signs of middle ear effusion (redness, opacification, bulging, decreased motility of the eardrum) must be present, together with acute ear-related symptoms of recent onset (otalgia, ear-tugging, irritability) [64]. Only 22 studies used the combination of clinical and physical diagnostic criteria to ensure that the condition treated was acute otitis media and not otitis media with effusion. Clinical signs are essential in this differentiation. In 39 studies, using only otoscopic signs, this important distinction was not clear.

Age group 0 - 12 years

Acute otitis media is predominantly a disease of early childhood, as incidence studies have shown [1,2]. Age is also an important factor influencing the course and sequelae of an episode of acute otitis media [65]. It is therefore important that the patients studied are in the 0 to 12 years age group. Our review showed this to be the case in the majority of studies.

Exclusion criteria

In 43 trials exclusion criteria were clearly stated. Allergy to the antibiotic used should be an obligatory exclusion criterion. Yet, in a total of 15 studies it was unclear if this was taken into account. We also checked whether recent antibiotic treatment was considered as an exclusion criterion. If so, we could be certain of the absence of possible interaction between two therapies. In only 22 of the 48 trials that did not ave recent previous antibiotic therapy as an essential prerequisite, an antibiotic-free period was obligatory. In 12 studies, two weeks were mandatory; one week in another five and in three it was 72 and in a remaining two 48 hours.

Baseline characteristics

To compare the results of different treatment groups, these should be similar in characteristics that might influence the

clinical course [66]. For the acute otitis media condition age, sex, race and socio-economic status can be of possible influence [7]. When randomization is done properly treatment groups should be comparable in this respect. A total of 37 studies describe the treatment groups as similar; in the remaining 13 this was unclear. This is in accordance with figures reported by other investigators, who found group characteristics described in 84% of the papers [63]. Most reports presented the treatment groups in table form; some simply stated that the groups were homogeneous.

CONCLUSIONS AND RECOMMENDATIONS

True meta-analysis of the studies reported so far is almost impossible to perform. Analysis of the studies shows that a definite recommendation based on their conclusions can hardly be given, due to their wide diversity. Also, our study illustrates that many clinical trials on acute otitis media have important methodological flaws. Randomized treatment allocation and statistical significance tests were performed in most of the studies. However, randomization design and statistical methods used are not reported sufficiently in a great number of studies. The essential combination of double-blind design, clearly defined inclusion criteria, and criteria for outcome both representative for acute otitis media were still lacking in many studies. These elements were present in only 13 studies [28-30,35-38,40,44,47,56-58]. However, a concise recommendation based on the conclusions reached in these 13 studies can hardly be obtained. This is due to failure to show an overall difference in favour of a specific treatment regimen. Though it may seem encouraging that all 13 were performed in the 1980s, 34 out of the surveyed 50 reports were published in that decade. Although knowledge of proper trial conduct increased sharply in the eighties as compared to the late sixties and early seventies, this progress was not reflected in most of the trials.

In addition to the prerequisites noted above, we may consider a placebo-controlled design as mandatory, since even therapy with antibiotics can still be questioned. In that case then only four studies remain [29,30,35,58]. In two of these, randomization was not mentioned [30,35]. In one of the remaining two studies however, the placebo group received myringotomy [58]. The other study found strong grounds for an attitude of watchful waiting [29]. For that study, however, the validity of the statistical analysis was questioned [67]. Furthermore, the age group under two years was not represented in this study. The above considerations show why it is difficult to unconditionally adopt the results of the clinical trials. This may also explain the lack of consensus on treatment strategies in acute otitis media.

Consequently, the necessity of initial antibiotic treatment, with or without myringotomy, is still in question. This literature review shows that there is still need for well-conducted, preferably placebo-controlled, trials in acute otitis media.

REFERENCES

1. Ingvarsson L, Lundgren K, Olofsson B. Incidence and risk factors of acute otitis media in children: longitudinal cohort studies in an urban population. In: Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 6-8.
2. Klein JO, Teele DW, Bernard A, et al. Epidemiology of acute otitis media in Boston children from birth to seven years of age. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 14-15.
3. Froom J, Culpepper L, Grob P, et al. Diagnosis and antibiotic treatment of acute otitis media: Report from international Primary Care Network. Br Med J 1990; 300: 582-586.
4. Karma P, Palva T, Kouvalainen K, et al. Finnish approach to the treatment of acute otitis media. Report of the Finnish Consensus Conference. Ann Otol Rhinol Laryngol 1987; 96 suppl. 129: 1-19.
5. Paradise JL. Otitis media in infants and children. Pediatrics 1980; 65: 917-943.
6. Grote JJ, Buchem FL van, eds. Otitis media bij kinderen. Nederlandse Vereniging voor K.N.O.-Heelkunde en Heel kunde van het Hoofd-Hals gebied. Leiderdorp: Uitg. De Medicus b.v., 1988.
7. Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: W.B. Saunders Company, 1988.
8. Consensus-bijeenkomst otitis media acuta.(1990) Utrecht. ISBN 90-6910-109-2.
9. Pocock SJ. Clinical Trials: A Practical Approach. Chichester England: John Wiley, 1983.

10. Rubenstein MM, McBean JB, Hedgecock L, et al. The treatment of acute otitis media in children. A third clinical trial. Am J Dis Child 1965; 109: 308-313.
11. Roddey OF, Earle jr. R, Haggerty R. Myringotomy in acute otitis media. A controlled study. JAMA 1966; 197 (11): 127-131.
12. Stickler GB, Rubenstein MM, McBean JB, et al. Treatment of acute otitis media in children. A fourth clinical trial. Am J Dis Child 1967; 114: 123-130.
13. Bass JW, Cohen SH, Corless JD, Mamunes P. Ampicillin compared to other antimicrobials in acute otitis media. JAMA 1967; 202 (8): 137-142.
14. Halsted C, Lepow ML, Balassanian N, et al. Otitis media. Clinical observations, microbiology, and evaluation of therapy. Am J Dis Child 1968; 115: 542-551.
15. Laxdal OE, Merida J, Trefor Jones RH. Treatment of acute otitis media: a controlled study of 142 children. Canad Med Ass J 1970; 102: 263-268.
16. Howie VM, Ploussard JH. Efficacy of fixed combination antibiotics versus separate components in otitis media. Clin Ped 1972; 11 (4): 205-214.
17. Bass JW, Cashman TM, Frostad AL, Yamaoka RM, et al. Antimicrobials in the treatment of acute otitis media. A second clinical trial. Am J Dis Child 1973; 125: 397-402.
18. Feigin RD, Keeny RE, Nusrala J, Shackelford PG, Lins RD. Efficacy of clindamycin therapy for otitis media. Arch Otolaryngol 1973; 98: 27-31.
19. Nassar WY, Allen BM. A double-blind comparative clinical trial of cephalexin and ampicillin in the treatment of childhood acute otitis media. Curr Med Res Opin 1974; 2: 198-203.
20. Stechenberg BW, Anderson D, Chang MJ, et al. Cephalexin compared to ampicillin treatment of otitis media. Pediatrics 1976; 58 (4): 532-53.

21. Howard JE, Nelson JD, Clahsen J. Otitis media of infancy and early childhood. A double blind study of four treatment regimens. Am J Dis Child 1976; 130: 965-970.
22. Lorentzen P, Haugsten P. Treatment of acute suppurative otitis media. J Laryngol Otol 1977; 91: 331-340.
23. Nelson JD, Ginsburg CM, Clahsen J, Hinton Jackson L. Treatment of acute otitis media of infancy with cefaclor. Am J Dis Child 1978; 132: 992-996.
24. Puhakka H, Virolaïnen E, Aantaa E, Tuohimaa P, Eskola J, Ruuskanen O. Myringotomy in the treatment of acute otitis media in children. Acta Otolaryngol 1979; 88: 122-126.
25. Jacobson JA, Metcalf TJ, Parkin JL, Wenerstrom LG, Matsen JM. Evaluation of cefaclor and amoxycillin in the treatment of acute otitis media. Postgrad Med J 1979; 55 (Suppl.4): 39-41.
26. Shurin PA, Pelton SI, Donner A, Finkelstein J, Klein JO. Trimethoprim-sulfamethoxazole compared with ampicillin in the treatment of acute otitis media. J Pediatrics 1980; 96 (6): 1081-1087.
27. Qvarnberg Y. Acute otitis media. A prospective clinical study of myringotomy and antimicrobial treatment. Acta Otolaryngol 1981; Suppl. 375: 1-157.
28. Mandel EM, Bluestone CD, Cantekin EI, Ghorbanian SN, Rockette HE. Comparison of cefaclor and amoxicillin for acute otitis media with effusion. Ann Otol Rhinol Laryngol 1981; 90 (3) Suppl 84: 48-52.
29. Buchem FL van, Dunk JHM, Hof MA van 't. Therapy of acute otitis media: Myringotomy, antibiotics, or neither? Lancet 1981; ii: 883-887.
30. Mygind N, Meistrup-Larsen KI, Thomsen J, Thomsen VF, Joseffson K, Sørensen H. Penicillin in acute otitis media: A double-blind placebo-controlled clinical trial. Clin Otolaryngol 1981; 6: 5-13.

31. Schwartz RH, Rodriguez WJ, Schwartz DM. Office myringotomy for acute otitis media: its value in preventing middle ear effusion. The Laryngoscope 1981; 91: 616-619.

32. McLinn SE, Goldberg F, Kramer R, Salstein E, Bomze JP, Deitch MW. Double-blind multicenter comparison of cyclacillin and amoxicillin for the treatment of acute otitis media. J Pediatrics 1982; 101 (4): 617-621.

33. Puhakka H, Virolaïnen E, Aantaa E. Treatment of acute otitis media in children: penicillin-V or amoxicillin ? Acta Otolaryngol 1982; Suppl. 386: 108-111.

34. Ingvarsson L, Lundgren K. Penicillin treatment of acute otitis media in children. A study of the duration of treatment. Acta Otolaryngol 1982; 94: 283-287.

35. Meistrup-Larsen KI, Sørensen H, Johnsen NJ, Thomsen J, Mygind N, Sederberg-Olsen J. Two versus seven days penicillin treatment for acute otitis media. A placebo-controlled trial in children. Acta Otolaryngol 1983; 96: 99-104.

36. Berman S, Lauer BA. A controlled trial of cefaclor versus amoxicillin for treatment of acute otitis media in early infancy. Ped Infect Dis 1983; 2 (1): 30-33.

37. Marchant CD, Shurin PA, Turcyzk RN, et al. A randomised controlled trial of cefaclor compared with trimethoprim-sulfamethoxazole for treatment of acute otitis media. J Pediatr 1984; 105 (4): 633-638.

38. Blumer JL, Bertino jr. JS, Husak MP. Comparison of cefaclor and trimethoprim-sulfamethoxazole in the treatment of acute otitis media. Ped Infect Dis J 1984; 3 (1): 25-29.

39. Howie VM, Dillard R, Lawrence B. In vivo sensitivity test in otitis media: efficacy of antibiotics. Pediatrics 1985; 75 (1): 8-13.

40. Odio CM, Kusmiesz H, Shelton S, Nelson JD. Comparative treatment trial of augmentin versus cefaclor for acute otitis media with effusion. Pediatrics 1985; 75 (5): 819-826.
41. Rodriguez WJ, Schwartz RH, Sait T, et al. Erythromycin-sulfisoxazole vs amoxicillin in the treatment of acute otitis media in children. Am J Dis Child 1985; 139 (8): 766-770.
42. Bain J, Murphy E, Ross F. Acute otitis media: clinical course among children who received a short course of high dose antibiotic. Br Med J 1985; 291: 1243-1246.
43. Buchem FL van, Peeters MF, Hof MA 't. Acute otitis media: a new treatment strategy. Br Med J 1985; 290: 1033-1037.
44. Marchant CD, Shurin PA, Johnson CA, et al. A randomised controlled trial of amoxicillin plus clavulanate compared with cefaclor for treatment of acute otitis media. J Pediatr 1986; 109 (5): 891-896.
45. Jones R, Bain J. Three-day and seven-day treatment in acute otitis media: a double-blind antibiotic trial. J R Coll Gen Pract 1986; 36: 356-358.
46. Hare GF van, Shurin PA, Marchant CD, et al. Acute otitis media caused by Branhamella catarrhalis: biology and therapy. Rev Infect Dis 1987; 9 (1): 16-27.
47. Kaleida PH, Bluestone CD, Rockette HE, et al. Amoxicillin-clavulanate potassium compared with cefaclor for acute otitis media in infants and children. Ped Infect Dis J 1987; 6 (3): 265-271.
48. Howie VM, Owen MJ. Bacteriologic and clinical efficacy of cefixime compared with amoxicillin in acute otitis media. Ped Infect Dis J 1987; 6 (10): 989-991.
49. Kenna MA, Bluestone CD, Fall P, et al. Cefixime vs. cefaclor in the treatment of acute otitis media in infants and children. Ped Infect Dis J 1987; 6 (10): 992-996.

50. McLinn SE. Randomised, open label, multicenter trial of cefixime compared with amoxicillin for treatment of acute otitis media with effusion. Ped Infect Dis J 1987; 6 (10): 997-1001.

51. Jenner PN, Tierney HE, Carle WK. A general practice study of a new approach to the use of antibiotics in the treatment of acute otitis media in children aged three and over. Br J Clin Pract 1987; 41 (7): 820-826.

52. Kaprio E, Haapaniemi J, Bondesson G. Clinical efficacy of amoxycillin-clavulanic acid and cefaclor in acute otitis media. Acta Otolaryngol 1988; 106 (suppl. 449): 45-46.

53. Jacobsson S, Rigner P, von Sydow C, Bondesson G. Recurrent and penicillin-V resistant otitis media. A treatment study with amoxycillin-clavulanate and cefaclor. Acta Otolaryngol 1988; 106: 171-177.

54. Harder H, Öhman L, Strand E. Early or late start of treatment in acute otitis media. A comparative study. Acta Otolaryngol 1988; 106 (suppl 449): 41-42.

55. Lidén M, Flodström A, Thore M. Treatment of early recurrences of acute purulent otitis media; value of myringotomy. Acta Otolaryngol 1988; 106: 441-447.

56. Feldman W, Momy J, Dulberg C. Trimethoprim-sulfamethoxazole v. amoxicillin in the treatment of acute otitis media. Canad Med Ass J 1988; 139: 961-964.

57. Aronovitz GH. Treatment of otitis media with cefuroxime axetil. South Med J 1988; 81 (8): 978-980.

58. Engelhard D, Cohen D, Strauss N, Sacks TG, Jorczak M, Sarni L, Shapiro M. Randomised study of myringotomy, amoxycillin-clavulanate, or both for acute otitis media in infants. Lancet 1989; ii: 141-143.

59. Puhakka HJ, Haapaniemi J, Tuohimaa P, Bondesson G. Clinical efficacy and tolerance of bacampicillin and amoxycillin suspensions in children with acute otitis media. J Int Med Res 1989; 17: 41-47.

60. Van Duijn NP, Dyserinck HC. Literatuuronderzoek via een computer-search. Doeltreffendheid en doelmatigheid van een search naar sinusitis. Huisarts Wet 1990; 33 (1): 9-13.
61. Liberati A, Himel HN, Chalmers TC. A quality assessment of randomised controlled trials of primary treatment of breast cancer. J Clin Oncol 1986; 4: 942-951.
62. Altman DG, Doré CJ. Randomization and baseline comparisons in clinical trials. Lancet 1990; 335: 149-153.
63. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. A survey of three medical journals. N Engl J Med 1987; 317 (7): 426-432.
64. Bluestone CD. State of the art: definitions and classifications. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Third International Symposium, Toronto: BC Decker, 1984: 1-4.
65. Howie VM, Ploussard JH, Sloyer J. The "Otitis prone" condition. Am J Dis Child 1975; 129: 676-678.
66. Altman DG. A fair trial? Br Med J 1984; 289: 336-337.
67. Saah AJ, Blackwelder WC, Kaslow RA. Commentary: treatment of acute otitis media. JAMA 1982; 248: 1071-1072.

Chapter V

EFFICACY OF AMOXICILLIN-CLAVULANATE IN RECURRENT ACUTE OTITIS MEDIA

a placebo-controlled study

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60. Van Duijn NP, Dyserinck HC. Literatuuronderzoek via een computer-search. Doeltreffendheid en doelmatigheid van een search naar sinusitis. Huisarts Wet 1990; 33 (1): 9-13.

61. Liberati A, Himel HN, Chalmers TC. A quality assessment of randomised controlled trials of primary treatment of breast cancer. J Clin Oncol 1986; 4: 942-951.

62. Altman DG, Doré CJ. Randomization and baseline comparisons in clinical trials. Lancet 1990; 335: 149-153.

63. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. A survey of three medical journals. N Engl J Med 1987; 317 (7): 426-432.

64. Bluestone CD. State of the art: definitions and classifications. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Third International Symposium, Toronto: BC Decker, 1984: 1-4.

65. Howie VM, Ploussard JH, Sloyer J. The "otitis prone" condition. Am J Dis Child 1976; 129: 676-678.

66. Altman DG. A fair trial? Br Med J 1984; 289: 336-337.

67. Bash AJ, Blackwelder WC, Kaslow RA. Commentary: treatment of acute otitis media. JAMA 1982; 248: 1071-1072.

Chapter V

EFFICACY OF AMOXICILLIN-CLAVULANATE IN RECURRENT ACUTE OTITIS MEDIA

a placebo-controlled study

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Chapter V

EFFICACY OF AMOXICILLIN-CLAVULANATE IN RECURRENT ACUTE OTITIS MEDIA

a placebo-controlled study

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ABSTRACT

Objective To determine the efficacy of amoxicillin-clavulanate in children from six months to 12 years of age with a recurrent acute otitis media.

Design A randomized double-blind placebo-controlled clinical trial.

Setting General practice.

Patients A total of 121 children with a recurrent acute otitis media, defined by onset of otalgia and otoscopic signs of middle ear infection within four to 52 weeks after the previous attack. Confirmation of diagnosis and randomization was done by otolaryngologists.

Intervention Oral amoxicillin-clavulanate or placebo in weight-related doses for seven days.

Outcome measure An irregular clinical course of the disease, defined as the presence of otalgia and/or a body temperature of 38° C or higher after three days.

Results The percentage of irregular courses was 16.4% (95% C.I.: 8.5, 27.5) in the amoxicillin-clavulanate group and 18.5% (95% C.I.: 9.3, 31.4) in the placebo group (non-significant). Age, dichotomized at two years, was the only significant prognostic factor for irregular course of the disease (odds ratio: 5.9, 95% C.I.: 1.8, 19.1). For children aged below two years (n=27) the percentages of irregular courses for amoxicillin-clavulanate and placebo were 26.7% and 58.3%. For children two years and older (n=94) these percentages were 13.5% and 7.1%.

Conclusions Patients with a recurrent acute otitis media are at greater risk for an irregular clinical course of the disease than children with a non-recurrent acute otitis media. Age appears to be the only significant prognostic factor for the irregular clinical course of the recurrent acute otitis media. The study did not show a significant benefit from

amoxicillin-clavulanate.
Because of the large difference between the percentages of irregular clinical courses of the two treatment groups for those under two years, clinicians may want to use amoxicillin-clavulanate in this age group until conclusive evidence is available.

INTRODUCTION

Acute otitis media is a common disease among children. Cumulative incidences of 65% to 93% have been reported up to the age of seven years [1,2]. Several therapeutic strategies have been employed to prevent complications and to enhance recovery from an episode of acute otitis media. Myringotomy, antibiotics, antihistamines, decongestants, and several combinations have been recommended. Placebo-controlled trials did not show a relevant difference in clinical outcome between placebo and antibiotics in children aged two years and older [3]. Nevertheless, the prescription of antibiotics is the first choice in medical management in most countries [4]. Without antibiotics, an irregular course is to be expected in less than 5% of the patients [5]. The current medical management in the Netherlands consists of the prescription of oral analgesics and decongestant nose drops in otherwise healthy children of two years and older. Antibiotics are prescribed only when no clinical improvement has occurred after three days. It is questionable however, if the attitude of watchful waiting is acceptable for a subpopulation in which the frequency of an complicated course and sequelae can be expected to be higher. We hypothesized that patients with recurrent acute otitis media were a particularly high-risk population [6]. The objective of the study was to establish the efficacy of amoxicillin-clavulanate among children of six months to 12 years old with a recurrent acute otitis media. We included patients younger than two years since little research has been conducted on this age category.

PATIENTS AND METHODS

Patients

Patients were recruited from an urban primary care setting by their general practitioner. They were enrolled if they had a recurrence of acute otitis media, characterized by a (sub)-acute onset of the episode, otalgia and otoscopic signs of middle ear infection within four weeks to 12 months of the previous attack. The previous report of a prior attack of acute otitis media had to be substantiated. It was considered to have occurred if it had been assessed by a physician and had been written down in the medical record of the patient. To be eligible for enrolment the patients had to be older than six months and younger than 12 years.

Exclusion criteria were the use of an antibiotic by the patient during the last four weeks; earlier participation in this study; allergy for penicillin; and a serious concurrent disease that requires treatment with an antibiotic. Informed consent was obtained by the general practitioner from the parent(s). The patient was referred to one of the otolaryngologists of the three participating hospitals, who again took the patient's history and repeated the examination. He evaluated the diagnosis and checked if all the criteria were met. In this way the diagnosis of acute otitis media was confirmed

Study design and treatment

A randomised placebo-controlled double-blind trial was carried out from September 1986 to April 1990. The protocol was approved by the ethics committee of the University Hospital of Utrecht. Random allocation to treatment was achieved by opening in numerical order a sealed envelope that contained the treatment code. The codes had been linked at random to the envelope numbers by a computer program. Allocation to treatment was done by the otolaryngologist in order to assure the

double-blindness of the study: neither patient nor general practitioner knew which treatment was given. Medication was supplied by the specialist and was started immediately upon confirmation of the diagnosis. Every child was given the analgesic paracetamol (Sinaspril®Paracetamol) orally as long as earache was present and oxymetazoline HCl nose drops for one week. The child was given either amoxicillin-clavulanate orally or placebo in an weight related doses for seven days. (Table I). Treatment compliance was determined by inquiry after three days and again after 14 days.

Table 1: Daily dosage schedules for study agents (in mg)

1.	analgestic:		
	paracetamol	½-1	yr.: 3 dd 60
	(as long as pain	1-2	yr.: 4 dd 60
	is present)	2-4	yr.: 3 dd 120
	Sinaspril®Paracetamol	4-7	yr.: 4 dd 120
		7-12	yr.: 3 dd 240
2.	decongestant nose drops:		
	oxymetazoline HCl	<6	yr.: 3 dd gtt 2 0.025%
	Nasivin®	6-12	yr.: 3 dd gtt 2 0.05 %
3.	antibiotic:		
	amoxicillin-	<3	kg.: 3 dd 25/ 6.25
	clavulanate	4-6	kg.: 3 dd 50/12.5
	(during 7 days)	7-10	kg.: 3 dd 75/18.75
	Augmentin®	11-13	kg.: 3 dd 100/25.0
		14-25	kg.: 3 dd 125/31.25
		26-35	kg.: 3 dd 250/62.5

Assessments

A history was taken by the general practitioner at the first visit. With regard to potential confounding variables, attention was paid to elevation of body temperature, the laterality of the acute otitis media, the onset of the episode, the dates of recurrences of the acute otitis media and the use of medication. The date of this first visit was recorded as well as the patient's sex, date of birth and type of health insurance. If the infant was too young to express verbally the presence of otalgia, pulling at the ear and irritability were inter-

preted as otalgia. The physical examination included the rectal measurement of the body temperature and description of the appearance of the tympanic membranes. Signs of inflammation reported classified reported to a classification used in the Netherlands [7]:

Stage I redness of the membrane at the periphery and at the malleus, absence of light reflex
Stage II total redness of the tympanic membrane
Stage III bulging of the tympanic membrane

Immediately after this visit the child was seen by the otolaryngologist, who also took the history. The physical examination was repeated and the diagnosis was confirmed.
After three days the general practitioner evaluated the clinical course of the disease by assessing the body temperature by means of rectal measurement and the presence or absence of otalgia.
The child was seen once more after 14 days by the general practitioner, who recorded the history and physical data and presence of otorrhoea. After one month the patient visited the otolaryngologist, who carried out otoscopy, tympanometry and in children over three years, an audiogram.
The general practitioner could contact the otolaryngologist at any time to inquire about the given treatment, if it was felt necessary. The therapy code could then be broken and the medication could be changed. In that event, a patient would be classified as a treatment failure.

Criteria for outcome measures

An irregular clinical course of the disease was defined as the presence of otalgia and/or a body temperature of 38° C or higher after three days.

Statistical methods

The analysis of the results was conducted by means of the difference in proportions of treatment failure and its 95%-confidence intervals. The chi-square test with Yates correc-

tion for small numbers was used for comparisons between two proportions. Logistic regression analysis was conducted to estimate the weight of risk factors. The results are expressed in odds ratios with 95% confidence intervals.
In the study protocol we agreed on a minimal relevant difference of 10% with an α of 5% and a power of 80% between the percentages of 'irregular courses' of the two treatment groups. This is based on the assumption that the percentage of 'irregular courses' would be 5% in the group treated with antibiotics.

RESULTS

During the period from 1 October 1986 until 30 April 1990 the participating general practitioners registered 799 patients with an acute otitis media (Table 2).

Table 2: Number of registered and enrolled patients with an AOM

patients with an AOM:		**799**
not meeting criteria:	614	185
no informed consent:	54	131
not eligible:	5	126
lost register forms:	5	
evaluable patients:		**121**

According to the general practitioners, 185 children fulfilled the entry criteria for recurrent acute otitis media. Informed consent was withheld in 54 children, the most common reason being difficulties in transportation to the hospital. These children were comparable to the trial population with regard to age, sex and date of onset. After investigation by the otolaryngologist one case was diagnosed as otitis media with effusion and four cases of acute otitis media failed to meet one of the eligibility criteria. A total 126 children were

randomly allocated to treatment. Of these, 70 received amoxicillin-clavulanate and 56 received placebo. For five patients analysis was not possible because of loss of the registration forms: three of these had received antibiotic and two had received placebo. The 121 evaluable patients had an age distribution similar to that of the total population with an acute otitis media (p=.192)(Figure 1).

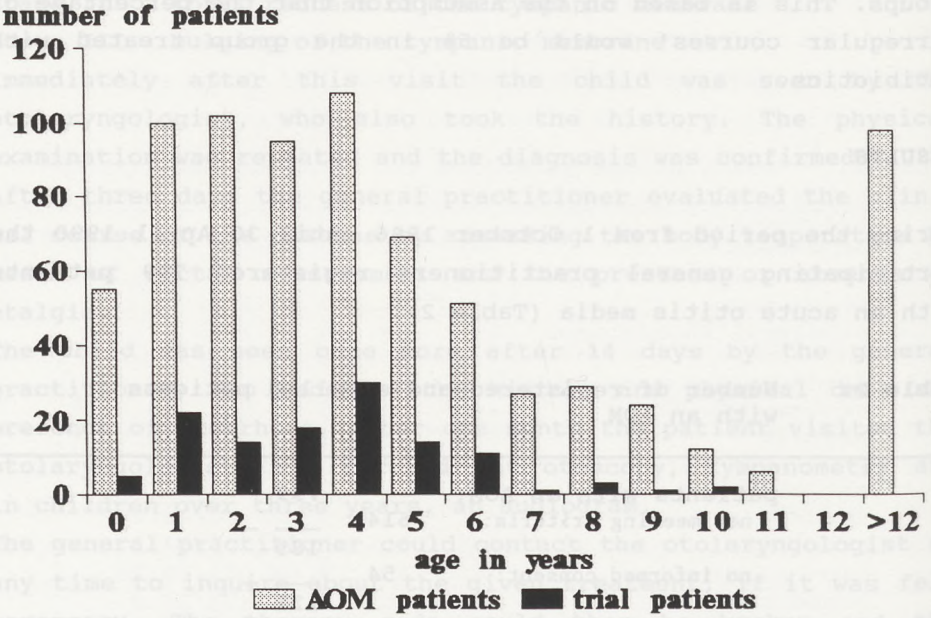

Figure 1: Total number registered AOMs and trial patients by age

The different ratio within the group younger than one year compared to the other classes is due to the selection criteria of recurrence and age.

The two treatment groups did not differ with regard to age, sex, insurance, laterality of the acute otitis media, season of onset, temperature at localisation onset of earache at enrolment or number of previous episodes (Table 3). None of the differences in the values of the variables exceeds the significance level of 0.05.

Table 3: Characteristics of treatment groups (n= 67, resp. 54)

	amoxic./clav.	placebo
age (mean, range)	3.9, 0.7-10.2	4.1, 1.1-10.2
sex (% male)	53.7%	53.7%
Ratio Public Health Plan to private insurance:	1.9	2.1
AOM according to otolaryngologist(*): ratio uni- to bilateral	1.14	2.06
season of onset (%):		
01.09 - 31.03	74.6%	74.1%
01.04 - 31.08	25.4%	25.9%
temp. at enrolment (%):		
<38° C	66.7%	67.3%
≥38° C	33.3%	32.7%
earache at enrolment (%):		
unilateral	78.8%	88.5%
bilateral	21.2%	11.5%
previous episodes (%):		
1	61.2%	59.3%
2	28.4%	27.8%
≥3	10.4%	12.9%

All patients reported taking the prescribed antibiotic/placebo for the required seven days. In one patient the treatment code was broken before the first outcome assessment due to the development of a pneumonia. This patient, who had been in the antibiotic group was classified as having an irregular course. There was no difference between the two treatment groups with respect to the clinical course after three days (Table 4).

Table 4: Clinical course after three days

	all (n=121)	amoxic-clav. (n=67)	placebo (n=54)
course			
regular	100	56	44
irregular	21	11	10
% irregular	17.4 %	16.4 %	18.5 %
95% C.I.	10.6, 24.8	8.5, 27.5	9.3, 31.4

Chi-square: 0.092, p=0.381; difference in percentage of irregular courses between amoxic-clav. and placebo: 2.1% (95% C.I.: -11.5, 15.7)

An irregular clinical course was associated with younger age (Figure 2).

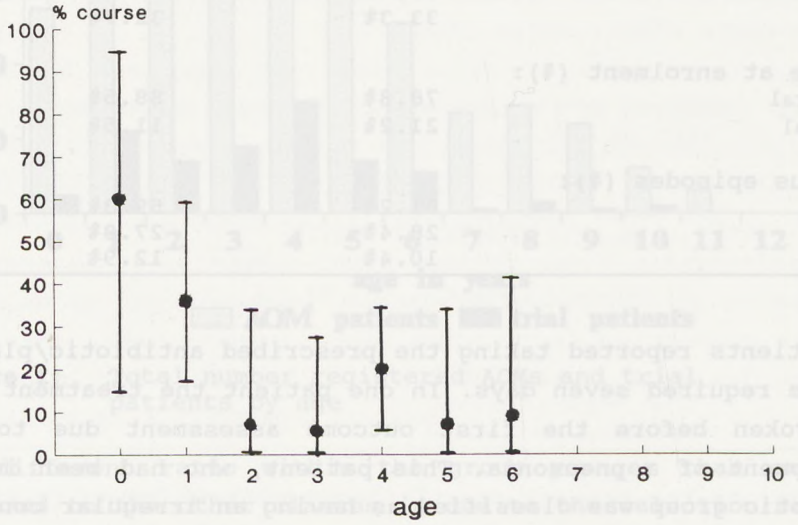

Figure 2: Percentage of irregular clinical course and 95% C.I. by age

Of the prognostic factors studied, only age and laterality of the acute otitis media appeared to have a prognostic value with respect to the course of the disease (Table 5).

Table 5: Prognostic factors with respect to irregular clinical course (n=121)

prognostic factor	odds ratio (95% C.I.)	adjusted(*) odds ratio (95% C.I.)
<2 yr. to ≥2 yr.	5.8 (2.1, 15.8)	5.9 (1.8, 19.1)
bilat. to unilateral	2.7 (1.0, 7.2)	1.6 (0.4, 7.7)
≥ 38° C to < 38° C	1.7 (0.6, 4.5)	1.2 (0.4, 3.7)
winter to summer	1.6 (0.5, 5.1)	2.0 (0.5, 7.9)
number of previous AOM	1.2 (0.7, 1.9)	1.1 (0.6, 1.9)
male to female	1.1 (0.4, 2.7)	1.1 (0.4, 3.5)

(*) adjusted by logistic regression

After multivariate logistic regression analysis, the only prognostic factor relevant to the course of the disease is age dichotomised at two years.(Table 5). The percentage of irregular courses in children younger than two years was 40.7% (95% C.I.: 22.4, 61.2); in children of two years and older, this was 10.6% (95% C.I.: 5.2, 18.7). The probability of an irregular course in children younger than two years is 5.9 times greater than in children of two years and older (odds ratio: 5.9, 95% C.I.: 1.8, 19.1).

The effect of the treatment was stratified for children below two years and two years and older (Table 6).

Table 6: Clinical course after three days stratified for age-category

	< 2 years		≥ 2 years	
	amoxic-clav.	placebo	amoxic-clav.	placebo
course				
regular	11	5	45	39
irregular	4	7	7	3
	X^2 = 1.613		X^2 = 0.424	
	p = 0.102		p = 0.257	
% irreg. course	26.7	58.3	13.5	7.1
difference in % irr. course	-31.6		6.4	
95% C.I.	-67.4, 4.1		-5.8, 18.4	

(Chi-square calculated with Yates correction)

The differences in percentage of irregular courses for the two age categories of -31.6% and 6.4% are statistically nonsig-

nificant.

DISCUSSION

We expected to find a greater risk of an irregular course for acute otitis media episodes in patients with a recurrent acute otitis media. In our total study population the percentage of children that did not recover clinically within three days was 17.4% (95% C.I.: 10.6, 24.8).

Comparisons of these results with those of other studies indicate the value of the characteristic recurrence as a predictive factor. In our category of patients of two years and older who received a placebo, the percentage with an irregular course was 7.1%. Van Buchem et al. found the percentage of patients with an irregular course to be 2.7% in untreated children of similar age with a first as well as with a recurrent acute otitis media episode [5]. Their conclusion that a history of previous attacks does not influence the course of the acute otitis media cannot confirmed by in our findings.

The percentage of irregular courses was 58.3% in our placebo group of children aged six months to two years. In patients aged 3-12 months, either with a first or a recurrent acute otitis media, Engelhard et al. report, an irregular course in 23.1% with regard to fever and 28.1% with regard to pain or irritability [8]. Children with a recurrent acute otitis media should be given special attention because of the increased risk of an irregular course.

The external validity of the study seems to be good. With regard to relevant variables - age, sex, season of onset, bilaterality of the acute otitis media, temperature and earache at enrolment - the study population corresponds to findings in other studies [9].

The internal validity also seems to be high: except for therapy no differences appeared to be present between the two treatment groups. For five children we were not able to analyse the data. The reason for the loss of information on these

patients was independent of the therapy given. The one child who dropped out was analysed as a treatment failure according to the 'intention-to-treat' principle.

We did not detect any difference between amoxicillin-clavulanate and placebo therapy with regard to the clinical recovery from acute otitis media. These results correspond to the findings of the only few reliable placebo-controlled clinical trials conducted since 1965. We could not detect any difference in failure rate of clinical recovery in the study of Halsted et al. between the 62 patients treated with ampicillin and the 27 patients given a placebo (Fisher's exact test: $p=0.353$) [10]. These children ranged from two to 66 months of age. Howie et al. estimated the placebo-controlled efficacy in 280 children with an acute otitis media: within four days all patients became afebrile and asymptomatic [11]. After a study in children of two years and older van Buchem et al. concluded that it was right to prescribe antibiotics in cases with an irregular course or complications or in cases with a persistent otorrhea after two weeks [3]. Mygind et al. studied 149 acute otitis media patients aged one to 10 years and found no difference between an antibiotic and placebo with regard to the disappearance of the clinical symptoms of pain and fever and the symptoms of an existing common cold [12]. Finally Engelhard et al. concluded that most of their patients improved clinically irrespective of the therapeutic measures taken [8].

Some investigators studied the prognostic value of several factors with regard to the course of the disease. Age appears to be of importance: the younger the child the larger the probability of developing an irregular clinical course irrespective of the given therapy [13-16]. The course of the disease is independent of the season [15,17]. The initial presence of a red or bulging eardrum does not influence the course of otitis media [3]. Of the factors investigated in our study, only age appears to have an independent prognostic value. Laterality of the acute otitis media, presence of

fever, season of onset, number of previous attacks and sex of the patients are not of any use to predict the prognosis. A dichotomy comprising the categories of <2 years and ≥2 years seems of most value. In the younger age category the difference between the percentages of irregular courses with antibiotic and with placebo treatment was 31.7% in favour of the antibiotic. In the older age category this percentage was 6.3% in favour of the placebo. None of these differences were statistically significant.

The most striking result of this study is that even in a population of 'otitis-prone' children ranging from six months to 12 years in age the natural course of the clinical improvement is not statistically different from the course of the disease when amoxicillin-clavulanate is prescribed. However, in view of the number of cases younger than two years, the statistical non-significant result in this category might be attributable to the low power alone. Moreover, since the result is close to significance, and taking into consideration the clinical relevance of the difference of 31.7%, we recommend an antibiotic treatment for children younger than two years with a recurrent acute otitis media In order to confirm this medical strategy further research is needed with larger numbers of patients.

In children of two years and older with recurrent acute otitis media, antibiotics do not affect the short-term course.

REFERENCES

1. Ingvarsson L, Lundgren K, Olofsson B. Incidence and risk factors of acute otitis media in children: longitudinal cohort studies in an urban population. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988, 6-8.
2. Klein JO, Teele DW, Rosner BA, et al. Epidemiology of acute otitis media in Boston children from birth to seven years of age. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent advances in otitis media with effusion. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988, 14-15.
3. Buchem FL van, Dunk JH, Hof MA van 't. Therapy of acute otitis media: myringotomy, antibiotics or neither. Lancet 1981; ii: 883-887.
4. Froom J, Culpepper L, Grob P, et al. Diagnosis and antibiotic treatment of acute otitis media: Report from International Primary Care Network. Br Med J 1990; 300: 582-586.
5. Buchem FL van, Peeters MF, Hof MA van 't . Acute otitis media: a new treatment strategy. Br Med J 1985; 290: 1033-1037.
6. Howie VM, Ploussard JH, Sloyer J. The "Otitis-prone" Condition. Am J Dis Child 1975; 129: 676-678.
7. Feenstra L. Acute ontsteking van het middenoor. Ned Tijdschr Geneeskd 1985; 129, 12: 532-536.
8. Engelhard D, Cohen D, Strauss N, Sacks TG, Jorczak-Sarni L, Shapiro M. Randomised study of myringotomy, amoxycillin/clavulanate, or both for acute otitis media in infants. Lancet 1989; ii: 141-143.
9. Pukander J, Luotonen J, Sipilä M, Timonen M, Karma P. Incidence of acute otitis media. Acta Otolaryngol 1982; 93: 447-453.

10. Halsted C, Lepow ML, Balassanian N, Emmerich J, Wolinsky E. Otitis Media, clinical observations, microbiology, and evaluation of therapy. Am J Dis Child 1968; 115: 542-551.
11. Howie VM, Ploussard JH. Efficacy of fixed combination antibiotics versus separate components in acute otitis media. Effectiveness of erythromycin, estolate, triple sulfanomide, ampicillin, erythromycin estolate - triple sulfonamide, and placebo in 280 patients with acute otitis media under two and one-half years of age. Clin Paediatr 1972; 11: 205-214.
12. Mygind N, Meistrup-Larsen KI, Thomsen J, Thomsen VF, Joseffson K, Sørensen H. Penicillin in acute otitis media: a double-blind placebo-controlled trial. Clin Otolaryngol 1981; 6: 5-13.
13. Bass JW, Cohen SH, Corless JD, Mamunes P. Ampicillin compared to other antimicrobials in acute otitis media. JAMA 1967; 202, 8: 137-142.
14. Lorentzen P, Haugsten P. Treatment of acute suppurative otitis media. J Laryngol Otol 1977; 91: 331-340.
15. Ingvarsson L, Lundgren K. Penicillin treatment of acute otitis media in children. A study of the duration of treatment. Acta Otolaryngol 1982; 94: 283-287.
16. Kaleida HP, Bluestone CD, Rockette HE, et al. Amoxicillin-clavulanate potassium compared with cefaclor for acute otitis media in infants and children. Paediatr Infect Dis J 1987; 6: 265-271.
17. Stickler GB, Rubenstein MM, McBean JB, Hedgecock LD, Hugstad JA. Treatment of acute otitis media in children. Am J Dis Child 1967; 114: 123-30.

Chapter VI

SEVERITY OF TYMPANIC MEMBRANE INFLAMMATION AS A PREDICTOR FOR THE CLINICAL COURSE IN RECURRENT ACUTE OTITIS MEDIA

Accepted for publication as short report in: Br Med J

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10. Halsted C, Iapov NL, Balassanian R, Emmerich J, Wolinsky E. Otitis media, clinical observations, microbiology, and evaluation of therapy. Am J Dis Child 1968; 115: 542-551.

11. Howie VM, Ploussard JH. Efficacy of fixed combination antibiotics versus separate components in acute otitis media. Effectiveness of erythromycin, estolate, triple sulfonamide, ampicillin, erythromycin estolate - triple sulfonamide, and placebo in 280 patients with acute otitis media under two and one-half years of age. Clin Pediatr 1972; 11: 205-214.

12. Mygind N, Melstrup-Larsen KI, Thomsen J, Thomsen VF, Josaffson E, Sørensen H. Penicillin in acute otitis media; a double-blind placebo-controlled trial. Clin Otolaryngol 1981; 6: 9-13.

13. Bass JW, Cohen SH, Corless JD, Mazunes P. Ampicillin compared to other antimicrobials in acute otitis media. JAMA 1967; 202, 8: 137-142.

14. Lorentzen P, Haugsten P. Treatment of acute suppurative otitis media. J Laryngol Otol 1977; 91: 331-340.

15. Ingvarsson L, Lundgren K. Penicillin treatment of acute otitis media in children. A study of the duration of treatment. Acta Otolaryngol 1982; 94: 283-287.

16. Kaleida PP, Bluestone CD, Rockette HE, et al. Amoxicillin-clavulanate potassium compared with cefaclor for acute otitis media in infants and children. Paediatr Infect Dis J 1987; 6: 265-271.

17. Stickler GB, Rubenstein NM, McBean JB, Hedgecock LD, Hugstad JA. Treatment of acute otitis media in children. Am J Dis Child 1967; 114: 123-30.

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SEVERITY OF TYMPANIC MEMBRANE INFLAMMATION AS A PREDICTOR FOR THE CLINICAL COURSE IN RECURRENT ACUTE OTITIS MEDIA

ABSTRACT

Objective To assess the inter-observer reliability of otoscopic examination in children with recurrent acute otitis media. To assess the otoscopic findings as a predictor of clinical course in recurrent acute otitis media.

Design Prospective study.

Setting Primary care.

Patients and methods A total of 121 children ranging from ½ to 12 years of age with a recurrent acute otitis media were enroled in a randomized placebo-controlled clinical trial. The general practitioner and otolaryngologist registered the findings of otoscopy independently and classified the grade of eardrum inflammation. After three days the clinical course was assessed by the general practitioner without knowledge of the prescribed therapy.

The results were analysed by chi-square and Mantel-Haenszel tests, where appropriate. The inter-observer reliability was analysed with Kendall's Tau B statistic.

Outcome parameter Irregular clinical course, defined as presence of fever and/or earache after three days.

Results Inter-observer agreement on assessing presence and grade of inflammation of the eardrum was good (Kendall's Tau B: .64). In children under two years, agreement was moderate (Kendall's Tau B: .57) compared to agreement in older children (Kendall's Tau B: .66).

The clinical course of disease was independent of severity of inflammation of the eardrum as assessed by the general practitioner (p= .98) and the otolaryngologist (p= .58). Age category and initial temperature were not confounding variables (p= .74 and .54 respectively). The duration of complaints before enrollment was not related to severity of inflammation, according to the otolaryngologist and general practitioner (p= .59 and .19 respectively). Within each category of severity, the effect of amoxicillin-clavulanate on the clinical course was not significantly different from the effect of the

placebo (p= .63).

Conclusions Inter-observer agreement between general practitioner and otolaryngologist in otoscopic examination of the tympanic membrane is good. Classification of the otoscopic findings of the eardrum is more difficult in infants than in children of two years and older.

The severity of middle ear inflammation does not enhance the prediction of the clinical course, nor provide support in decision-making concerning antimicrobial therapy.

INTRODUCTION

The diagnosis of an acute otitis media is based on the patient's history and the otoscopic examination. The diagnosis can be further confirmed by assessing an impaired mobility of the tympanic membrane, either by pneumatic otoscopy or by tympanometry.

In describing the inflammatory signs of the tympanic membrane attention is paid to the position, colour, degree of translucency and mobility of the tympanic membrane [1]. The description of the otoscopic signs in very young infants is said to be more difficult. The different position and the greater thickness of the eardrum, as well as the hyperaemia during crying, explain this phenomenon.

The severity of the acute otitis media is distinguished by considering the extent of redness of the eardrum and whether the eardrum is bulging or not [2,3]. Of course, this ordinal classification does not reflect the real course of the inflammatory process, which is continuous and does not proceed abruptly from one grade to another. The classification just indicates the momentary situation of the natural course of the inflammation at the time that the examination takes place. However, after one day the otoscopic signs might have increased, stabilized, or even decreased. Nevertheless, clinicians often assign a meaning to their findings that has implications for the severity of the infectious process and

the prognosis of the disease. In this way the otoscopic findings sometimes have implications for the medical management and the prescription of antibiotics.

We investigated the question whether the severity of an acute otitis media, as assessed by the appearance of the tympanic membrane, is an independent variable for predicting the clinical course of the disease. Age younger than two years and an elevated initial body temperature are known to be prognostic though interdependent variables for an irregular clinical course [4]. For this reason we had to stratify the relationship between severity of the eardrum inflammation and clinical course for these variables.

In order to use the severity of the acute otitis media as a predictor it is first necessary to assess the reliability of the otoscopic classification made by the physician. For this reason we also investigated the inter-observer agreement for otoscopic examination.

In this paper we address the following questions:

* What is the extent of inter-observer agreement for otoscopic examination in children with a recurrent acute otitis media? Does age have an influence upon diagnosis?
* Is the severity of eardrum inflammation in either one or both ears of a child with a recurrent acute otitis media a predictor for the clinical course? Do age category and initial body temperature confound the assessment? Does amoxicillin-clavulanate affect the clinical course in any subgroup with different severity of eardrum inflammation?

PATIENTS AND METHODS

We conducted a randomized, placebo-controlled double-blind clinical trial in children, ½ to 12 years old, with a recurrent acute otitis media to estimate the efficacy of amoxicillin-clavulanate [4]. The general practitioner selected the patients and assessed whether one or both ears were affected by an acute otitis media. He inquired about the presence of

earache and elevated temperature and about the duration of the complaints. When an inflammation of the eardrum was present, the physician was asked to describe the stage of inflammation as follows:

Stage I: hyperaemia at the malleus handle and the annulus of the tympanic membrane; opacification of the drum; and light reflex still visible

Stage II: thickening of the eardrum with complete redness; absence of the light reflex

Stage III: bulging or perforated eardrum

This categorization is commonly used in the Netherlands. Internationally it is more usual to distinguish between moderate and severe inflammation. The criteria for stages I and II are comparable to those used to identify the subcategory of moderate inflammation. Stage III compares to severe inflammation. We used this international classification to analyse the data, except for estimating the inter-observer agreement.

The patient was immediately referred to the otolaryngologist. He confirmed the diagnosis and, as he was not informed of the staging done by the general practitioner, repeated the examination. Then the child was randomized to antibiotic or placebo treatment. After three days the general practitioner assessed the clinical course. It was considered irregular if earache and/or fever still present, or regular if earache and fever were absent.

To estimate the inter-observer agreement, each tympanic membrane was considered as the observational unit. The grade of inflammation of the eardrum according to the general practitioner and the grade of the same eardrum according to the otolaryngologist were defined as the parameters of interest. And the age category served as the control variable. The level of mutual agreement was analysed by means of Kendall's Tau B estimator (>.75 excellent, .58 - .75 good, .40 - .57 moderate, <.40 poor). This technique is used if more than two values are assigned to an ordinal variable [5]. When used with a dichotomized value of the variable, this estimator corre-

sponds to Kappa's coefficient.
When we take the clinical course as the outcome parameter, the child is regarded as the observational unit for the detection of the predictor and confounding variables. If both ears showed an acute otitis media, the highest grade of inflammation of the two eardrums was taken as the independent variable for analysis. Age category (<2 years or ≥2 years), presence of fever at enrolment, long previous duration of complaints, and therapy were considered as possible confounders. Statistical analysis was done by means of either the chi-square test or the Mantel-Haenszel technique, where appropriate [6].

RESULTS

The ears were examined in 121 children, who were enrolled in the clinical trial with a recurrent acute otitis media. In five of them both eardrums could not be inspected by the general practitioner and/or the otolaryngologist. They were thus excluded from this study. In 16 children one eardrum could not be visualized at otoscopy by the general practitioner and/or the otolaryngologist. So 216 ears as observational units were analysed to estimate the inter-observer agreement. In 13 children one of the possible confounding variables was not registered. Hence, the findings of 103 children could be analysed in order to assess the severity of inflammation as a predictor variable.
The agreement in the findings of the examination of the tympanic membrane between otolaryngologist and general practitioner was reflected in a Kendall's Tau B of .64 (Table 1).

Table 1: Classification of inflammation of tympanic membrane by otolaryngologist and general practitioner (n=216 ears).

General practitioner \ Otolaryngologist	Normal	Grade I	Grade II	Grade III	Otorrhoea	
Normal	49	9	5			63
Grade I	12	19	24	4		59
Grade II	5	15	20	20		60
Grade III		2	8	19		29
Otorrhoea					5	5
Total	66	45	57	43	5	216

Kendall's Tau B: .64, good agreement

It is evident that the diagnosis of a perforated eardrum with otorrhoea is quite simple. But even analysing the numbers, while omitting the cases with otorrhoea, the agreement was upheld (Kendall's Tau B: .62). Also when the results of the observers were dichotomized into acute otitis media present and acute otitis media absent, the mutual agreement was good (Kendall's Tau B: .66).

Further analysis showed a moderate agreement in children younger than two years (Kendall's Tau B: .57), while in the children of two years and older the agreement was good (Kendall's Tau B: .66). If the cases with an otorrhoea were again omitted, all of which occurred in the older age group, the agreement remained good (Kendall's Tau B: .64). After dichotomizing the results of the otoscopic examination into acute otitis media present and acute otitis media absent, the agreement in the youngsters is moderate (Kendall's Tau B: .55) and in the older age category the agreement is again good (Kendall's Tau B: .68).

There was no relation between severity of inflammation, as assessed by the otolaryngologist, and the clinical course of the acute otitis media (chi-square: p= .58). Also when the assessment of the general practitioner was considered, such a relationship was lacking (chi-square: p= .98) (Table 2).

Table 2: Number of patients with irregular clinical course after three days (and percentage) by severity of inflammation, assessed by otolaryngologist and by general practitioner

Severity:	Otolaryngologist	General practitioner
Moderate	13/62 (21.0%)	14/73 (19.2%)
Severe	6/41 (14.6%)	5/30 (16.7%)
	19/103	19/103

In Table 3 the numbers of patients with severe inflammation according to the otolaryngologist and the general practitioner are presented by previous duration of complaints. The differences were not statistically significant.

Table 3: Number of patients (n=101)* with severe inflammation (and percentage) by previous duration of complaints.

	Otolaryngologist	General practitioner
<24 h:	27/62 (43.5%)	20/62 (32.3%)
24-48 h:	7/21 (33.3%)	7/21 (33.3%)
>48 h:	6/18 (33.3%)	2/18 (11.1%)
	40/101	29/101
Chi-square:	p = .59	p = .19

* missing values due to unknown duration of previous complaints: 2

The relationship was estimated between the possible confounding variables: age category, temperature at enrolment, and therapy on the one hand, and severity of inflammation according to the otolaryngologist on the other. The results are

shown in Table 4.

Table 4: Number of patients with irregular course due to possible confounding variables by severity of inflammation, assessed by otolaryngologist

	Severity of inflammation: Moderate	Severe	Mantel-Haenszel Chi-square
Age category:			
<2 yr	5/16	3/8	
≥2 yr	6/46	3/33	p = .74
Initial temp.:			
<38° C	6/43	4/27	
≥38° C	7/19	2/14	p = .54
Therapy:			
amox./clav.	5/31	4/25	
placebo	8/31	2/16	p = .63

None of the variables masked an assumed relationship between severity of inflammation and clinical course.

DISCUSSION

The agreement between general practitioner and otolaryngologist in diagnosing the presence and the grade of an inflamed eardrum appears to be good. However, the relevance of assessing the severity of inflammation for the clinical course of acute otitis media could not be demonstrated. Even after controlling for assumed confounders, the severity of inflammation does not support the clinician in the process of decision-making.

There is no scientific evidence confirming the correlation, which is often assumed in clinical practice, between the severity of otoscopic signs and the stage of the infectious process in the middle ear itself. Nor is there any proof of its predictive value for the clinical course.

Morphometric, histopathological, and histochemical studies in animals with experimentally induced otitis media suggest epithelial and subepithelial involvement of middle ear mucope-

riosteum along a continuum [7,8]. Studies in human temporal bones show similar findings at the level of the promontory [9,10]. The continuum is suggested for the progression of the specific acute infection itself, as well as for development between the different forms of otitis media (acute purulent, serous, mucoid, chronic).

Otoscopy is performed to evaluate the tympanic membrane, which consists of three layers: an outer epithelial layer, a middle fibrous layer, and an inner mucosal layer [11]. We might postulate that the parameters used in morphometric evaluation of the inflammatory process may be reflected as otoscopic phenomena. Accordingly, evaluation at the level of the promontorium, that reveals thickness of subepithelial space, vascularization, and vasodilatation may appear in the layers of the tympanic membrane as opacification, increased thickness, and redness, respectively.

There is no documentation of the chronological development of the morphological and histopathological changes in acute otitis media in humans. We assume that considerable diversity must exist among individuals cases. Animal experiments presuppose subjects carefully matched in disposition to disease, defense mechanisms and disease conditions in a way incomparable to the common conditions under which humans live. To extrapolate unconditionally with respect to the changes seen in the course of time in animal experimental studies is therefore not correct. Furthermore, it has been shown that increased thickness and vascularization show considerable overlap in all forms of otitis media. It has also been demonstrated that vasodilatation occurs in both serous and purulent otitis media [9].

Let us assume that the tympanic membrane directly reflects the inflammatory process itself. And let us also assume that the continuum revealed in animal experiments exists in humans. Even then, from the point of view of fundamental research it is still not justified to base management mainly on otoscopic findings, since considerable overlap of features exists

between different forms of otitis media.
In our study the agreement between the general practitioners and otolaryngologists regarding the normal or abnormal appearance of the eardrum was good. Agreement was also good with regard to the grade of inflammation of the tympanic membrane. However, in patients younger than two years, the agreement was moderate; and this group of patients has the highest incidence of acute otitis media. Nevertheless, in all but one of the cases presented by the general practitioner for the clinical trial, the presence of an acute otitis media in the patient was confirmed by the otolaryngologist [4]. We conclude that, in combination with history taking, otoscopy enables the clinician to assess this diagnosis with high reliability. In contrast, assessing the grade of inflammation of the eardrum is less trustworthy.
This drawback is relatively unimportant, however, since the severity of the inflammation of the eardrum did not predict a regular or irregular clinical course after three days of the disease. Nor was this a reliable predictor when the observations were stratified by age category and initial temperature. Such a correlation would have been of importance, because an irregular course after three days is regarded as a reason to prescribe an antibiotic [12].
The duration of complaints deriving from the middle ear infection prior to the consultation did not show a correlation to the severity of signs of the inflammation. We conclude that, contrary to the findings in animal models, the natural course of acute otitis media in humans is fluctuating. This seems plausible since we may expect that the biological resistance varies among children, depending on endogenous and exogenous factors.
The use of an antibiotic appeared not to be a confounding factor for the absence of a correlation between severity of the otoscopic signs and the clinical course.
Our final conclusion is that the assessment of the severity of inflammation of the eardrum in a child with an acute otitis

media does not support the clinician in predicting the course of the disease or in making a decision with regard to the medical management of the patient.

REFERENCES

1. Bluestone DB, Klein JO. Diagnosis. In: Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: WB Saunders Company, 1988: 73.
2. Feenstra L. Acute ontsteking van het middenoor. Ned Tijdschr Geneeskd 1985; 129: 532-536.
3. Glasscock ME, Shambaugh GE. In: Glasscock ME, Shambaugh GE, eds. Surgery of the ear. Philadelphia: WB Saunders Company, 1990: 170-178.
4. Appelman CLM, Claessen JQPJ, Touw-Otten FWMM, Hordijk GJ, Melker RA de. Efficacy of co-amoxiclav in recurrent acute otitis media: placebo controlled study. Br Med J, 1991; 303: 1450-1452.
5. Siegel S. Nonparametric statistics for the behavioral sciences. Tokyo: McGraw-Hill Kogakusha Ltd., 1956.
6. Schlesselman J. Case-control studies. New York: Oxford Univ. Press, 1982: 175, 177, 183, 206.
7. Juhn SK, Paparella MM, Kim CS, Goycoolea MV, Giebink GS. Pathogenesis of otitis media. Ann Otol Rhinol Laryngol 1977; 86: 481-492.
8. Goycoolea MV, Paparella MM, Carpenter AM, Juhn SK. A longitudinal study of cellular changes in experimental otitis media. Otolaryngol Head Neck Surg 1979; 87: 685-700.
9. Yoon TH, Paparella MM, Schachern PA, Lindgren BR. Morphometric studies of the continuum of otitis media. Ann Otol Rhinol Laryngol 1990; 99 (Suppl. 148): 23-27.
10. Paparella MM, Sipilä P, Juhn SK, Jung TTK. Subepithelial space in otitis media. Laryngoscope 1985; 95: 414-420.
11. Wright A. Anatomy and ultrastructure of the human ear. In: Kerr AG, Groves J eds. Scott-Brown's otolaryngology. London: Butterworths, 1987: 1-46.
12. Hordijk GJ. Consensus over therapie bij otitis media acuta. Ned Tijdschr Geneeskd 1992; 136: 85-88.

Chapter VII

PERSISTENCE OF MIDDLE EAR EFFUSION AFTER RECURRENT ACUTE OTITIS MEDIA

REFERENCES

1. Bluestone CD, Klein JO. Diagnosis. In: Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: WB Saunders Company, 1988: 72.
2. Feenstra L. Acute ontsteking van het middenoor. Ned Tijdschr Geneeskd 1985; 129: 533-536.
3. Glasscock ME, Shambaugh GE. In: Glasscock ME, Shambaugh GE, eds. Surgery of the ear. Philadelphia: WB Saunders Company, 1990: 170-178.
4. Appelman CLM, Claessen JGBJ, Touw-Otten FWMM, Nordijk GJ, Melker RA de. Efficacy of co-amoxiclav in recurrent acute otitis media: placebo controlled study. Br Med J 1991; 303: 1450-1452.
5. Siegel S. Nonparametric statistics for the behavioral sciences. Tokyo: McGraw-Hill Kogakusha Ltd., 1956.
6. Schlesselman J. Case-control studies. New York: Oxford Univ. Press, 1982: 175, 177, 181, 206.
7. Juhn SK, Paparella MM, Kim CS, Goycoolea MV, Diebink CE. Pathogenesis of otitis media. Ann Otol Rhinol Laryngol 1977; 86: 481-492.
8. Goycoolea MV, Paparella MM, Carpenter AM, Juhn SK. A longitudinal study of cellular changes in experimental otitis media. Otolaryngol Head Neck Surg 1979; 87: 693-700.
9. Yoon TH, Paparella MM, Schachern PA, Lindgren BR. Morphometric studies of the continuum of otitis media. Ann Otol Rhinol Laryngol 1990; 99 (Suppl. 148): 23-27.
10. Paparella MM, Sipila P, Juhn SK, Jung TTK. Subepithelial space in otitis media. Laryngoscope 1988; 98: 414-418.
11. Wright A. Anatomy and ultrastructure of the human ear. In: Kerr AG, Groves J eds. Scott-Brown's otolaryngology. London: Butterworths, 1987: 1-46.
12. Nordijk GJ. Consensus over therapie bij otitis media acuta. Ned Tijdschr Geneeskd 1992; 136: 85-88.

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PERSISTENCE OF MIDDLE EAR EFFUSION AFTER RECURRENT ACUTE OTITIS MEDIA

Submitted for publication in: Int J Ped Otorhinolaryngol

Authors: J.Q.P.J. Claessen, C.L.M. Appelman, F.W.M.M. Touw-Otten, R.A. de Melker, G.J. Hordijk

Chapter VII

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Authors: J.G.P.J. Cleessen, G.L.M. Appelman, P.W.M.M. Touwen, R.A. de Melker, G.J. Bordijk

In this Chapter the referred publications are listed in alphabetical order and numbered accordingly. This is due to the instructions for authors of the International Journal of Pediatric Othorhinolaryngology.

ABSTRACT

Persistent otitis media with effusion (OME) is a possible etiologic factor in the development of chronic otitis media. Effects on language acquisition are also reported. A history of acute otitis media (AOM) enhances the risk of persistent OME. We investigated the overall presence of OME and high negative pressure (-200 to -400 mmH_2O)(HNP) in the follow-up of a randomized double-blind placebo-controlled trial on the efficacy of amoxicillin-clavulanic acid in a recurrent episode of AOM. All children in this study were recruited from a general practice population. Tympanometry results one month from start of the AOM episode were taken as outcome criteria. The influence of age, sex, season, laterality of the AOM, therapy, and clinical course of the AOM episode was also established. Bilateral middle ear dysfunction was defined as bilateral OME, unilateral OME and contralateral HNP or bilateral HNP. Bilateral middle ear dysfunction was present in 47.9% of the patients. Of all the investigated factors, only season showed a statistically significant influence on the persistence of OME/HNP ($p=0.001$).

INTRODUCTION

Otitis media with effusion (OME) is frequently encountered in children. In a population aged two to six years screened by monthly tympanometry, Casselbrant et al. found cumulative incidences of 53% to 61% per annum [3]. A study of Dutch preschool children showed a cumulative incidence of 80% up to the age of four [28].

Persistent OME has been mentioned as a possible etiologic factor in the development of chronic otitis media [20]. It stimulates atrophic changes in the tympanic membrane that subsequently increase the risk of progression to chronic otitis media with a permanent conductive hearing loss [23]. Effects of persistent OME on language development are still

not fully understood [13]. In a recently conducted study in the Netherlands, strong evidence was found for a negative effect of bilateral persistent middle ear effusion on language development in children [15,25]. This is in accordance with the findings of others who found a delay in the development of speech and language in children with OME [17,21]. Some investigators could not find clear evidence of a delay in language acquisition in children with recurrent acute otitis media (AOM) and persistent middle ear effusion [16,27].
These possible sequelae of persistent OME justify further research on the presence of OME in children recovering from a recurrent episode of AOM, since a history of AOM has been suggested by several investigators as a risk factor for the development of persistent OME [5,18,19,26].
We were interested in the overall presence of OME and high negative pressure (HNP) one month from onset of a recurrent episode of AOM in an 'otitis-prone' population of children. Also, we explored the possible role of age, sex, season, laterality of the AOM, antibiotic therapy, and clinical course of the AOM episode as risk factors for persistent OME/HNP. In the Netherlands AOM is a disease for which primarily the general practitioner is consulted; thus children were recruited from general practices. In the Netherlands it is not customary to perform routine follow-up after a recurrence of AOM to assess the presence of middle ear dysfunction.

PATIENTS AND METHODS

This study was part of the follow-up of a randomized double-blind placebo-controlled clinical trial on the efficacy of amoxicillin-clavulanic acid on the clinical course of a recurrent attack of AOM [1]. That trial was carried out from September 1986 to April 1990. Patients were selected for the trial by their general practitioner if the following entry criteria were met: a recurrent AOM, characterized by otalgia of recent onset and otoscopic signs of middle ear infection

(redness and/or bulging of the tympanic membrane), within four weeks to 12 months after the previous attack, in children aged six months to 12 years. When informed consent was obtained, patients were referred to the otolaryngologist; upon confirmation of diagnosis and selection they were enrolled in the trial. Patients revisited the otolaryngologist one month from start of therapy for the episode. At this follow-up visit all children underwent otoscopy and tympanometry. In children aged four and over, audiometry was also performed. Tympanometry results were taken as outcome criteria (tympanometer: Tympanometer type 85 AR, probe tone frequency 220 Hz, American Electromedics Co.). For classification of tympanometry results the modified Jerger nomenclature was used. (Table I) [6].

Table I: Tympanometry classification

Type A	: compliance: ≥ 0.2 ml	pressure: ≥ -100 mmH_2O
Type C_1	: compliance: ≥ 0.2 ml	pressure: -100 - -199 mmH_2O
Type C_2	: compliance: ≥ 0.2 ml	pressure: -200 - -400 mmH_2O
Type B	: compliance: < 0.2 ml	absence of peak

Tympanometer: Tympanometer type 85 AR, probe tone frequency 220 Hz, American Electromedics Co.

Patients were grouped according to the relative severity of their middle ear dysfunction. For further analysis three groups were formed, based on the clinical severity of the bilateral tympanometry outcome (Table II).

Table II: Patients by bilateral tympanometry outcome, formation of tympanometry groups for further analysis

Tympanometry ADS (ADS = right + left ear):		Group
[AA]:	no OME	Normal
[AC_1, C_1A, C_1C_1]:	no OME, low negative pressure of no clinical consequence	Normal
[AC_2, C_2A, AB, BA, C_1B, BC_1, C_2C_1, C_1C_2]:	unilateral normal, contralateral OME or HNP	Intermediate
[BB]:	bilateral OME	Abnormal
[BC_2, C_2C_2, C_2B]:	unilateral OME and contralateral	Abnormal
	HNP or bilateral HNP	Abnormal

The data are presented in 'right ear first' order (i.e. AB: right ear type A tympanogram, left ear type B). Signs of HNP also were considered abnormal [2]. For classification into age categories, rounded calendar years were used (i.e. 9 months is 0 years, 3 years and 11 months is 3 years). Also, patients were dichotomized in age groups (<2 years and ≥2 years) and then analysed for tympanometry out-come. The influence of the clinical course of the AOM episode on tympanometry outcome was

An irregular course was defined as the presence of*p275) otalgia and/or a body temperature of ≥38° C three days from start of therapy. Furthermore we established the influence of laterality of the AOM and season of onset. Winter was defined as 1 October to 31 March, summer as 1 April to 30 September. Patients were also assigned to the placebo and antibiotic therapy groups and analysed accordingly. Finally, this relation-ship was controlled for the age categories <2 years and ≥2 years as well as for season.

Analysis of all tympanometry results is on child level. Results were analysed with Chi-square test, Fishers' exact test, and one-way analysis of variance, where appropriate.

RESULTS

Of the total of 121 children included and analysed for the clinical trial, 23 patients did not return for the one-month follow-up visit. In two patients proper assessment of the middle ear status was impossible because of lack of cooperation at follow-up. Mean age of the remaining 96 patients was 3.47 years, whereas mean age of the patients lost was 2.84 years. This difference is not statistically significant. When dichotomizing according to age categories <2 years and ≥2 years, the lost group contained a significantly higher number of patients younger than two years (Chi-square, p=0.034, not in table). For the parameters sex, season, laterality of the AOM, clinical course and therapy received, no significant difference existed.

Overall results showed that 32.3% of the children were free of effusion or had low negative pressure (LNP) of no clinical consequence and can be classified as clinically 'normal' (tables III and IV).

Table III: Children by tympanogram type, n=96

Tympanogram ADS (ADS = right + left ear):		
[AA]:	16	16.7 %
[AC_1, C_1A, C_1C_1]:	15	15.6 %
[AC_2, C_2A, AB, BA, C_1B, BC_1, C_2C_1, C_1C_2]:	19	19.8 %
[BB]:	27	28.1 %
[BC_2, C_2C_2, C_2B]:	19	19.8 %

Table IV: Distribution of tympanometry groups over population, n=96

Normal:	31	(32.3 %)
Intermediate:	19	(19.8 %)
Abnormal:	46	(47.9 %)

In 19.8% of the patients one ear was normal, whereas the contralateral ear showed signs of OME or HNP, classifying them as clinically 'intermediate'. Yet 47.9% of the patients who could be analysed had clear signs of OME and/or HNP in both ears and were clinically 'abnormal'. Signs of either uni- or bilateral effusion as indicated by a type B tympanogram were present in 46.8% of the patients (data not in table).
No influence of age on tympanometry findings could be established (F=1.47, p=0.22, Table V).

Table V: Mean age per tympanometry outcome, n=96

	mean age	95% C.I.for mean
Tympanogram ADS: (ADS = right + left ear):		
[AA]:	4.06	2.89 - 5.24
[AC_1,C_1A,C_1C_1]:	3.73	2.40 - 5.07
[BB]:	2.89	2.13 - 3.65
[BC_2,C_2C_2,C_2B]:	4.21	3.43 - 4.99
[AC_2,C_2A,AB,BA,C_1B,BC_1,C_2C_1,C_1C_2]:	3.68	2.67 - 4.70

F ratio = 1.4716, p= 0.2173
* Lost to follow-up: mean age 2.84; 95% C.I.: 1.94 - 3.75

AA showed a slight trend toward the older patients; BB toward the youngest age group; and BC_2, C_2B and C_2C_2 toward the older age group. Age category, sex, laterality and clinical course had no statistically significant influence on the distribution of tympanometry outcome (Table VI).

Table VI: Influence of possible risk factors on tympanometry distribution, n=96 (except where noted)

Tympanometry	: Normal	Intermed.	Abnormal	p
	31 (32.3%)	19 (19.8%)	46 (47.9%)	
Risk factor:				
age < 2	: 5 (29.4%)	4 (23.5%)	8 (47.1%)	p=0.904
≥ 2	: 26 (32.9%)	15 (19.0%)	38 (48.1%)	N.S.#
male	: 19 (35.2%)	10 (18.5%)	25 (46.2%)	p=0.783
female	: 12 (28.6%)	9 (21.4%)	21 (50.0%)	N.S.#
unilateral*	: 17 (32.1%)	12 (22.6%)	24 (45.3%)	p=0.829
bilateral*	: 14 (37.8%)	7 (18.9%)	16 (43.3%)	N.S.#
regular course	: 25 (31.7%)	15 (19.0%)	39 (49.3%)	p=0.819
irregular course	: 6 (35.3%)	4 (23.5%)	7 (41.2%)	N.S.#
summer	: 5 (20.8%)	11 (45.8%)	8 (33.4%)	p=0.001
winter	: 26 (36.1%)	8 (11.1%)	38 (52.8%)	S.#

*: n=90 (6 missing values)
#: Chi-square test

In six patients the records did not clarify whether the attack was uni- or bilateral, and for this parameter the records of 90 patients were analysed. Only season showed a significant influence on the persistence of OME owing to a higher percentage of the abnormal group in the winter and the intermediate group in the summer (Table VI). No statistically significant differences between the placebo and the amoxicillin/clavulanic acid group could be established (Table VII).

Table VII: Tympanometry distribution over therapy groups, n=96

Tympanometry:	Normal	Intermed.	Abnormal	Total
Therapy group:				
placebo:	13 (28.9%)	7(15.6%)	25 (55.6%)	45
antibiotic:	18 (35.3%)	12(23.5%)	21 (41.2%)	51

Chi-square: p=0.349 N.S.

When controlling this relation for age, dichotomizing the population according to age categories <2 years and ≥2 years, again no statistically significant difference could be found (Table VIII).

Table VIII: Tympanometry results by therapy groups, controlled for different predictors

Tympanometry:	Normal	Intermed.	Abnormal	Total
Age < 2 years*:				
placebo:	2 (18.2%)	2 (18.2%)	7 (63.6%)	11
antibiotic:	3 (50.0%)	2 (33.3%)	1 (16.7%)	6
Age ≥ 2 years**:				
placebo:	11 (32.4%)	5 (14.7%)	18 (52.9%)	34
antibiotic:	15 (33.3%)	10 (22.2%)	20 (44.4%)	45
Summer*:				
placebo:	3 (30.0%)	3 (30.0%)	4 (40.0%)	10
antibiotic:	2 (14.3%)	8 (57.1%)	4 (28.6%)	14
Winter*:				
placebo:	10 (28.6%)	4 (11.4%)	21 (60.0%)	35
antibiotic:	16 (43.2%)	4 (10.8%)	17 (45.9%)	37

* = Tested with Fishers' exact
dichotomized Normals / (Intermediates + Abnormals)
none significant, all $p > 0.05$
** = Tested with Chi-square
not significant, $p > 0.05$

Finally, we investigated the influence of season on tympanometry outcome in the two therapy groups. Here too, no significant influence could be established (Table VIII).

DISCUSSION

We have no clear explanation, other than disinclination to revisit the hospital with a young child for mere investigative reasons, for the fact that 23 patients did not return for a follow-up visit one month from start of therapy for their recurrent AOM episode. Although these patients were in the

younger age categories, this difference was not statistically significant when analysed per year category. When dichotomizing by age categories <2 years and ≥2 years, the group lost to follow-up was significantly younger (p=0.034). However, in regard to sex, season, laterality of the AOM, therapy received and clinical course, this group did not differ from the patients seen at follow-up. From the general practitioners' follow-up records, we have no indication that the general health condition of these children at the moment of follow-up differed from that of the 96 patients who could be analysed.

Analysis of tympanometry results was on child level, not only for methodological reasons, but also because a possible interdependency of both ears for the presence of OME cannot be entirely ruled out. This phenomenon has been clearly illustrated in earlier studies [8]. We formed patient groups according to the relative severity of their middle ear dysfunction, because clinical management is based on findings on child level. We searched for the presence of type B tympanograms, indicative for effusion, and for type C_2, which indicates high negative pressure. It has been shown that in a high number of C_2 ears, effusion is present at myringotomy [24]. But it has also been demonstrated that type B tympanograms relatively often change to type C_2 and back again to type B [24]. Moreover, prolonged severe retraction is a possible risk factor for development of attic cholesteatoma [23].

The total percentage of children with signs of OME and/or HNP either uni- or bilaterally is 67.7%, which is remarkably high. A type B tympanogram was either uni- or bilaterally present in 46.8% of the cases. Bilateral signs of middle ear dysfunction were present in 47.9%.

A number of previous investigators have screened children for the persistence of middle ear effusion following an episode of acute otitis media. In the study by Shurin et al. 42.1% of the patients showed persistence of middle ear effusion in a follow-up period of maximally 90 days [19]. In that study there was however an unequal total follow-up duration and the previ-

ous otitis media history was only roughly specified as 'yes' or 'no' prior 'otitis media'. Mills reported that 41% of the children studied still had tympanometrical signs of OME at their two-month follow-up visit following a recurrent attack of AOM [10]. Mandel et al. found 38.7% of the children still having OME at tympanometry 42 days from the start of their episode of AOM [8]. In a study by Odio 45% of the children had persistent middle ear effusion at their one-month follow-up visit [12]. In that study 27% of the patients had three or more episodes of AOM within the previous six months. For the other 73% of the study population, no further specification was given than less than three episodes. Yet one may assume that a considerable part of the population was at risk for acute otitis media. In contrast to the results mentioned above, which are comparable to our finding of 46.8% OME, a study by Pukander and Karma showed that only 21.1% of the children had persistent effusion at a four-week follow-up visit, as objectified by aspiration [14]. This difference from our results might be explained by a difference in procedures and patient histories. In that study myringotomy and aspiration were almost always performed when effusion was suspected at the two-week follow-up visit. In this way a more rapid clearance may have been achieved. Secondly, our group of children had a history of recurrent episodes of acute otitis media, whereas this distinction is not clear in the Pukander population. In another study on treatment in AOM, only 14% of the children showed signs of OME at a 28 to 30 day follow-up, as assessed by pneumatic otoscopy done by experienced otologists. Again, for these children prior AOM history was not a prerequisite [4].

The finding that the mean age of our patients with C_2 tympanograms showed a trend toward the older age-group, although not statistically significant, has been reported earlier by Tos [24]. He suggested that secretory otitis media has a more protracted course in children of four years and older.

When age groups were divided in <2 years and ≥ 2 years, a

difference in the presence of OME could not be detected. This is in contrast to Shurin's findings, but in accordance with the results of Mills, who also could not find a difference related to age [10,19]. The 'otitis-prone' condition seems to be a more important risk factor than age alone.

We could not establish a statistically significant influence of sex on tympanometry outcome after an AOM episode. This is in agreement with the findings of other investigators [9].

Our finding that antibiotic therapy did not influence the persistence of effusion and/or HNP after an AOM episode is confirmed by others. Mygind and co-workers found OME and HNP present in 52% of the penicillin group, compared to 46% in the placebo group [11]. Their placebo-controlled study can be compared with ours in terms of trial size, use of identical tympanometry criteria for HNP and effusion, and similar age groups. Our overall higher figures, with either uni- or bilateral OME and/or HNP in 71.2% of the placebo-treated patients compared to 64.7% of the antibiotics group, may again be explained by the fact that our study comprised otitis-prone patients.

A relation between laterality of the initial AOM and persistence of OME could not be established in our study. Earlier studies reveal that unilateral AOM never resulted in bilateral OME at follow-up, either at 14 or at 42 days [8]. This may be explained by the fact that in a unilateral AOM this ear always underwent tympanocentesis and aspiration, thus possibly clearing more rapidly, whereas in bilateral AOM one or both ears received myringotomy at the physicians' discretion. Furthermore, the population was not primarily 'otitis-prone'.

We found a statistically significant higher overall percentage of OME/HNP in the winter compared to the summer. This agrees with current knowledge that the incidence of OME/HNP is generally higher in the winter. Pukander also reported a higher percentage of persistent middle ear effusion following AOM in the winter months [14].

Antibiotic therapy showed no influence on tympanometry outcome

one month after an AOM episode, when controlling for season. So far this cannot be compared with findings reported by other investigators. We still cannot answer the question whether our patients were 'otitis-prone' because of underlying OME or if proneness to recurrent AOM predisposes them to developing persistent middle ear effusions following AOM. Yet the high overall percentages of OME/HNP found in the absence of a significant influence of age but under a strong influence of season suggest that AOM might be the underlying cause. This would contradict the theory stressed by other investigators that OME is premorbid when it is found following AOM [7,22]. Our study shows that a high percentage of children with a history of recurrent acute otitis media suffer from OME/HNP one month after an episode of acute otitis media. This number seems higher than in children who are less 'otitis-prone'. Longer follow-up monitoring is needed to evaluate if this effect is temporary or lasting. Keeping in mind the possible risks of persistent OME/HNP, we advocate follow-up of patients recovering from a recurrent episode of AOM, especially in the wintertime.

REFERENCES

1. Appelman CLM, Claessen JQPJ, Touw-Otten FWMM, Hordijk GJ, de Melker RA. Co-amoxiclav in recurrent acute otitis media, a placebo-controlled study. Br Med J 1991; 303: 1450-1452.
2. Bluestone CD, Klein JO, Tympanometric screening for otitis media with effusion. In: Bluestone CD and Klein JO, eds. Otitis media in infants and children. Philadelphia: W.B. Saunders Company, 1988: 90-91.
3. Casselbrant ML, Brostoff LM, Cantekin EI, et al. Otitis media with effusion in pre-school children. Laryngoscope 1985; 95: 428-436.
4. Ingvarsson L, Lundgren K. Penicillin treatment of acute otitis media. Acta Otolaryngol 1982; 94: 283-287.
5. Ishidoya M, Takasaka T, Shimizu H. Risk factors for otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 1-3.
6. Jerger J. Clinical experience with impedance audiometry. Arch. Otolaryngol 1970; 92: 311-324.
7. Leth N, Tos M. Middle ear ventilation after acute otitis media. ORL 1977; 39: 278-284.
8. Mandel EM, Bluestone CD, Rockette HE, et al. Duration of effusion after antibiotic treatment for acute otitis media: comparison of cefaclor and amoxicillin. Ped Infect Dis 1982; 1: 310-316.
9. Marchisio P, Bigalli L, Massironi E, Principi N. Risk factors for persisting otitis media with effusion in children. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 3-5.

10. Mills RP. Persistent middle ear effusions in children with recurrent acute otitis media. Clin Otolaryngol 1987; 12: 97-101.
11. Mygind N, Meistrup-Larsen KI, Thomsen J, Thomsen VF, Josefsson K, Sørensen H. Penicillin in acute otitis media: a double-blind placebo-controlled trial. Clin Otolaryngol 1981; 6: 5-13.
12. Odio CM, Kusmiesz H, Shelton S, Nelson JD. Comparative treatment trial of augmentin versus cefaclor for acute otitis media with effusion. Pediatrics 1985; 75: 819-826.
13. Paradise JL. Otitis media during early life: how hazardous to development? A critical review of the evidence. Pediatrics 1981; 68: 869-873.
14. Pukander JS, Karma PH. Persistence of middle ear effusion and its risk factors after an acute attack of otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 8-11.
15. Rach GH, Zielhuis GA, Van den Broek P. The influence of chronic persistent otitis media with effusion on language development of 2 to 4 year olds. Int J Pediatr Otorhinolaryngol 1988; 15: 253-261.
16. Roberts ER, Sanyal MA, Burchinal MR, Collier AM, Ramey CT, Henderson FW. Otitis media in early childhood and its relationship to later verbal and academic performance. Pediatrics 1985; 78: 423-430.
17. Sak RJ, Ruben RJ. Recurrent middle ear effusion in childhood: implications of temporary auditory deprivation for language and learning. Ann Otol Rhinol Laryngol 1981; 90: 546-551.
18. Schutte PK, Beales DL Dalton R. Secretory otitis media- a retrospective general practice survey. J Laryngol Otol 1981; 95: 17-22.
19. Shurin PA, Pelton SI, Donner A, Klein JO. Persistence of

middle-ear effusion after acute otitis media in children. N Engl J Med 1979; 300: 1121-1123.

20. Smyth GDL. Middle ear effusions. A consideration of factors involved in their etiology, maintenance and treatment. Clin Otolaryngol 1978; 52: 583-58.
21. Teele DW, Klein JO, Rosner BA, et al. Otitis media with effusion during the first three years of life and development of speech and language. Pediatrics 1984; 74: 282-287.
22. Tos M. Etiologic factors in secretory otitis. Arch Otolaryngol 1979; 105: 582-588.
23. Tos M. Sequelae of secretory otitis media and the relationship to chronic suppurative otitis media. Ann Otol Rhinol Laryngol 1990; Suppl 146: 18-19.
24. Tos M, Holm-Jensen S, Sørensen CH, Mogensen C. Spontaneous course and frequency of secretory otitis in 4-year-old children. Arch Otolaryngol 1982; 108: 4-10.
25. Van den Broek P, Rach GH, Zielhuis GA. Is otitis media met effusie schadelijk voor de taalontwikkeling van jonge kinderen? Ned Tijdschr Geneeskd 1988;132:1885-1888.
26. Van Cauwenberge P, Secretory Otitis Media. An Epidemiological, Clinical and Experimental Study. Thesis. 1988: University of Ghent.
27. Wright PF, Sell SH, McConnell, KB, et al. Impact of recurrent otitis media on middle ear function, hearing, and language. J Pediatrics 1988; 113: 581-587.
28. Zielhuis GA, Rach GH, Van den Broek P. The occurrence of otitis media with effusion in Dutch pre-school children. Clin Otolaryngol 1990; 15: 147-153.

Chapter VIII

A ONE-YEAR-LONG FOLLOW-UP STUDY

of trial patients with recurrent
acute otitis media and their siblings
in primary care

C.L.M. Appelman, J.Q.P.J. Claessen, G.J. Hordijk, F.W.M.M. Touw-Otten, R.A. de Melker

Chapter VIII

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INTRODUCTION

The success or failure of medical management is more than the demonstrated power of the therapy to cure the disease. There are four therapeutic objectives in the management of a child with acute otitis media. These are: to cure the episode, to prevent or shorten the duration of residual serous effusions, to prevent recurrent episodes, and to clear persistent mucoid effusions [1]. This preventive approach is especially important with regard to our study population. These patients exhibit a high percentage of irregular clinical courses and persistent abnormal tympanometry after the episode. Furthermore, our study population contains a subgroup of 'otitis-prone' children, and one of the characteristics of this subgroup is a high rate of recurrences [2].

It would be useful to the clinician to know about the 'otitis-prone' condition of a child as early as possible in the child's life. An initial acute otitis media in the first year of life is a known indicator of this condition [2,3,4]. This indicator is, however, neither specific nor sensitive enough to predict recurrence [5].

The children who were enrolled in our study had at least one recurrent acute otitis media, defined as an episode at least one month and at most one year after the preceding one. The 'otitis-prone' condition is defined in different ways by several authors [5]. The definitions vary from $\geq$2 episodes in 24 months to $\geq$6 episodes in 12 months. Accordingly, the percentage of children with 'otitis-proneness' in the general population ranges from 1.8% to 41.2%. We assumed that our study population included the 'otitis-prone' group, since we used the broad definition of two episodes within one year as an inclusion criterion. One indication that this assumption is warranted is the high percentage of irregular clinical courses found in this group [6]. But more specific guidelines would be welcome, enabling the physician to identify the individual patients at risk. Furthermore, we wanted to know whether or

not an antibiotic given during one week as a therapy for an acute otitis media would postpone the next recurrence. Very few reports of placebo-controlled clinical trials have described a follow-up period that is long enough to draw valid conclusions. For this reason we conducted a one-year-long follow-up study for all children after their enrolment in the clinical trial.

The purpose of this study was to answer the following questions:

* What is the rate of occurrence, as measured during one year of follow-up, of subsequent upper respiratory tract infections (URTIs) and, more specifically, of acute otitis medias?
* Which of the following variables are related to the occurrence of more than one acute otitis medias in a year: age, laterality of the acute otitis media, antimicrobial therapy, clinical course, abnormal tympanogram one month after the acute otitis media, the presence of siblings, and rank in the family?
* Is the occurrence of URTIs in siblings during the year of follow-up related to subsequent acute otitis medias in the trialpatients?

PATIENTS AND METHODS

All of the 121 children included in the clinical trial were followed up for one year. During that year their general practitioner registered all contacts for complaints related to URTIs, including acute otitis media. As soon as a child entered the study, the general practitioner was sent a study form. For each contact he was asked to record date, diagnosis, therapy given, course of the disease, and whether or not the child was referred to a specialist. Furthermore, study forms were used by the general practitioner to record similar contacts with every sibling of the trial patient.

At the end of the follow-up period, the study forms were col-

lected by the investigator in person. On this occasion, data on the study form were compared to data from the physician's own patient record in order to complete the study form if necessary. If a patient had moved or taken another general practitioner, the name of the new general practitioner was asked. Only if this name was known were we able to obtain and complete the study form.
Reports of patient contacts regarding the same illness were condensed to refer to one episode. The date of the first consultation for one bout was taken as the date of onset of the episode. It was possible for one episode to consist of several contacts with different diagnoses; for instance, common cold and angina tonsillaris. The last diagnosis made was applied to the entire episode. All trial patients entered the study with a recurrent acute otitis media. Therefore, a subsequent attack during the first month of follow-up was only considered to be a recurrence on one condition: at the check-up 14 days after enrolment, the general practitioner must have described the patient as having developed a regular course. In order to assess the relation between an abnormal tympanogram one month after enrolment and occurrence of subsequent acute otitis medias, patients having recurrences within a month were excluded from this analysis.

Method of describing occurrence of disease

In attempting to measure the frequency of the occurrence of acute otitis media in a population, it is insufficient merely to record the number of children or the proportion of the population that is affected. It is also necessary to take into account the time elapsed before the disease recurs [7]. A measure that fulfils these conditions is the **incidence rate**, defined as:

$$\frac{\text{no. disease episodes}}{\Sigma \text{ time periods}}$$

where Σ indicates the sum of time periods for all individuals between enrolment and recurrence. In case of no recurrence,

the total follow-up period of one year was counted as the observation period.

For the sake of clinical understanding, it is better to use a more readily interpretable measure of disease occurrence, for instance the **cumulative incidence**. This may be defined as the proportion of a fixed population that becomes affected by the disease in a stated period of time. It can be seen as a measure of average risk. There are several methods to derive estimates of cumulative incidence from the incidence rate. We used the exponential method by application of the formula $CI_t = 1 - e^{-I\delta t}$. To calculate the cumulative incidence of a second occurrence for the original population we used the formula:

$$CI_T = \frac{1}{1/CI_1 + 1/CI_2}$$

where CI_T is the total population cumulative incidence; CI_1 is the cumulative incidence of the first recurrence; and CI_2 is the cumulative incidence of the second recurrence in the population that already had a first recurrence [8].

Statistics

The Fisher exact probability test was used to compare the proportion of patients lost to follow-up between the two groups. To estimate the existence of a risk factor for an occurrence, we used the Chi-square statistic. The weight of potential risk factors was calculated by odds ratios with 95% confidence intervals. To compare the antibiotic and placebo group, we assessed the significance of the difference between average time elapsed before recurrence, using Student's T-test. The difference between sequential recurrence in the two treatment groups was assessed by means of univariate survival data analysis according to the Kaplan-Meier method [9]. Two non-parametric statistical tests were used for comparison of the two survival distributions defined by the given therapy (either antibiotic or placebo): the Cox-Mantel (log-rank) test [10,11] and Breslow's generalized Wilcoxon test [12].

RESULTS

We obtained information from the general practitioners on 109 children out of the initial 121. Twelve were 'lost to follow-up' (9.9%) through moves or taking another family physician. For 11 of these patients, the identity of the new general practitioner, to whom the patient's study form was sent, was not known to the previous physician. One general practitioner refused to hand over the information to protect privacy of his patient.
The relevant characteristics of these 12 children compared to the total group of 121 patients are shown in Table 1.

Table 1: Characteristics of trial patients (n=121) and patients lost to follow-up (n=12)

	Trial patients:	Patients lost to follow-up:
Therapy:		
placebo	54	10
antibiotic	67	2
Age category:		
< 2 years	27	4
≥ 2 years	94	8
Abnormal tympanogram after 1 mo:		
no	31	1
light	19	3
yes	46	6
unknown	25	2
Clinical course in trial:		
regular	100	6
irrigular	21	6

The larger proportion of children treated with placebo who were lost to follow-up compared with the proportion of

children treated with an antibiotic was statistically significant (Fisher's exact: p=0.005). Also, more children with an irregular clinical course were lost to follow-up than those with a regular course. This difference was even statistically more significant (Fisher's exact: p=0.006). The proportions lost to follow-up in the two age categories are not significantly different. Nor are they significantly different in two other categories: normal or lightly abnormal tympanometry, and abnormal tympanometry. Nevertheless, we cannot assume that any variables are causally related to the loss to follow-up; this was due to the removal of the family, entailing transfer to another general practitioner.

Accuracy of follow-up

The 109 remaining trial patients were followed up for one year by 43 general practitioners. There were 123 siblings under study.

Table 2 shows the total number of episodes of URTIs and acute otitis medias recorded during the follow-up period.

Table 2: Number (and range) of episodes of URTIs (including acute otitis media (AOM) and AOMs in trial patients (n=109) and siblings (n=123)

	URTIs	AOMs
Trial patients: (n=109)	205 (0-6)	78 (0-4)
Siblings: (n=123)	145 (0-8)	37 (0-3)
Total: (n=232)	350	115

We compared the data entered on the study forms with the data on the patients' records kept by the general practitioners. We discovered that an episode was often described on a patient's record but not on the study form. The investigator completed

the study forms by copying the findings from the patient records of the general practitioner.

Epidemiology of recurrences

During the year of follow-up, 53 children (48.6%; 95% C.I.: 39.2, 58.0) out of the 109 had one or more acute otitis medias. Since some of them had more than one acute otitis media during this year, the total number of acute otitis medias that occurred was 78. This implies an incidence per year of 71.6% (95% C.I.: 63.1, 80.0).

These incidences do not take into account the time lapse between enrolment in the study and first recurrence during follow-up. Therefore, incidence rates have been calculated. For the 53 patients who had at least one recurrence, the average episode-free interval was 138 days. So the incidence rate for the first recurrence during follow-up is 0.697. The corresponding cumulative incidence for at least one recurrence after one year is 0.502. Of these 53 children, 17 had a second recurrence during the year of follow-up, with an average lapse after the first recurrence of 112 days. The incidence rate for a second recurrence during follow-up is 0.642 $year^{-1}$, with a cumulative incidence for one year of 0.474. The overall incidence rate for at least two recurrences during a one-year follow-up for the total population is 0.334 $year^{-1}$. This results in a cumulative incidence for at least two recurrences during one year of 0.284. For the third and fourth recurrence during the year of follow-up, the corresponding figures are shown in Table 3.

Table 3: Incidence rates and cumulative incidences for recurrent AOMs during follow-up in the 109 trial patients

	Number of recurrences during one-year follow-up:					
	0	1	2	3	4	total
Number of patients:	56	36	11	4	2	109
Average time since previous AOM: (days)		138	112	79.5	75	
	0	≥1	≥2	≥3	4	
Number of patients:	56	53	17	6	2	
Incidence rate: ($year^{-1}$)		0.697	0.642	1.184	1.608	
One-year cumulative incidence:		0.502	0.474	0.694	0.800	
Incidence rate for total population: ($year^{-1}$)		0.697	0.334	0.261	0.224	
One-year cumulative incidence for total population:		0.502	0.284	0.230	0.201	

The one-year cumulative incidence rate for the total study population can be interpreted as follows: 50% of a similar population will have one or more recurrences; 28% of such a population will have at least two recurrences; 23% will have three or more recurrences; and 20% will have at least four recurrences over a period of a year following a recurrent acute otitis media.

The age distribution of the recurrences during the year of follow-up is shown in Table 4. The age of the child is determined at the time of enrolment in the study. The age category zero years only includes children from ½ to 1 year old.

Furthermore, Table 4 shows the amount of patients with at least one recurrence during follow-up, both in absolute numbers and as a proportion of the total number of patients per

age category. Finally, the total number of acute otitis medias during the year-long is shown follow-up by age category.

Table 4: Number of patients and recurrences during follow-up by age category

Age:	Number of recurrences: 0	1	2	3	4	total	Number of patients with ≥1 recurrence:	%	Number of AOMs:
0	3	1	0	1	0	5	2	40.0	4
1	8	6	2	1	1	18	10	55.5	17
2	8	5	0	1	0	14	6	42.9	8
3	8	5	3	0	1	17	9	52.9	15
4	12	10	4	1	0	27	15	55.6	21
5	5	5	2	0	0	12	7	58.3	9
6	7	3	0	0	0	10	3	30.0	3
7	1	0	0	0	0	1	0		0
8	2	1	0	0	0	3	1	33.3	1
10	2	0	0	0	0	2	0		0
total:	56	36	11	4	2	109	53	48.6	78

Taking into consideration the absolute numbers, no statistics are available for non-grouped data. Thus, we cannot test the hypothesis that no relation exists between the proportion "≥1 recurrence" and age. However, the numbers give the impression that this proportion is independent of age.

Risk factors for recurrence

Several patient characteristics were analysed as possible risk factors for the occurrence of at least one acute otitis media during the follow-up period of one year (Table 5). Age was dichotomized in the categories <2 years and ≥2 years, since this appeared to be an important cut-off point in the analysis of the clinical trial. For family size, children who were the only child in the family were compared with children who had one or more siblings.

Laterality of the acute otitis media at enrolment, as assessed by the general practitioner and the otolaryngologist, has two values: uni- or bilateral acute otitis media. In six children the eardrum could either not be visualized by the general

practitioner or his assessment of the eardrum inflammation was not reported on the record. Hence, for laterality according to the general practitioner, six cases are missing. In the same way the laterality of acute otitis media at enrolment could not be described on the basis of records kept by the otolaryngologist in nine children, who are missing from this analysis. Rank in the family takes into consideration whether or not a child has older brothers or sisters. Since 24 patients did not have a sibling, they were excluded from this analysis. Therapy is either amoxicillin/clavulanate or placebo. After three days of medication for acute otitis media at enrolment, the clinical course was assessed, by means of the outcome parameter: irregular course for presence of fever (≥ 38° C) and/or earache, and regular course for absence of fever or earache. Abnormal tympanogram after four weeks was assessed four weeks after enrolment by means of tympanometry. The presence of an abnormal tympanogram is defined as a C_2 or B tympanogram for at least one ear. In 23 cases these data were not obtained, because patients cancelled the appointment. In four children who had undergone tympanometry, the first recurrence during follow-up took place within four weeks. For this reason they were excluded from analysis. Hence, 27 cases are missing from this analysis.

Table 5: Number of patients without and with at least one recurrence during follow-up, stratified for the presence of possible risk factors (n=109).

	No recurrence: (n=56)	Recurrence: (n=53)	Chi-square p value:	Odds ratio:	95% C.I.:
Age category:					
< 2 years	11	12		1.20	0.48, 3.01
≥ 2 years	45	41	0.88		
Family size:					
siblings	45	40		0.75	0.30, 1.87
no siblings	11	13	0.70		
Laterality GP:*					
bilateral	18	25		2.23	1.01, 4.97
unilateral	37	23	0.07		
Laterality ENT:**					
bilateral	19	23		1.49	0.67, 3.31
unilateral	32	26	0.44		
Rank in family:					
not oldest	32	22		0.50	0.18, 1.33
oldest	13	18	0.19		
Therapy:					
placebo	23	21		0.94	0.44, 2.03
amox.-clav.	33	32	0.97		
Clinical course:					
irregular	5	10		2.37	0.67, 8.73
regular	51	43	0.22		
Abnormal tympanogram after four weeks:***					
present	22	30		3.75	1.28, 11.3
absent	22	8	0.013		

* missing: 6
** missing: 9
*** missing: 27

Of all risk factors analysed, only an abnormal tympanogram at four weeks after the previous acute otitis media appeared to increase the risk of a subsequent recurrence in a significant way. This risk was nearly fourfold compared to the patients with a normal tympanogram.

The effect of therapy on recurrences

Besides the effect on the clinical course and sequelae of this episode, it is also important to estimate the effect of therapy on the occurrence of new acute otitis medias.

This question can be specified in three different ways:

* What is the effect of therapy on whether another acute otitis media occurs or not?
* If a subsequent acute otitis media occurs, what is its effect on the average time interval between episodes?
* What is the effect of therapy on the distribution of subsequent recurrences in time?

Table V reveals that in the group treated with an antibiotic, the proportion of patients who developed another acute otitis media (0.492) is statistically not different from the group treated with a placebo (0.477).

In the group treated with an antibiotic, the average number of days after which another acute otitis media occurred was 139.22 (S.D. 87.82). On the other hand, in the group treated with a placebo this average number of days came to 136.19 (S.D. 110.01). The difference between the two averages, 3.02 days, is statistically not significant (Student's t-test: t=0.1105, d.f.=51, p=0.91). The 95% confidence interval of the difference between 139.22 and 136.19 days is -52.0 and 58.0 days.

Figure I shows the proportional development through time of the occurrence of new acute otitis medias in the two treatment groups.

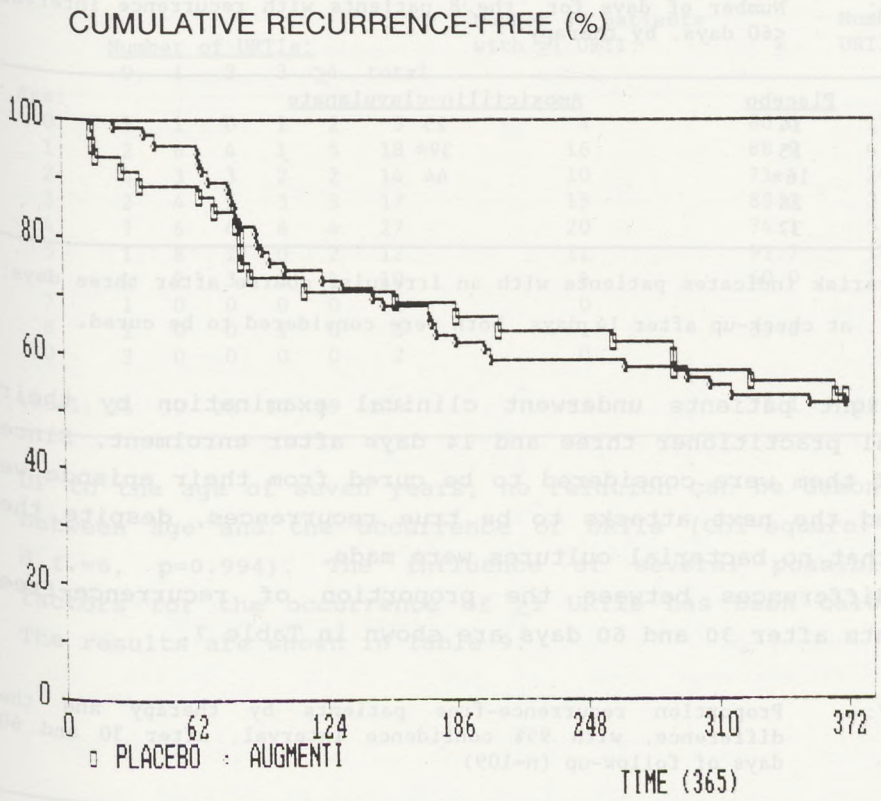

Figure 1

There was no statistical difference between the course of the two curves (Cox-Mantel [log-rank] statistic: 0.0071, d.f.=1, p=0.933; generalized Wilcoxon [Breslow] statistic: 0.0032, d.f.=1, p=0.955). Upon closer inspection, the figure suggests that in the group treated with placebo, recurrences happened earlier than in the group treated with amoxicillin-clavulanate. Table 6 shows the therapy and the exact number of days after which the recurrence took place in patients whose recur-

rence interval was less than 60 days.

Table 6: Number of days for the 8 patients with recurrence interval <60 days, by therapy

Placebo	Amoxicillin-clavulanate
14	25
15	39*
16*	44
28	
37	

The asterisk indicates patients with an irregular course after three days; however, at check-up after 14 days, both were considered to be cured.

All eight patients underwent clinical examination by their general practitioner three and 14 days after enrolment. Since all of them were considered to be cured from their episode we assumed the next attacks to be true recurrences, despite the fact that no bacterial cultures were made.
The differences between the proportion of recurrence-free patients after 30 and 60 days are shown in Table 7.

Table 7: Proportion recurrence-free patients by therapy and the difference, with 95% confidence interval, after 30 and 60 days of follow-up (n=109)

	Placebo:	Amox.-clav.:	difference:	95% C.I.:
after 30 days:	.909	.985	-.076	-.166, .015
after 60 days:	.886	.954	-.068	-.174, .034

So, even for the beginning of the follow-up period no statistically significant difference was found between the two treatment groups.

Upper respiratory tract infections

The total number of episodes of URTI in the 109 patients is 205. Of these 205 episodes, 78 included an acute otitis media and 127 were due to other URTIs. The age-related distribution of the episodes during the follow-up year is shown in Table 8.

Table 8: Number of patients and episodes of URTI during follow-up by age category (n=109)

Age:	Number of URTIs: 0	1	2	3	≥4	total	Number of patients with ≥1 URTI:	%	Number of URTIs:
0	1	1	0	1	2	5	4	80.0	15
1	2	6	4	1	5	18	16	88.9	43
2	4	3	3	2	2	14	10	71.4	24
3	2	4	5	3	3	17	15	88.2	37
4	7	6	4	6	4	27	20	74.1	53
5	1	8	1	0	2	12	11	91.7	18
6	4	2	3	0	1	10	6	60.0	12
7	1	0	0	0	0	1	0		0
8	2	0	0	1	0	3	1	33.3	3
10	2	0	0	0	0	2	0		0
total:	26	30	20	14	19	109	83	76.1	205

UP to the age of seven years, no relation can be demonstrated between age and the occurrence of URTIs (Chi-square: 0.732, d.f.=6, p=0.994). The influence of several possible risk factors for the occurrence of ≥1 URTIs has been calculated. The results are shown in Table 9.

Table 9: Number of patients with and without at least one URTI during follow-up, stratified for the presence of possible risk factors (n=109).

	No URTI: (n=26)	≥1 URTI: (n=83)	Chi-square p value:	Odds ratio:	95% C.I.:
Age category:					
< 2 years	3	20		2.43	0.66, 8.97
≥ 2 years	23	63	0.27		
Family size:					
siblings	23	62		0.39	0.11, 1.41
no siblings	3	21	0.23		
Laterality GP:*					
bilateral	9	34		1.49	0.59, 3.77
unilateral	17	43	0.53		
Laterality ENT:**					
bilateral	9	33		1.28	0.50, 3.28
unilateral	15	43	0.78		
Rank in family:					
not oldest	15	39		0.96	0.30, 2.73
oldest	8	23	0.96		
Therapy:					
placebo	12	32		0.73	0.30, 1.78
amox.-clav.	14	51	0.65		
Clinical course:					
irregular	1	14			
regular	25	69	Fisher's exact p=0.08		
Abnormal tympanogram after four weeks:***					
present	9	43		3.65	1.18, 11.5
absent	13	17	0.021		

* missing: 6
** missing: 9
*** missing: 27

Only the presence of an abnormal tympanogram four weeks after enrolment increased the risk of ≥1 URTIs during the next 11 months. These episodes of URTI included episodes of acute otitis media. A relation appeared to exist between the presence of an abnormal tympanogram and the occurrence of at least one acute otitis media during the follow-up period. Consequently we estimated the risk of occurrence of URTIs other than acute otitis media in the presence of an abnormal tympanogram four weeks after enrolment (Table 10).

Table 10: Number of patients, with number of URTIs other than AOM, by presence of abnormal tympanogram four weeks after enrolment.

	No URTI:	≥1 URTI:
Abn. tymp.:		
present	18	34
absent	16	14

Chi-square: p=0.15, odds ratio: 2.16 (95% C.I.: 0.78, 6.00)

This risk appeared not to be significantly higher than in children who did not have a persistently abnormal tympanogram after the recurrent acute otitis media exhibited at enrolment. Thus, in children with an abnormal tympanogram after four weeks, only the risk of developing at least one acute otitis medias during the year of follow-up was significantly higher.

Aspects of family medicine

Of the 109 patients in follow-up, 24 children had no brothers or sisters. It has been demonstrated that these patients are not at lower risk of developing either URTIs (odds ratio: 2.56, 95% C.I.: 0.71, 9.09) or, more specifically, acute otitis medias (odds ratio: 1.33, 95% C.I.: 0.53, 3.33) (Table 9 and 5, respectively). The other 85 patients belonged to families varying in size from two to six children:

family size:	2 children:	59 patients
	3 children:	18 "
	4 children:	5 "
	5 children:	2 "
	6 children:	1 "

Fifty-four patients of the 85 had at least one older sibling. Table 9 en 5 show that these children are not at higher risk of developing either URTIs (odds ratio: 0.96, 95% C.I.: 0.30, 2.73) or, more specifically, acute otitis medias (odds ratio: 0.50, 95% C.I.: 0.18, 1.33).

Table 11 shows the number of patients with or without recurrent acute otitis media, depending on whether URTIs occurred

during the year of follow-up in their siblings or not.

Table 11: Number of patients with or without at least one recurrent AOM, by siblings with or without URTIs

	No recurrence:	≥1 recurrence:	Total:
≥1 URTI in sibling(s):			
no	14	7 (33.3%)	21 (100%)
yes	31	33 (51.6%)	64 (100%)

Chi-square: p=0.23

Of patients who had siblings with ≥1 URTI, a higher percentage had a recurrent acute otitis media than those who had siblings without an URTI. Nonetheless, the difference of 18.2% is not statistically significant (95% C.I.: -5.4, 41.8).

DISCUSSION

We were able to obtain the follow-up data on 109 (90.1%) of the 121 children included in the clinical trial. A loss to follow-up of less than 10% is acceptable in this study. The reasons for loss (all but one moved away), are not causally related to any of the factors under study. The accuracy and validity of the data was improved, when the investigator compared the data entered on the study form with the patients records kept by the general practitioner. We recommend doing this when unstructured forms are used by participants who are not directly involved in running the study.

In our clinical trial, 799 persons were registered with an acute otitis media [13]. Of them, 684 were aged ≤ 12 years. Among these children, 185 (27%, 95% C.I.: 24, 30) had a recurrent acute otitis media. This episode was defined as an acute otitis media following a previous one after an interval of one month to one year [14]. In our trial population of children with a recurrent acute otitis media, 48.6% (95% C.I.: 39.2, 58.0) had another recurrence within one year. This increased risk of recurrence can be shown by calculating the incidence per year of the episodes of acute otitis media in our popula-

tion during the year of follow-up. This incidence is 71.6%. For the age category 0-14 years in the general population Lamberts found a year incidence of 13.5%, and Van de Velden describes an incidence of 13.6% [15,16]. We can conclude that once a child had a recurrence, the risk for another recurrence is increased. This finding is consistent with the literature [17]. This phenomenon is furthermore shown in our data by the more accurate estimation of the frequency of recurrence by means of the one-year cumulative incidence. The risk of a subsequent acute otitis media increases to 80% for the subpopulation with three recurrences. It is clear that whereas the incidences increase in the subgroups with a higher number of recurrences, the corresponding one-year cumulative incidences for the total population approach a fixed estimation. In our study population of children aged $\leq$ 12 years with at least one recurrence, this cumulative incidence of at least four consecutive recurrences during one year is 20.1%. Since our study population is 27.0% of the total population of children with acute otitis media, we can estimate the 'otitis-prone' group to be 5.4% (95% C.I.: 8.4, 2.9) of all children with acute otitis media.

This percentage compares to the 10.8% found by Alho et al. [5]. They attempted to specify the 'otitis-prone' condition in operational terms after a review of all criteria used earlier by other investigators. The criterion of $\geq$ four episodes within nine months and a 30-day cut-off point had the best fit. The fact that the percentage of 5.4% we found is lower can be explained by our decision to exclude the acute otitis media with which the patient was enrolled. If we do include this episode in the calculation, our percentage of the 'otitis-prone' group increases to 6.2%. Furthermore, Ahlo et al. concluded that onset of the first episode of acute otitis media early in life was only a weak predictor. The results of our study suggest that an abnormal tympanogram at four weeks after an acute otitis media can increase the prediction of the 'otitis-prone' condition in an individual.

The incidence rate we found, 0.697 recurrence per year, virtually equals the rate that Pukander et al. found in children younger than 10 years in Finland (0.71) [18], the rate that Bäckström-Järvinen et al. found before the age of 5 years (0.7) [19], and the rate of attacks in England per child-year before the age of 15, reported by Lowe et al. (0.9) [20].
Age is known to be an important risk factor for the occurrence of acute otitis media [21]. However, our data did not show such a relation with respect to recurrences during the first six years of life. This is in agreement with the results of the study by Kaleida et al. They show the absence of influence of age category upon new early recurrences, independent of the therapy given (amoxicillin, placebo, and/or myringotomy) [22]. Onion et al. did not observe a decreasing incidence of recurrences with age either [23]. The 'otitis-prone' condition seemed to be expressed more or less constantly under the age of seven years and only to lose its importance gradually.
Of the possible risk factors for recurrence, only the persistence of an abnormal tympanogram at four weeks after the previous episode was of prognostic value (odds ratio: 3.75). This finding is concordant with results of a study by Kaleida et al. in patients between three months and 12 years of age [24]. Effusion in the middle ear was measured at day 10. Sixteen of the 80 effusion-free children (20%) developed a recurrence within 90 days after entry, while 16 of the 47 patients with effusion (34%) did so.
These findings support the hypothesis that the 'otitis-prone' children have frequent recurrences in combination with or superimposed upon persistent middle-ear effusion.
An irregular clinical course of the acute otitis media at entry did not increase the risk of a subsequent recurrence (odds ratio: 2.37; 95% CI: 0.67, 8.73). Marchant et al. reported that recurrences happen independent of whether an antibiotic, prescribed for the preceding acute otitis media, eradiated the pathogenic bacteria [25].
If the previous acute otitis media was bilateral, the data

suggest that the risk of another recurrence is larger, but this relation is statistically only near to significance.
We found that antimicrobials given for the preceding episode of acute otitis media did not influence the possibility of occurrence of a new episode. Nor did it prolong the recurrence-free interval. Diamant et al. [26] argue that antimicrobial treatment interferes with the natural systemic and local immune response to bacterial infection, thereby predisposing children to recurrent infection. Yet our findings confirm more recently published studies [27,28,29]. Burke et al. conclude from their placebo-controlled study in children aged three to 10 years that recurrence rates of earache seem not to be influenced substantially by treatment [30]. Kaleida et al. also find no placebo-controlled effect of amoxicillin whether or not in combination with myringotomy on new recurrences [19].
Our data did not show a relation between age and the occurrence of URTI's up to the age of seven. There seemed to be a relation between a persistently abnormal tympanogram after the preceding acute otitis media and the occurrence of URTI, which is clinically not very plausible. However, when we excluded the URTI's related to the episodes of acute otitis media, this relation disappeared. Thus, it is mainly acute otitis media that is related to a persistent effusion in the middle ear. This supports the hypothesis that acute otitis media is caused under certain conditions, among which the abnormal local factor of a dysfunctioning eustachian tube causing effusion to persist. No other risk factors could be discrened in our study. Family size is known to be a risk factor of respiratory infections. However, the importance of this factor, as a component of the crowding factor, has decreased in the Netherlands, since large families are no longer common. On the other hand, it is more important to study the effect of daycare centres as an expression of the crowding factor, resulting in more respiratory and middle ear infections [31]. Antibiotics, given as therapy for the preceding acute otitis media, do not

prevent the child from developing an URTI later on. This is not surprising, since all of these infections start as a viral infection.
Aspects of family medicine seem to have become less important. This might be due to the diminishing significance of the family as an epidemiological unit in the Netherlands; families have become smaller, while the extra-familial social relations have gained in influence at a younger age.
The finding that URTIs in siblings does not significantly increase the risk of recurrence indicates that host factors are of more importance than exogenous factors in causing 'otitis-prone' condition.

CONCLUSIONS

In short, we can draw the following conclusions:

* The accuracy of research data may be improved by verification of the medical records by the investigator in person.
* The percentage of 'otitis-prone' children in the Netherlands is 5.4%, whereby 'otitis-prone' is defined as $\geq$4 episodes per year.
* Once a child has had a recurrent acute otitis media, the risk of new recurrences increases, independent of age.
* Of the investigated possible risk factors, only a persistently abnormal tympanogram measured four weeks after an episode of acute otitis media improves the prediction of an 'otitis-prone' condition, which was already assumped at the onset of the initial episode in the first year of life.
* Antibiotic therapy for an episode of recurrent acute otitis media does not prevent the occurrence of a new one. It neither diminished the number of recurrences in the next year nor postpones a subsequent recurrence.
* Because of the small family size now prevalent in the Netherlands and the altered social patterns of children, family size has become a weak measure of the crowding factor, as an influence on the risk of upper respiratory tract infections.
* Upper respiratory tract infections in siblings do not sig-

nificantly increase the risk of new recurrences of acute otitis media. Host factors seem to be of more importance to the 'otitis-prone' condition.

REFERENCES

1. Berman S, Murphy JR. Persistent and Recurrent Otitis Media. A review of the "Otitis-Prone" Condition. Primary Care 1984; Vol 11: 407-417.
2. Howie VM, Ploussard JH, Sloyer J. The "Otitis-Prone" Condition. Am J Dis Child 1975; 129: 676-678.
3. Harsten G, Prellner K, Heldrup J, Kalm O, Kornfalt F. Recurrent acute otitis media. Acta Otolaryngol 1989; 107: 111-119.
4. Lundgren K, Ingvarsson L. Epidemiology of acute otitis media in children. Scand J Infect Dis 1983; Suppl.39: 19-25.
5. Alho OP, Koivu M, Sorri M. What is an 'otitis-prone' child? Int J Pediatr Otorhinolaryngol 1991; 21: 201-209.
6. This thesis. Chapter V.
7. Rothman KJ. Modern Epidemiology. Boston/Toronto: Little, Brown and Company, 1986.
8. Morrison AS. Sequential pathogenic components of rates. Am J Epidemiol 1979; 109: 709-718.
9. Campos-Filho N, Franco EL. Microcomputer-assisted univariate survival data analysis using Kaplan-Meier life table estimators. Comp Meth Prog Biomed 1988; 27: 223-228.
10. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chem Rep 1966; 50: 163-170.
11. Cox DR. Regression models and life tables. J Roy Stat Soc 1972; 34: 187-220.
12. Breslow N. A generalized Kruskal-Wallis test for comparison K samples subject to unequal patterns of censorship; Biometrika 1970; 57: 579-594.
13. Appelman CLM, Claessen JQPJ, Hordijk GJ, Touw-Otten FWMM, Melker RA de. Efficacy of co-amoxiclav in recur-

rent acute otitis media: placebo controlled study. Br Med J 1991; 303: 1450-1452.

14. This thesis. Chapter V.

15. Lamberts H. In het huis van de huisarts. Verslag van het transitieproject. Lelystad: Meditekst; 1991: 175.

16. Van der Velden J. Basisrapport morbiditeit in de huisarts-praktijk. Nationale studie naar ziekten en verrichtingen in de huisartspraktijk. 1991.

17. Lidén M, Flodström A, Thore M. Treatment of early recurrences of acute purulent otitis media: value of myringotomy. Acta Otolaryngol 1988; 106: 441-447.

18. Pukander J, Karma P, Sipilä M. Occurrence and recurrence of acute otitis media among children. Acta Otolaryngol 1982; 94: 479-486.

19. Bäckström-Järvinen L, Tiisala R, Kantero RL, Hallman N. Illness among normal Finnish children during the first 5 years of life. Ann Paediatr Fenn 1966; 12: 13.

20. Lowe JF, Bamforth JS, Pracy R. Acute otitis media, One year in general practice. Lancet ii, 1129.

21. This thesis. Chapter V.

22. Kaleida PH, Casselbrant ML, Rockette HE, Paradise JL, Bluestone CD et al. Amoxicillin or Myringotomy or Both for Acute Otitis Media: Results of a Randomized Clinical Trial. Pediatrics; 1991: 87: 466-474.

23. Onion DK, Taylor C. The epidemiology of recurrent otitis media. Am J Public Health 1977; 67: 472-474.

24. Kaleida PH, Bluestone CD, Rockette HE, Bass LW, Wolfson JH et al. Amoxicillin-clavulanate potassium compared with cefaclor for acute otitis media in infants and children. The Pediatr Infect Dis J 1987; 6: 265-271.

25. Marchant CD, Shurin PA, Turcyzk CA, Feinstein JC, Johnson CE et al. A randomized controlled trial of cefaclor compared with trimethoprim-sulfamethoxazole for treatment of acute otitis media. The Journal of

Pediatrics 1984; 105: 633-638.

26. Diamant M, Diamant B. Abuse and timing of use of antibiotics in acute otitis media. Arch Otolaryngol Head Neck Surg 1974; 100: 226-232.

27. Buchem L van, Peeters MF, Hof MA van 't, Acute otitis media: a new treatment strategy. Br Med J 1985; 290: 1033-1037.

28. Mygind N, Meistrup-Larsen KI, Thomsen J, Thomsen VF, Josefsson K, Sorensen H. Penicillin in acute otitis media: a double-blind placebo-controlled trial. Clin Otolaryngol 1981; 6: 5-13.

29. Buchem FL van, Dunk JHM, Hof MA van 't. Therapy of acute otitis media: myringotomy, antibiotics or neither? The Lancet 1981; ii: 883-887.

30. Burke P, Bain J, Robinson D, Dunleavy J. Acute red ear in children: controlled trial of non-antibiotic treatment in general practice. Br Med J 1991; 303: 558-562.

31. Strangert K. Infections in young children attending day-care centres. 1976 Dissertation. Karolinska Institutet.

Chapter IX

A ONE-YEAR-LONG FOLLOW-UP STUDY

on referral of trial patients to an otolaryngologist, therapy, and possible predictive factors for referral

G.P.J. Claessen, C.L.M. Appelman, R.A. de Melker, F.W.M.N. Hoes-Otten, G.J. Hordijk.

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27. Buchem L van, Peeters BF, Hof MA ven 't, Acute otitis media: a new treatment strategy. Br Med J 1985; 290: 1033-1037.

28. Mygind N, Melstrup-Larsen KI, Thomsen J, Thomsen VF, Josefsson K, Sorensen H. Penicillin in acute otitis media: a double-blind placebo-controlled trial. Clin Otolaryngol 1981; 6: 5-13.

29. Buchem FL van, Dunk JHM, Hof MA van 't. Therapy of acute otitis media: myringotomy, antibiotics or neither? The Lancet 1981; ii: 883-887.

30. Burke P, Bain J, Robinson D, Dunleavy J. Acute red ear in children: controlled trial of non-antibiotic treatment in general practice. Br Med J 1991; 303: 558-562.

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INTRODUCTION

Management and prevention of recurrent acute otitis media and its sequelae is subject to ongoing debate. The first part of this chapter briefly reviews pathophysiological mechanisms of recurrent acute otitis media and otitis media with effusion, as well as the treatment strategies currently advocated. The second part analyses data from the long-term follow-up of the trial patients on referral to an otolaryngologist. This analysis seeks to identify possible predictive factors distinguishing these children. Finally, the therapy in this population is specified and discussed.

A REVIEW OF THE PATHOPHYSIOLOGY OF RECURRENT ACUTE OTITIS MEDIA AND OTITIS MEDIA WITH EFFUSION AND CURRENTLY ADVOCATED TREATMENT REGIMENS

Pathophysiology

A history of acute otitis media is an important risk factor for the development of otitis media with effusion. Many cases of otitis media with effusion can be considered a sequela of acute otitis media [1-4]. Yet, according to other investigators, otitis media with effusion is premorbid when it follows acute otitis media [5,6]. Also, a residual effusion can become reinfected; children may alternate between acute otitis media and otitis media with effusion without clearing their effusion [7]. Upper respiratory tract infections (URTIs) are strongly interrelated with acute otitis media, recurrent acute otitis media and otitis media with effusion, although simultaneous occurrence is by no means obligatory [8-11]. Recovery from an upper respiratory tract infection may occur even when the otitis media with effusion is not cured [9].

Dysfunction of the eustachian tube plays a crucial role in the etiology of recurrent acute otitis media and otitis media with effusion [12-14]. Stenstrøm et al. showed that there is no difference in the degree of eustachian tube dysfunction

between children with recurrent acute otitis media alone or those with otitis media with effusion in between recurrent acute otitis media episodes [12].

The adenoids play an important role in the pathophysiology of eustachian tube dysfunction [8,15,16]. This dysfunction is primarily based on obstruction, which may be mechanical and/or functional [21]. In the mechanical concept of dysfunction of the eustachian tube, the size and position of the adenoids causing extrinsic obstruction may be of importance. Yet research has shown that adenoid size, assessed by lateral skull radiographs, in children with otitis media with effusion, was equal to that of controls [16,18]. The palatal airway size seemed to be a more important factor, as it is significantly smaller in children with otitis media with effusion than in normal controls [16,19]. Functional impairment of the clearance function of the eustachian tube may be a more likely cause of otitis media with effusion than direct organic obstruction [14].

This intrinsic obstruction is mostly the result of inflammation [17]. A role of the adenoid bed, primarily as a source of infection causing eustachian tube malfunction may be plausible. But research has shown that this is by no means sufficient as the sole explanation, and much is still unclear [15]. Eustachian tube dysfunction is caused by a combination of factors, of which the adenoids may be part. Various other mechanisms, of which many are still poorly understood, for instance local or systemic immune factors, seem to affect in the development of recurrent acute otitis media and otitis media with effusion [20,21].

Adenoidectomy has been shown to improve the active tubal function, irrespective of adenoid size [22]. However, other investigators could not detect any improvement in passive or active function of the eustachian tube following adenoidectomy, illustrating that further research is warranted [23]. Active tubal function is the muscular opening function that actively equilibrates the static pressure differences. The

passive tubal function is the decrease in pressure required to force the tube open and the residual overpressure when the tube closes again [13].
The size-independent improvement after adenoidectomy was confirmed in clinical trials. These trials demonstrated that the beneficiary effect of adenoidectomy on the clearance of otitis media with effusion was not related to adenoid size [24-26].

Introduction to current management
Many different non-surgical and surgical treatment strategies are advocated for recurrent acute otitis media and otitis media with effusion. These include antibiotic treatment, antibiotic prophylaxis, systemic or local decongestants, antimicrobial vaccines, adenoidectomy, sinus wash-out, and the placement of tympanostomy tubes.
A comprehensive treatment regimen for recurrent acute otitis media can hardly be given, due to the multifactorial character of the disease. In general, it is relevant to determine whether recurrent acute otitis media episodes resolve completely after each episode, or if otitis media with effusion persists following the recurrent acute otitis media episode [27,28].
An estimate of the proportion of these two categories is difficult to make. Although several studies have focused on the persistence of otitis media with effusion after an episode of acute otitis media, little knowledge exists of the proportions of children suffering from recurrent acute otitis media with and those without persisting otitis media with effusion. Stenstrøm et al. comparing eustachian tube function in healthy and otitis-prone children. They selected 50 otitis-prone children with at least 11 episodes of acute otitis media. In this group, 18 (36%) children had a history without otitis media with effusion between the acute otitis media episodes, as compared to 32 (64%) with otitis media with effusion in between acute otitis media episodes [13]. These proportions

were not controlled for the influence of various variables as interval between acute otitis media recurrencies, or age. As 11 previous acute otitis media episodes were a prerequisite, probably a very high risk group was selected. It is therefore haphazard to conclude that the majority of patients with recurrent acute otitis media have otitis media with effusion in between attacks. Further research addressing this question is needed.

Management in recurrent acute otitis media without otitis media with effusion between attacks; Non-surgical treatment

Before reviewing this management option, it is essential to point out the differences existing internationally in treatment advocated for a first episode of acute otitis media. In the USA and Scandinavia, antibiotic treatment is advocated regardless of whether it is a first acute otitis media or a recurrence [29,30], whereas in the Netherlands episode an attitude of watchfull waiting is advocated for a first episode [31,32]. These recommendations are reflected in current daily practice [33].

In patients with completely resolving episodes, each subsequent acute otitis media attack can be treated as a new one, with the basic assumption that every episode is treated with an antibiotic [27,29]. The same authors advocate a more aggressive attitude and prophylaxis with antibiotics when the frequency of these recurrencies, all having been treated actively with a course of antibiotics, exceeds three episodes in six months or four episodes in 12 months; and in children younger than six months with two episodes in the preceding three months [27,34]. Only a limited number of studies are reported on the efficacy of chemoprophylaxis with antibiotics in reducing the number of recurrent attacks. But in all of these studies a decrease in the incidence of attacks of acute otitis media was claimed [35-38]. The antibiotics used were ampicillin[35], sulfisoxazole[36] and sulfamethoxazole[37,38].

At present, clinical studies have not established a positive effect of systemic or local decongestive therapy with antihistamines or decongestant nose drops in preventing recurrent acute otitis media [39].

Finally, immunoprophylaxis constitutes a special treatment option in those patients whose recurrent acute otitis media is caused by Streptococcus pneumoniae and the acute otitis media associated serotypes. However, so far the efficacy of immunoprophylaxis in reducing recurrent attacks has been limited [40-42]. Only those infections caused by serotypes present in the vaccine were reduced. Furthermore, in children younger than two years, the results were relatively poor. This latter finding was most likely due to an insufficient immune response at this young age [42]. Recently, immunoprophylaxis has been considered for recurrent acute otitis media caused by Haemophilus influenzae type b [44].

However, as illustrated earlier in Chapter III, in the vast majority of acute otitis media attacks caused by Haemophilus influenzae a non-typable non-capsular Haemophilus species is cultured, which makes immunoprophylaxis of very limited value.

Surgical treatment

Another treatment option in patients who have recurrent acute otitis media without residual effusion is the placement of tympanostomy tubes. Prospective studies monitoring the effect of tube placement in this particular disease entity are sparse; only one study was found [45]. In this study a beneficiary effect was clearly established.

Especially for children in whom recurrent acute otitis media attacks are frequently accompanied by URTIs, adenoidectomy alone or in combination with tonsillectomy or sinus wash-outs may be rational. Again, clinical evidence from prospective studies that such a beneficial effect on the frequency of recurrent acute otitis media exists is sparse. In this respect, we must take in account that surgical studies almost invariably lack distinction between patients with persisting otitis media with effusion and those with complete clearance.

Consequently the otitis media with effusion may cause considerable bias on outcome with reference to the effect on recurrent acute otitis media itself.

Management in recurrent acute otitis media with persisting otitis media with effusion between attacks

As previously indicated, the second group of patients with recurrent acute otitis media to be distinguished are those whose effusion persists between the acute otitis media episodes. Management in these patients does not essentially differ from management in otitis media with effusion, and focuses more closely on the clearance of this effusion. The non-surgical and surgical treatment options above apply to this group as well.

Epidemiological studies show that otitis media with effusion is a self-limiting disease in the majority of cases [46-48]. Therefore it is justified to adopt an attitude of watchful waiting when confronted with a first otitis media with effusion. However, in cases of otitis media with effusion persisting between recurrent acute otitis media episodes, a more aggressive treatment may be required.

Non-surgical treatment

Results from placebo-controlled studies show a beneficial effect of antibiotic treatment, albeit a temporary one [49-51]. Others also report a temporary clearance of effusion following antibiotic treatment [52]. Cantekin et al. could not detect a true difference in persistence of effusion after a two-week course of amoxicillin compared with a placebo [53].

To date we have no conclusive evidence from placebo-controlled studies that antibiotic treatment has a long-lasting beneficial effect on the resolution of otitis media with effusion. A number of recently reported well-conducted studies fail to show a positive effect of systemic decongestants and antihistamines or topical decongestants in the treatment of otitis media with effusion [54-57].

Surgical treatment

The insertion of tympanostomy tubes is the most common treatment for persistent otitis media with effusion. Since Armstrong reintroduced the concept suggested earlier by Politzer this surgical treatment has found widespread application [58]. Prospective studies have dealt with the possible benificial effect of adenoidectomy in the treatment of otitis media with effusion. A few earlier studies did not report a positive influence on the middle ear function [59-62]. Lately, however evidence is increasing that adenoidectomy has a benificial effect on recurrent acute otitis media and otitis media with effusion [63-67].

Inquiries among clinicians on treatment in recurrent acute otitis media and otitis media with effusion

Having reviewed current opinions on the management of recurrent acute otitis media with or without otitis media with effusion, we were interested in whether everyday clinical practice reflects these opinions, especially with respect to the treatment carried out by otolaryngologists.

In a recent review of management in otitis media with effusion, Smith and Maw illustrate that many different treatment strategies exist and that the degree of agreement between otolaryngologists is only moderate [68].

Nevertheless, adenoidectomy accompanied by myringotomy with or without ventilating tubes was carried out by a major proportion of the respondents (45.5% of the consulted ENT surgeons) [68]. Another inquiry among otolaryngologists, paediatricians and general practitioners showed a positive effect of adenoidectomy in decreasing the number of episodes of recurrent acute otitis media and URTI in general [69].

These inquiries, along with the conclusions reached in a number of recent prospective studies on surgical management in recurrent acute otitis media and otitis media with effusion, allow us to draw the following conclusions. Adenoidectomy, with or without the placement of tympanostomy tubes, now seems

to be the most important basic treatment modality in the management of recurrent acute otitis media and otitis media with effusion. The revaluation of adenoidectomy as part of the treatment seems to firmly grounded in pathophysiological aspects of recurrent acute otitis media and otitis media with effusion, although many questions remain unanswered and more research is needed. Adenoidectomy seems to be of special value in those patients were otitis media with effusion persists after recurrent acute otitis media.

A ONE-YEAR-LONG FOLLOW-UP STUDY ON REFERRAL OF TRIAL PATIENTS TO AN OTOLARYNGOLOGIST, THERAPY, AND POSSIBLE PREDICTIVE FACTORS FOR REFERRAL

Introduction

As discussed in Chapter VII, a large proportion of the trial population had persisting middle ear effusion and/or high negative pressure (HNP), one month after an episode of recurrent acute otitis media.

Chapter VIII showed that persistence of otitis media with effusion/HNP increased the risk of a new acute otitis media episode, again demonstrating the close link between these disease entities.

We were interested in the children referred as out-patients to an otolaryngologist during the follow-up year. Specifically we sought predictive factors distinguishing these children from those who were not referred. Also, we investigated the therapy given by the specialist to compare it to the treatment currently advocated.

Methods

For the follow-up, the general practitioners' study form was screened, on which referral and subsequent treatment should have been indicated. This information was supplemented by data obtained at the final tympanometric assessment of middle ear

function at the end of the follow-up, one year after entry into the study. We also had access to the patient records of the majority of the otolaryngologic practices to which the patients were referred. The total number of patients referred was established and the treatment after referral was recorded.
We investigated any differences between referred and non-referred patients with respect to age at entry in years, as well as in the age-groups <2 years and ≥2 years. We also checked differences in other variables sex, clinical course of the recurrent acute otitis media episode, therapy for this episode, season of acute otitis media onset, laterality of the acute otitis media episode and tympanometry outcome after one month. Furthermore, for a part of our study population we compared and analysed the tympanometry data after one month and one-year. Only those patients were analysed for whom this outcome assessment took place in the same season and with a delay of maximally three months. We then investigated whether previous treatment by an otolaryngologist was related to referral as well as to therapy after referral in the follow-up year.
Finally, we looked for a difference between referred and non-referred patients in the average number of URTIs in general (with and without recurrent acute otitis media) in the follow-up year, as noted in the general practitioner's record, as well as of recurrent acute otitis media episodes alone.
Age in years upon referral was analysed for all referred patients. All further analyses referral or subsequent treatment were done only for patients seen by the otolaryngologist as compared to the non-referred children; we left out the children visiting a pediatrician. The tympanometry groups formed were identical to those described in Chapter VII, using the modified Jerger criteria.
The results of audiometry were not analysed because the total number of audiograms, was too small due to the fact that most children were younger than four years.

Statistics

The results were analysed with the Chi-square test, Fisher's exact test, or Kruskal-Wallis one-way analysis of variance when appropriate. In addition, multivariate logistic regression was used in the search for possible risk factors. The weight of a potential risk factor was calculated by odds ratios with 95% confidence intervals. For comparison of tympanometry outcome between the one-year and the one-month follow-up, the McNemar test of symmetry was used. The difference between referred and non-referred patients in URTIs and racute otitis media episodes in the follow-up year was analysed, assuming a Poisson distribution with over dispersion and using GLIM 3.77, update 1 (1985).

Results

The data on seven out of 121 trial patients was unclear about whether referral had taken place or not. The distribution of sex, therapy, clinical course, and season for these seven was equal to that in the rest of the population. Age was not of influence, ranging from one to nine years. The characteristics of the seven patients which left us unclear about possible referral did not differ for the risk factors screened and can therefor be ruled out as a confounding factor. For the final one-year follow-up visit, 86 patients (71%, n=121) could be retrieved. By the final one-year follow-up meeting, 35 patients had been lost. In 20 of these patients this was due to refusal of the parents to revisit the hospital; in all 20 cases this was because they had lost interest in the study. The parents of the other 15 lost patients did not respond to telephone calls or repeated written appeals; some had moved away.

The comparison of tympanometry outcome after one month and one year left out four patients that had not shown up at the one-month follow-up visit. Furthermore, we chose to analyse only those patients whose one-year follow-up met our criteria: less than three months delay; and taking place in the same season

as the one month follow-up visit, because of the earlier finding of a significant influence of season on tympanometry outcome (Chapter VII). Then 53 patients were left. When comparing referred and non-referred groups, one patient was dropped because it was unclear whether that child had been referred. Another child was dropped because of referral to a pediatrician. This left 51 patients in the analysis.
Of the 114 patients for whom referral was indicated, 72(63.2%) were not referred; 38 (33.3%) were referred to an otolaryngologist and four (3.5%) were sent to a paediatrician (Table 1).

Table 1: Number of patients referred (n=121)

Non-referred	:	72
Referred	:	42
Otolaryngologist	:	38
Paediatrician	:	4
Lost to follow-up	:	7

The treatment by the otolaryngologists was recorded. In 25 patients an adenoidectomy was part of the surgical treatment, and in seven patients tympanostomy tubes were placed(Table 2).

Table 2: Treatment in children referred to otolaryngologist (n=38)

Adenoidectomy (A)	5
Myringotomy ADS (M)	1
Tonsillectomy (TE)	0
Tympanostomy Tubes (TT)	3
Inferior meatal antrostomy (IMA)	1
A + M	9
A + TE	2
A + TT	4
A + TE + M	5
A + TE + TT	0
TE + M	0
TE + TT	0
Medical management	2
Unknown	6
Total of adenoidectomies	25

We found a significant difference in age between referral groups (p=0.02, Table 3). This finding was attributable to the fact that the four patients referred to the paediatrician were significantly younger at entry. Two children were under one year at entry, one child was a year old and one child was four years of age. For these patients, no subsequent referral to an otolaryngologist took place in the follow-up year.

Table 3: Mean age (SD) of non-referred and referred patients (n=114)

	Mean age	SD
Patients not-referred	3.79 years	2.13
Patients referred to otolaryngologist	3.08 years	1.73
Patients referred to paediatrician	1.25 years	1.89

Kruskal-Wallis: p=0.02

Age, dichotomized as younger than 2 years and 2 years and older, not related to referral to an otolaryngologist nor were sex, and

Table 4: Non-referred and referred patients according to age category, sex and laterality* of the recurrent AOM (n=110, *:n=103)

	<2 yr	≥2 yr	Male	Female	Unil	Bil
Non-referred:	12	60	40	32	45	24
Referred:	9	29	18	20	17	17
Fisher's exact:	p=0.45		p=0.43		p=0.20	

unil = unilateral
bil = bilateral

Season, outcome of the recurrent acute otitis media episode after three days and therapy for the episode were not related to referral to an otolaryngologist either (not shown in Table 4). Tympanometry outcome after one month showed a significant difference between the referred and non-referred groups, in univariate analysis (p=0.0004, Table 5).

Table 5: Non-referred and referred patients according to tympanometry outcome at one month follow-up (n=86)

Tympanometry	Normal	Intermed.	Abnormal
Non-referred:	22	15	16
Referred:	7	2	24

Chi-square: p=0.0004
Odds ratio abnormal + normal intermediate: 6.2 (95% C.I. 2.3, 16.2) p=0.00002

Patients with bilateral middle ear dysfunction as indicated by a bilaterally abnormal tympanogram showing effusion (otitis media with effusion) and/or high negative pressure (HNP), were highly represented in the referred group. For this dysfunction 86 patients could be analysed, due to the fact that five patients in the referred group and 19 in the non-referred

group had not shown up at the one month follow-up. Also, the four patients referred to the pediatrician were left out.
We established the value of an abnormal bilateral tympanogram for predicting referral in terms of the odds ratios. This showed that a child in the abnormal tympanogram group had from two to 16 times more chance of referral to an otolaryngologist in the follow-up year (odds ratio 6.2, 95% C.I.: 2.3, 16.2, Table 5).
In multivariate logistic regression analysis, with referral as the dependent variable, tympanometry outcome was also the only significant risk factor.
Tympanometry outcome at one-year follow-up was analysed for a possible influence of age, sex, season, therapy, laterality and clinical course of the recurrent acute otitis media. Age in mean years at entry was of significant influence, with a preponderance of younger children in the abnormal tympanogram group after one-year (Kruskal-Wallis, p=0.03, Table 6).

Table 6: Mean age at entry of tympanometry groups after one-year (n=57)

	Mean age	SD
Tympanometry group		
Normal :	4.81 yr	SD: 2.46
Intermediate :	3.23 yr	SD: 1.30
Abnormal :	3.08 yr	SD: 1.89
Kruskal-Wallis: p=0.03		

Boys showed significantly more persisting middle ear dysfunction after one-year (p=0.005, Table 7).

Table 7: Distribution of season and sex over tympanometry groups at one-year follow-up (n=57)

	Male	Female	Summer	Winter
Tympanometry group				
Normal :	13	18	12	19
Intermediate :	5	8	2	11
Abnormal :	12	1	1	12
Chi-square (Pearson):	p=0.005			p=0.06

Season was of no significant influence on tympanometry at one-year follow-up, although there was a trend toward abnormal bilateral tympanograms after entry in winter (p=0.06, Table 7). The remaining factors were equally distributed over the tympanometry groups (not shown in tables).
Tympanometry outcome at the one-year follow-up point was compared with that at the one-month check-up visit. Overall, a tendency for improvement of the middle ear status was present (McNemar's test of symmetry, 0.01<p<0.025, Table 8).

Table 8: Tympanometry distribution compared between one month and one-year follow-up (n=53)

Tympanometry One month :	Normal	Intermed.	Abnormal
One-year :			
Normal :	14	7	7
Intermediate :	2	4	6
Abnormal :	1	1	11

McNemar's test of symmetry: 0.01<p<0.025

When we condensed this into the categories 'normal + intermediate' against 'abnormal', the significance of improvement reached p=0.007 (Table 9).

Table 9: Tympanometry distribution compared between one month and one-year follow-up.two groups: normal+intermediate and abnormal (n=53)

Tympanometry group month:	Normal+intermed.	Abnormal	Total one year
Tympanometry group year :			
Normal+intermed. :	27	13	40
Abnormal :	2	11	13
Total one month :	29	24	

McNemar's test of symmetry: p=0.007

The non-referred group showed no significant difference (p=0.688), whereas the tendency to improve was significant in the referred group (p=0.008, Tables 10 and 11 resp.).

Table 10: Tympanometry distribution compared between one-month and one-year follow-up, non-referred patients (n=34)

Tympanometry group month:	Normal+intermed.	Abnormal	Total one year
Tympanometry group year :			
Normal+Intermed. :	23	4	27
Abnormal :	2	5	7
Total one month :	25	9	

McNemar's test of symmetry: p=0.688

Table 11: Tympanometry distribution compared between one month and one-year follow-up, referred patients (n=17)

Tympanometry group month:	Normal+intermed.	Abnormal	Total one year
Tympanometry group year :			
Normal+Intermediate :	3	8	11
Abnormal :	0	6	6
Total one month :	3	14	

McNemar's test of symmetry: p=0.008

Furthermore, the otolaryngologist-referred and non-referred groups were compared regarding therapy before and after referral.

To analyse whether previous adenoidectomy was related to referral, data for three of the non-referred children did not clarify if earlier adenoidectomy had taken place or not. In the remaining 107 patients, no significant relationship existed between referral and previous adenoidectomy (p=0.29, Table 12).

Table 12: Previous adenoidectomy as possible factor for referral to otolaryngologist (n=107)

	No adenoidectomy	Adenoidectomy
Not referred:	59	10
Referred:	29	9

Fisher's exact: p=0.29 N.S.

Also, previous tonsillectomy (missing data: 7) or tympanostomy tube insertion (missing data: 9) showed no significant relationship to referral (p=0.55 and p>0.99 respectively, not in table). The surgical therapy in the follow-up year (adenoidectomy, tympanostomy tube insertion, tonsillectomy) was not

significantly related to previous surgical therapy (not in table).

For the referred patients no significant influence of sex, season, age (dichotomized as <2 years and ≥2 years, or age in years) was present between the group treated with an adenoidectomy and the group not receiving adenoidectomy (not in table).

Analysis to detect an influence of type of therapy on tympanometry outcome was impossible because of the small numbers in the respective cells.

Finally, we compared the 72 non-referred patients with the 38 patients who consulted the otolaryngologist in the follow-up year. We were looking for a difference in the average number of URTIs in general (i.e. with or without recurrent acute otitis media episodes), and/or recurrent acute otitis media episodes for which the general practitioner was consulted. We found a significant difference in the average number of URTIs in the follow-up between referred and non-referred patients: 1.42 in the referred and 0.97 in the non-referred group ($0.025<p<0.05$). This showed that the referred group had 1.5 times more URTIs than the non-referred group (95% C.I.: 1.0, 2.1, Table 13).

Table 13: Distribution of average number of upper respiratory tract infections (URTIs) and recurrent AOM episodes (rAOM) over non-referred and otolaryngologist-referred groups (n=110)

	Average no. URTIs*	Average no. rAOM**
Non-referred:	0.97	0.47
Referred:	1.42	0.95

*: $0.025<p<0.05$.
1.5 more URTIs in the referred group, 95% C.I.: 1.0, 2.1

**: $0.001<p<0.01$.
2 times more rAOM in the referred group, 95% C.I: 1.3, 3.2

In the referred group, an average of 0.95 recurrences were presented to the general practitioner, compared to 0.47 in the non-referred group ($0.001<p<0.01$). This showed that 2.0 times more recurrent acute otitis media episodes were registered by the general practitioner than in the non-referred group (95 % C.I. 1.3, 3.2, Table 13).

Discussion

Due to the nature of the follow-up, which was entirely retrospective and dependent on the data noted in the patients' records, we were not able to consistently detect the exact diagnosis on referral. In the majority of the cases, the diagnosis was not reliably indicated on the patients 'charts', nor on these hospital out-patient records to which we had access.

For various reasons we do not consider this to be an important drawback. Firstly, we are certain of the reason for referral in all referred patients: a recurrent acute otitis media, persisting otitis media with effusion or a combination of the two, either alone or along with a recurrent URTI. This much was clear from the charts and was also confirmed in retrospect, as the number of URTIs and acute otitis media recurrences was significantly more frequent in the referred patients.

As pointed out in the introduction to this chapter, these disease entities are closely interrelated as far as their etiology is concerned. Furthermore, the treatment options are multiple and occur in many combinations. Thirdly, our main question was whether predictive factors already existed upon of consultation for a recurrent acute otitis media and after one month distinguishing those children to be referred in a later stage.

Our finding that the children referred to the paediatrician were significantly younger is not surprising. When the medical condition of very young children necessitates referral, it is best to refer to a paediatrician for a broad evaluation of their health.

We can offer no opinion on whether the total number of patients referred to an otolaryngologist was high. The reason is that no data exists on referral in a comparable patient population. One may be inclined to conclude that the proportion (33.3%) of the patients referred is high and that this illustrates the high-risk character of our trial population. However one must consider the effect of the previous admission of this patient group in to the trial. This may form an incentive for the general practitioner to refer the child more quickly than ohterwise likely.

The fact that only tympanometry is predictive for referral is consistent with the findings on the general practioner follow-up dealing with acute otitis media recurrences (Chapter VIII). The general practitioner was ignorant of the tympanometry-results after one month, and therefore was not influenced by them. So far this cannot be compared with the findings of other investigators as no comparable study has been carried out yet.

At the one-year follow-up, sex and age at entry were significantly related to tympanometry outcome after one-year, in accordance with the general knowledge on risk factors for otitis media with effusion. Season showed a trend toward abnormals in winter. At this point in time the effect of a previous recent acute otitis media has ebbed and the natural risk factors again become more important. Of course, since the numbers are small, these findings must be interpreted cautiously. A similar attitude is necessary regarding the apparent general improvement of the middle ear status at one-year follow-up, which also seemed positively related to referral.

Again, numbers were far to small to take this as strong evidence for benefit from referral to an otolaryngologist. Looking back at treatment given a high number of adenoidectomies was performed, with relatively few insertions of tympanostomy tubes. This trend is not explained by the fact that treatment history showed that a majority of these children were not treated earlier by an otolaryngologist, nor did they undergo

prior surgery.
Dutch otolaryngologists are trained to consider the general status of the upper respiratory tract in a child with recurrent acute otitis media and/or otitis media with effusion, since these disease entities are closely related to upper respiratory tract infections in general. An infected and/or obstructive adenoid is considered to be very important in this respect, which probably explains the high number of adenoidectomies in the study population. This is in accordance with current opinion and daily practice, as we pointed out in the first part of this chapter.
The second striking fact was the relatively low number of tympanostomy tube insertions in the study population (only seven) during the follow-up year. This reflects a reluctance to place tympanostomy tubes at the beginning of surgical treatment in children with recurrent acute otitis media and/or otitis media with effusion. When the decision on surgery is made, Dutch otolaryngologists apparently prefer to wait fo beneficial effect of adenoidectomy alone, or of the combination with myringotomy, as we have seen in nine of the patients. Currently, knowledge is amassing that tympanostomy tubes may also have a detrimental effect on the middle ear, leading to scarring and tympanosclerosis [70]. In that light, the reluctance to insert these tubes seems a sensible approach
In conclusion, we can state that the high predictive value of the tympanometry outcome one month after a recurrent acute otitis media for referral, justifies a re-evalution after a recurrent acute otitis media after one month in order to perform tympanometry. The apparent high predictive value of bilateral middle-ear dysfunction for a new acute otitis media recurrency (Chapter VIII), also supports this recommendation. Results indicate that tympanometry is highly predictive even at this early follow-up stage. Nevertheless we advise another re-evaluation after a few weeks. The design of our study did not permit a more accurate monotoring between the one-month and the one-year follow-up visit. It is possible that a few

more children will have improved, thus not requiring referral. According, the check-up visit should be with a doctor equipped with a tympanometer. Keeping in mind that the truly 'otitis-prone' group is only a minority of the population (Chapter VIII) and that the sequence may have detrimental effects on language development [71,72] and middle ear status [73,74], we do not consider this advice to put an unjustified burden on health care.

Our study does not allow us to draw conclusions on therapy advised in cases with recurrent acute otitis media and/or persisting otitis media with effusion. Current treatment regimens in the Netherlands seem to conform to general knowledge on the pathophysiology of the disease entities subject to treatment.

REFERENCES

1. Schutte PK, Beales DL, Dalton R. Secretory otitis media a retrospective general practice survey. J Laryngol Otol 1981; 95: 17-22.
2. Shurin PA, Pelton SI, Donner A, Klein JO. Persistence of middle-ear effusion after AOM in children. N Engl J Med 1979; 300: 1121-1123.
3. Cauwenberge P van. Secretory Otitis Media. An Epidemiological, Clinical and Experimental Study (Thesis) 1988 University of Ghent.
4. Ishidoya M, Takasaka T, Shimizu H. Risk factors for otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 1-3.
5. Leth N, Tos M. Middle-ear ventilation after acute otitis media. ORL 1977; 39: 278-284.
6. Tos M. Etiologic factors in secretory otitis. Arch Otolaryngol 1979; 105: 582-588.
7. Berman S, Murphy JR. Persistent and recurrent otitis media. A review of the 'otitis-prone' condition. Primary Care 1984; 11(3): 407-417.
8. Cauwenberge P van. Derycke A. The relationship between nasal and middle-ear pathology. Acta Oto-Rhino-Laryng. Belg. 1983; 37 (6): 830-840.
9. Otten FWA, Grote JJ. Otitis media with effusion and chronic upper respiratory tract infection in children: A randomised, placebo-controlled clinical study. Laryngoscope 1990; 100: 627-633.
10. Grote JJ, Kuijpers W. Middle ear effusion and sinusitis. J Laryngol Otol 1980; 94: 177-183.
11. Tos M, Poulsen G, Borch J. Etiologic factors in secretory otitis. Arch Otolaryngol 1979; 105: 582-588.

12. Bluestone CD, Klein JO. Physiology, pathophysiology and pathogenesis. In: Bluestone CD, Klein JO, eds. Otitis Media in Infants and children. Philadelphia: W.B. Saunders Company, 1988: 15.
13. Stenstrφm C, Bylander-Groth A, Ingvarsson L. Eustachian tube function in otitis-prone and healthy children. Int J Ped Otorhinolaryngol 1991; 21: 127-138.
14. Takahashi H, Hayashi M, Sato H, Honjo I. Primary deficits in Eustachian tube function in patients with otitis media with effusion. Arch Otolaryngol Head Neck Surg 1989; 115: 581-584.
15. Osborne JE, Telford D, Barr G, Roberts C. Adenoid infection: its relationship to otitis media, glue ear and tonsillitis. Clin Otolaryngol 1987; 12: 261-264.
16. Phillips DE, Maw AR, Harvey K. The nasopharynx and adenoid in children with glue ear compared with normal controls. Clin Otolaryngol 1987; 12: 255-260.
17. Bluestone CD, Klein JO. Physiology, pathophysiology and pathogenesis. In: Bluestone CD, Klein JO, eds. Otitis Media in Infants and children. Philadelphia: W.B. Saunders Company, 1988: 21.
18. Hibbert J, Stell PM. The role of enlarged adenoids in the aetiology of glue ear. Clin Otolaryngol 1982; 7: 256.
19. Maw AR, Smith IM, Lance GN. Morphology of the nasopharynx in children with otitis media with effusion: a comparison with age and sex matched normal controls. Abstract of the Fifth International Symposium Recent Advances in Otitis Media. Ft. Lauderdale, Florida; May 20-24, 1991; pg 61.
20. Bernstein JM, Tomasi TB, Ogra P. The immunochemistry of middle ear effusions. Arch Otolaryngol 1974; 99:320-326.

21. Pelton SI, Teele DW, Reimer CB et al. Immunologic characteristics of children with frequent recurrencies of otitis media. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 144-146.

22. Bylander-Groth A, Jessen M. Eustachian tube function before and after adenoidectomy. In: Sadé J, ed. Basic Aspects of the eustachian tube and middle ear diseases, Proceedings of a Conference on the Eustachian Tube and Middle Ear Diseases, Geneva, Switzerland. Amstelveen: Kugler & Ghedini, 1991: 205-208.

23. Honjo I, Tashima K, Mitoma JT, Hamada E. Effect of adenoidectomy on Eustachian tube function. Auris Nasus Larynx (Tokyo) 1991; 12/1 (Suppl): 231-233.

24. Gates GA, Avery CA, Cooper JC, Prihod TJ: Chronic secretory otitis media: Effects of surgical management. Ann Otol Rhinol Laryngol 1989; 138 (Suppl 98): 1-25.

25. Bluestone CD, Cantekin EI, Beery QC: Certain effects of adenoidectomy on Eustachian tube ventilatory function. Laryngoscope 1975; 85: 113-127.

26. Maw AR. Chronic otitis media with effusion (glue ear) and adenotonsillectomy: a prospective randomised controlled study. Br Med J 1983; 287: 1586-1588.

27. Pelton SI, Whitley P. Otitis media: current concepts in diagnosis and management. Pediatr Ann 1983; 12(3): 207-218.

28. Bluestone CD, Klein JO. Management. In: Bluestone CD, Klein JO, eds. Otitis Media in Infants and children. Philadelphia: W.B. Saunders Company, 1988: 125-128.

29. Bluestone CD, Klein JO. Management. In: Bluestone CD, Klein JO, eds. Otitis media in infants and children. Philadelphia: W B Saunders Company, 1988: 127.

30. Karma P, Palva T, Kouvalainen K et al. Finnish approach to the treatment of acute otitis media. Report of the Finnish Consensus Conference. Ann Otol Rhinol Laryngol 1987; 96 Suppl 129: 1-19.
31. Hordijk GJ. Otitis media acuta; verslag van een consensus bijeenkomst. Ned Tijdschr Geneeskd 1992; 136: 85-88.
32. Otitis media acuta, standaard M09. Huisarts Wet 1990; 33 (6): 242-245.
33. Froom J, Culpepper L, Grob P et al. Diagnosis and antibiotic treatment of AOM: Report from international Primary Care Network. Br Med J 1990; 300: 582-586.
34. Bluestone CD, Klein JO. Management. In: Bluestone CD, Klein JO, eds. Otitis Media in Infants and children. Philadelphia: W.B. Saunders Company, 1988: 165.
35. Maynard JE, Fleshman JK, Tshopp CF. Otitis media in Alaskan Eskimo children: a prospective evaluation of chemoprophylaxis. JAMA 1972; 219: 597-599.
36. Perrin JM, Charney E, MacWhinney JB Jr, Miller TK. Sulfisoxazole as chemoprophylaxis for recurrent otitis media: a double blind crossover study in pediatric practice. N Engl J Med 1974; 291: 664-667.
37. Schwartz RH, Puglese J, Rodriguez WJ. Sulfamethoxazole prophylaxis in the otitis-prone child. Arch Dis Child 1982; 57: 590-593.
38. Schuller DE. Prophylaxis of otitis media in asthmatic children. Pediatr Infect Dis 1983; 2: 280-283.
39. Bluestone CD, Klein JO. Management. In: Bluestone CD, Klein JO, eds. Otitis Media in Infants and children. Philadelphia: W.B. Saunders Company, 1988: 126.
40. Teele DW, Klein JO. Use of pneumococcal vaccine for prevention of recurrent AOM in infants in Boston. Rev Infect Dis 1981; 3 (Suppl): 113-118.
41. Sloyer JL Jr, Ploussard JH, Howie VM. Efficacy of pneumococcal polysaccharide vaccine in preventing acute otitis media in infants in Huntsville, Alabama. Rev Infect Dis 1981; 3 (Suppl): 119-123.

42. Mäkelä PH, Leinonen M, Pukander J, Karma P. A study of the pneumococcal vaccine in prevention of clinically acute attacks of recurrent otitis media. Rev Infect Dis 1981; 3(Suppl): 124-130.
43. Douglas RM, Paton JC, Duncan SJ, Hansman. Antibody response to pneumococcal vaccination in children younger than five years of age. J Infect Dis 1983; 148: 131-137.
44. Bluestone CD, Klein JO. Management. In: Bluestone CD, Klein JO, eds. Otitis Media in Infants and children. Philadelphia: W.B. Saunders Company, 1988: 194.
45. Gebhart DE. Tympanostomy tubes in the otitis-prone child. Laryngoscope 1981; 91: 849-866.
46. Tos M, Holm-Jensen S, Sφrensen CH. Spontaneous course and frequency of secretory otitis in 4 year old children. Arch Otolaryngol 1982; 108: 4-10.
47. Lieberman A, Bartal N. Untreated persistent middle ear effusion. J Laryngol Otol 1986; 100: 875-878.
48. Buckley G, Hinton A. Otitis media with effusion in children shows a progressive resolution with time. Clin Otolaryngol 1991; 16: 354-357.
49. Thomsen J, Sederberg-Olsen J, Balle V, Vejlsgaard R, Stangerup SE, Bondesson G. Antibiotic treatment of children with secretory otitis media. Arch Otolaryngol Head Neck Surg 1989; 115: 447-451.
50. Schloss MD, Dempsey EE, Rishikof E, Sorger S, Grace MG. Double-blind study comparing erythromycin-sulfisoxazole (pediazole) T.I.D. to placebo in chronic otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, Nelson JD, eds. Recent Advances in Otitis Media. Proceedings of the Fourth International Symposium. Toronto: BC Decker, 1988: 261-263.
51. Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ. Efficacy of amoxicillin with and without decongestant-antihistamine for otitis media with effusion in children: Results of a double-blind, randomised trial. N Engl J Med 1987; 316: 432-437.

52. Chan KH, Mandel EM, Rockette HE, Bluestone CD et al. A comparative study of amoxicillin-clavulanate and amoxicillin. Arch Otolaryngol Head Neck Surg 1988; 114: 142--146.
53. Cantekin EI, McGuire TW, Hughson TL. Antimicrobial therapy for otitis media with effusion ("Secretory" otitis media). Otolaryngol Head Neck Surg 1987; 97 (spec issue): 182.
54. Olson AL, Klein SW, Charney et al. Prevention and therapy of serous otitis media by oral decongestant: a double-blind study in pediatric practice. Pediatrics 1978; 61: 679-684.
55. Sorri M, Sipilä, Palva A, Karma P. Can secretory otitis media be prevented by oral decongestants? Acta Otolaryngol 1982 ; Suppl 386: 115-116.
56. Lildholdt T, Cantekin EI, Bluestone CD, Rockette HE. Effect of a topical nasal decongestant on Eustachian tube function in children with tympanostomy tubes. Acta Otolaryngol 1982; 94: 93-97.
57. Cantekin EI, Mandel EM, Bluestone CD et al. Lack of efficacy of a decongestant-antihistamine combination for otitis media with effusion ("secretory" otitis media) N Engl J Med 1983; 308: 297-301.
58. Armstrong BW. A new treatment for chronic secretory otitis media. Arch Otolaryngol 1954; 69: 653.
59. Rynnel-Dagoo B, Ahlborn A, Schiratzki H. Effects of adenoidectomy: a controlled two-year follow-up. Ann Otology 1978; 87: 272-278.
60. Fiellau-Nikolajsen M, Falbe-Hamsen J, Knudstrup P. Adenoidectomy for middle ear disorders: a randomised controlled trial. Clin Otolaryngol 1980; 5: 323-327.
61. Roydhouse N. Adenoidectomy for otitis media with mucoid effusion. Ann Otol Rhinol Laryngol 1980; 89 (suppl 68): 312-315.

62. Black N, Crowther J, Freeland A. The effectiveness of adenoidectomy in the treatment of glue ear: a randomized controlled trial. Clin Otolaryngol 1986; 11 : 149-155.

63. Maw AR, Herod F. Otoscopic, impedance, and audiometric findings in glue ear treated by adenoidectomy and tonsillectomy. Lancet 1986; ii; 1399-1402.

64. Gates GA, Avery CA, Prihoda TJ, Cooper JC. Effectiveness of adenoidectomy and tympanostomy tubes in the treatment of chronic otitis media with effusion. N Engl J Med 1987; 317: 1444-1451.

65. Maw AR, Parker A Surgery of the tonsils and adenoids in relation to secretory otitis media in children. Acta Otolaryngol 1988; Suppl. 454: 202-207.

66. Austin DF. Adenoidectomy for secretory otitis media. Arch Otolaryngol Head Neck Surg 1989; 115: 936-939.

67. Paradise JL, Bluestone CD, Rogers KD et al. Efficacy of adenoidectomy for recurrent otitis media in children previously treated with tympanostomy-tube placement. Results of parallel randomised and nonrandomised trial. JAMA 1990; 263-(15): 2066-2073.

68. Smith IM, Maw AR. Secretory otitis media: a review of management by Consultant Otolaryngologists. Clin Otolaryngol 1991; 16: 266-270.

69. Novak VJ, Müller W. Einfluss der Adenotomie auf die Frequenz von Otitis Media und rhinogenem Infekt. Otorhinolaryngol Nova 1991; 1: 194-196.

70. Skinner DW, Lesser TH, Richards SH. A 15 year follow-up of a controlled trial of the use of grommets in glue ear. Clin Otolaryngol 1988; 13: 341-346.

71. Van den Broek P, Rach GH, Zielhuis GA. Is otitis media met effusie schadelijk voor de taalontwikkeling van jonge kinderen? Ned Tijdschr v Geneeskd 1988;132:1885-1888.

72. Rach GH, Zielhuis GA, Van den Broek P. The influence of chronic persistent otitis media with effusion on language development of 2 to 4 year olds. Int J Pediatr Otorhinolaryngol 1988; 15: 253-261.

73. Smyth GDL. Middle ear effusions. A consideration of factors involved in their etiology, maintenance and treatment. Clin Otolaryngol 1978; 52: 583-589.

74. Tos M. Sequelae of secretory otitis media and the relationship to chronic suppurative otitis media. Ann Otol Rhinol Laryngol 1990; Suppl 146: 18-19.

Chapter X

GENERAL DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

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73. Smyth GDL. Middle ear effusions. A consideration of factors involved in their etiology, maintenance and treatment. Clin Otolaryngol 1978; 3:571-588.

74. Tos M. Sequelae of secretory otitis media and the relationship to chronic suppurative otitis media. Ann Otol Rhinol Laryngol 1990; Suppl 146: 18-19.

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INTRODUCTION

This thesis is the result of an attempt to answer the question, how to treat an episode of acute otitis media in otherwise healthy children? Taking account of scientific results and contemporary socio-cultural standards in the Dutch population, physicians in the Netherlands do not immediately prescribe antibiotics in children two years or older. This attitude of watchful waiting is usually sufficient to enable the child to recover from an episode through its natural factors of resistance. However, a small percentage of all patients need antibiotics because of an irregular course after three days. We wondered if the physician could be helped to identify this subpopulation at the onset of the disease. Moreover, we were interested to know if antibiotics can improve the course of the acute otitis media in the subpopulation older than six months. For these reasons, we conducted a randomized placebo-controlled clinical trial.

In this chapter we shall discuss several aspects of acute otitis media, especially in patients at a higher risk for recurrence and an abnormal clinical course. The aspects that will be considered are definitions of the disease, pathogenesis, epidemiology, diagnosis, natural clinical course, medical management, and surveillance. The objectives of our thesis have already been described in the previous chapters. This chapter will offer a synthesis of our findings and describe the current 'state of the art'. We will draw some conclusions and, at the end, offer some guidelines for daily practice, as concretely and completely as possible.

DEFINITIONS

Several definitions are used to describe acute otitis media (Chapter II). Many of them attempt to do so in a non-clinical way; for instance as an acute inflammatory process of the

epithelium and mucoperiost of the middle ear, which comprises the eustachian tube, the tympanic cavity, and the cells of the mastoid. Definitions that use clinical terms are often loose and differ one from another. The most commonly used definition nowadays in the Netherlands is: an infection of the middle ear with an acute onset and a duration of no longer than three weeks, characterized by an abnormal tympanic membrane, with or without earache, fever, perforation of the eardrum, and signs of general illness. In this definition the presence of an effusion in the middle ear is not included, contrary to the definitions used in North America, Britain and Scandinavia. The clear clinical distinction between acute otitis media and otitis media with effusion consists of the acute ear-related symptoms, but they are often used inconsistently. Otherwise these two entities are closely interrelated in many ways that still are not fully understood.

PATHOGENESIS

Acute otitis media is considered to be a nosologic entity by many physicians. This implies that acute otitis media is regarded as a disease in itself, with its own specific pathogenesis and pathophysiology, its own characteristic clinical signs and symptoms, and a known natural course and prognosis. However, it can be questioned if acute otitis media fulfils these criteria. The illness occurs with a high frequency and is perceived to be rather harmless and self-limiting. Yet the many unanswered questions may give reason to consider acute otitis media as a syndrome instead. Furthermore, acute otitis media is mostly not a disease in itself. It often appears as a sequela or as an expansion, posing as a clinical entity, of an upper respiratory tract infection of viral nature, such as a common cold. Acute otitis media is known to be accompanied or preceded by clinical manifestations of such an infection in the vast majority of cases.
The viral infection induces alterations in the eustachian

tube, causing its dysfunction, as well as in the middle ear itself, enabling the development of an infectious inflammation. One might assume that in the remaining cases a viral infection of the upper respiratory tract has been present as well, though without clinical manifestations. We consider this type of otitis media as a 'normal' acute otitis media, which occurs in most children once in their lifetime.

On the other hand, one might postulate that for a small group, partly due to host factors, local resistance at the level of the middle ear itself is low as a result of previous infections. This induces the possibility that an acute otitis media can also occur without any preceding viral infection in the upper respiratory tract. There are also indications that systemic immunologic factors play a role, although much in this field is still poorly understood. The low incidence of acute otitis media in children aged younger than six months may, for instance, be explained by the fact that these children are still protected by maternal immunologic serum factors.

This last form of acute otitis media is probably very similar to the one that occurs in 'otitis-prone' children. This may partly explain the higher risk of an irregular clinical course, the high percentage of middle ear dysfunction after the episode, and the higher recurrence rate. Although a sharp distinction between these two types of acute otitis media cannot be made, this differentiation in clinical terms might be useful with regard to medical management.

More detailed knowledge is needed on regarding the onset of the first episode in life. This is likely to take place earlier in 'otitis-prone' children than in the overall population. Although acute otitis media is generally understood as a local inflammatory process of infectious origin, this cannot be verified by bacterial cultures of middle ear aspirates in all cases (Chapter III). In about 70% of the cultures, growth of bacterial micro-organisms could be assessed. In more recent studies, 84% to 93% of the cultures revealed bacterial growth,

confirming the important role of bacteria in the disease process.

EPIDEMIOLOGY

In our study, 788 episodes with acute otitis media were registered. Of these, 684 were aged ≤12 years. Among these children, 185 (27%) had a recurrent acute otitis media, defined as an episode of acute otitis media after the previous one within a period ranging from four weeks to one year.
During the follow-up year, a number of patients developed one or more recurrent attacks. We were able to calculate the percentage of children with ≥4 recurrences during one year (20.1%). The percentage of this group of children is calculated as follows: 0.27 multiplied by 0.201 is 5.4% of the total population. We regard this subpopulation to be the 'otitis-prone' group (Chapter VIII).
The only independent risk factor of the factors we investigated, was the presence of a bilaterally abnormal tympanogram one month after the episode of a recurrent acute otitis media. This relation was independent of age, up to the age of seven years. An episode of acute otitis media in the first year of life has also been described as a risk factor for the 'otitis-prone' condition. We have not been able to assess whether the date of occurrence of the first episode in life is a risk factor, since the validity of this information was influenced too much by recall bias. Further research is recommended to assess the joint predictive value of these two risk factors in order to identify the 'otitis-prone' child as early in life as possible.
In our study, in which all children had a recurrent acute otitis media, the persistence of bilateral middle ear dysfunction appeared to be independent of age. New recurrences also appeared to be independent of age. We conclude that the condition 'otitis-prone' is independent of age in the studied children. This condition is unlike the vulnerability to acute

otitis media in general, which is known to be high, especially in younger children, and to decrease with age. An explanation for the difference between these two categories might be found in differing local anatomical relations and/or in differing immunological response to infectious diseases.

DIAGNOSIS

The assessment of the mobility of the eardrum is not a prerequisite to establish the diagnosis of acute otitis media in the Netherlands. We questioned if the validity of the diagnostic procedure, including history taking, physical examination and otoscopy, is sufficient. In the literature, it has been shown that none of the signs and symptoms used for diagnosis have a very high sensitivity and specificity in itself. However, our study results show that, once the diagnosis was made by the general practitioner, it was done in an appropriate way according to the otolaryngologist. Nevertheless, further study is recommended in order to estimate the additional value of the assessment of the mobility of the tympanic membrane in the diagnostic process for acute otitis media.
Otoscopy is an essential diagnostic procedure in acute otitis media. Yet further subclassification of the otoscopic findings in stages of severity is of no additional value in predicting the clinical course of the disease. Nor is it of value in taking a decision with regard to medical management.

NATURAL CLINICAL COURSE

We assume that local decongestant nose drops and analgesics do not influence the infectious process itself. Furthermore, we could not find any indications to the contrary in the literature. Therefore, we consider the clinical course in the placebo group to be similar to the natural course of a recurrent acute otitis media. The clinical course of a recurrent acute otitis media differs in many ways from the course in a first

acute otitis media. The percentage of patients who still have fever and/or earache after three days is higher (Chapter V). For the category of patients with a recurrence, the proportion of irregular clinical courses is higher in children younger than two years. Furthermore, persistent effusion at four weeks after the onset of the episode is still present in a higher percentage of children with a recurrence, as compared to data in literature of children with a first acute otitis media (Chapter VII). In our study population, the persistence of effusion is only dependent on the season: it occurs in the winter more than in the summer. Finally, the rate of subsequent recurrences in children who already have a recurrent acute otitis media is higher than in children with a first attack (Chapter VIII). This rate is independent of age.

MEDICAL MANAGEMENT

In the Netherlands, physicians have adopted an attitude of watchful waiting for acute otitis media in children of two years and older. This stance is based on findings in one of the very few placebo-controlled studies of this disease. We wondered whether such an attitude is also justified in a population considered at risk for acute otitis media, being children with a recent previous history of acute otitis media, and more specifically, children in the age group six months to two years.

In our study the prescribed antibiotic did not improve the natural clinical course in children of two years and older. Nor did the antibiotic reduce the proportion of patients with a persistent effusion. We have not found a decrease in the recurrence rate. We conclude, that an attitude of watchful waiting is also justified in children older than two years with a recurrent acute otitis media. In children with a recurrent acute otitis media, aged six months to two years, the efficacy of the antibiotic was only near significance. Nonetheless we advise a course of antibiotics. Moreover, we do so,

in view of the clinical relevance of the high percentage of irregular courses in both treatment groups. And we uphold this recommendation despite the fact that the antibiotic did not diminish either the risk of persistent effusion or the risk of subsequent recurrences in this age category.

FOLLOW-UP

Children with a recurrent acute otitis media should revisit their doctor one month after onset of the acute phase of the disease to establish their middle ear status by tympanometry. The outcome of this assessment contributes to the identification of those patients who have an 'otitis-prone' condition. They are at higher risk of persistent effusion, and thus of hearing and speech disorders, and of subsequent recurrences. These patients should be carefully monitored because this subpopulation is truly at risk of further otolaryngology-related problems. As this group of children is only a minority of the total population, and in view of the possible detrimental effects on language development and middle ear condition, we do not consider this advice to entail an unjustified burden on the health care system.

According to our study, the possibility that a child will be referred by the general practitioner to the otolaryngologist during the year of follow-up was independent of the therapy for the acute otitis media given at enrolment. On the other hand, the chance of being referred was related to the middle ear status one month after enrolment. This indicates that the subpopulation with a persistently abnormal tympanogram is at risk for acute otitis media and its sequelae.

Overall, the middle ear status at the one-year end point showed some improvement compared to the middle ear status after one month, especially in the children who had been referred to the otolaryngologist.

In conclusion, with regard to medical management of acute otitis media we recommend the following treatment protocol:

	First episode since one year	Recurrent episode since one year
6 months to 2 years	no antibiotic unless irregular course after 3 days analgesic decongestants	antibiotic analgesic decongestants
≥2 years	no antibiotic, unless irregular course after 3 days analgesic local decongestants	no antibiotic, unless irregular course after 3 days analgesic local decongestants

Contrary to the other recommendations, the recommendation for children between six months and two years with a first episode is not based on results of research.
In a recurrent acute otitis media in children between six months to two years the difference in efficacy between an antibiotic and placebo is only near significance but clinically relevant. In view of this finding, we expect that initial antibiotic treatment in a first episode of acute otitis media is probably not indicated.
However further investigation of these children is necessary.

With regard to the monitoring of a patient with an acute otitis media, we recommend re-examining the patient after three days in order to assess the clinical recovery. We also advise re-examining the patient with a recurrent acute otitis media after one month in order to assess the middle ear status.

In the latter examination, the physician fulfils his task to assess the 'otitis-prone' condition of a child by finding:

* an episode of acute otitis media during the first year of life,
  and/or
* an abnormal tympanogram one month after a recurrent episode of acute otitis media.

6 months to 2 years	no antibiotic unless irregular course after 3 days analgesic decongestants	antibiotic analgesic decongestants
2-12 years	no antibiotic, unless irregular course after 3 days analgesic local decongestants	no antibiotic, unless irregular course after 3 days analgesic local decongestants

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SUMMARY

Acute otitis media is a common disease in children. In the Netherlands an incidence of approximately 20 patients per 1000 persons is reported, of which 80% is 12 years old or younger. In the age category zero to four years 200 episodes of acute otitis media occur per 1000 children.

Most of the episodes will heal without complications. In otherwise healthy children an attitude of watchful waiting and treatment with analgesics and local decongestants generally suffices. In the majority of children earache and/or fever will have disappeared within three days and initial prescription of antibiotics is not indicated.

At present the advice for the Dutch situation is to start antibiotic treatment only when the course of the disease has not improved after three days in otherwise healthy children.

In the Netherlands sofar no study existed on the clinical course of acute otitis media in children six months to two years and thus scientific grounds on which management can be based are lacking. Also, it is necessary to investigate whether the children with persistent earache and/or fever after three days, or a subgroup within these patients, benefit from initial treatment with antibiotics.

Due to a greater number of recurrent bouts of the disease, a subpopulation of the children suffering from an episode of acute otitis media must be considered 'otitis-prone'. A first episode of acute otitis media within the first year of life is associated with this condition.

However, this predictive factor lacks sufficient specificity and sensitivity.

Whether these children benefit from initial antibiotic treatment of a recurrent episode of acute otitis media is not scientifically proved. There are differences in management internationally. In the Netherlands an attitude of 'watchful waiting' is customary, whereas the opinion internationally is in favour of initial antibiotic treatment.

In spite of the apparent differences in management there is little variation in the clinical course of the disease in the respective countries.
The controversies and unanswered questions on management of acute otitis media illustrate the incessant need for more well-conducted clinical trials. Therefore, a double-blind placebo controlled clinical trial was carried out to adress the objectives of this thesis.
The natural course of recurrent acute otitis media and the efficacy of amoxicillin-clavulanate in a population of children from six months to two years of age. Also, the inter-observer reliability between general practitioners and otolaryngologists in diagnosis and otoscopic classification of acute otitis media was assessed, as well as the value of otoscopic findings as a predictor of the clinical course.
The persistence of middle ear dysfunction one month after an episode of recurrent acute otitis media and its possible predictive factors were established. The long-term clinical course with respect to renewed recurrences of acute otitis media, persistence of middle ear effusion and upper respiratory tract infections as well as their possible therapy during a one-year follow-up was investigated.

In Chapter II the study methods of the clinical trial are motivated and described.
To elucidate the design of the study, epidemiology and the criteria for diagnosis of acute otitis media are reviewed.

In Chapter III the current state of knowledge on microbiological aspects of acute otitis media is reviewed.

In Chapter IV a critical review of 50 clinical trials is given concerning treatment in acute otitis media. These trials, conducted between 1965 and 1989, illustrate how current controversies in management can exist in spite of the apparent multitude of studies. Only four clinical trials were placebo-

controlled and also of otherwise good methodological design.

In Chapter V the results of our clinical trial are presented and discussed. Children with a recurrent episode of acute otitis media were at higher risk for an irregular course. The age category six months to two years was a prognostic factor for an irregular course of the disease (adjusted odds ratio: 5.9).
Initial therapy with amoxicillin-clavulanate did not significantly improve the clinical course of the disease in children of two to 12 years of age. For children of six months to two years suffering from a recurrent episode of acute otitis media we recommend initial treatment with an antibiotic.

In Chapter VI the inter-observer reliability of otoscopic examination as diagnostic procedure is estimated. In children of two years and older the agreement on otoscopic features between the general practitioner and the otolaryngologist is good (Kendall's Tau B: 0.66).
The severity of middle ear inflammation assessed by otoscopy does not enhance the prediction of the clinical course, nor provide support in decision making concerning antimicrobial therapy.

In Chapter VII the persistence of middle ear dysfunction one month after a recurrent acute otitis media and its predictive factors are studied. This was done in view of the possible detrimental effects on language acquisition and its role in the development of chronic otitis media. Bilateral middle ear dysfunction was present in 47.9% of the children.
Only season showed a statistically signicant influence on the persistence of middle ear dysfunction, with a preponderance in the winter.

In Chapter VIII data of a one-year follow-up study in family practice are given, analysed and discussed.

The group of 'otitis-prone' children (defined as four or more episodes per year) is 5.4% of all children. With every new recurrence within one year the chance for a new recurrence increases, independent of age. The persistence of middle ear dysfunction after a recurrent episode of acute otitis media is a risk factor for a next recurrence.
Treatment with amoxicillin-clavulanate does not postpone the next recurrence, nor the total amount of recurrences in the follow-up year.
The occurrence of upper respiratory tract infections in other children of the same family as the child entered in the study, has no elation with next recurrences in trial patients. Host factors seem of more importance for the presence of the 'otitis-prone' condition.

In Chapter IX pathophysiology of recurrent acute otitis media and otitis media with effusion and treatment options currently advocated are reviewed.
In the second part, data of one-year follow-up with respect to possible referral and specialist therapy are given, analysed and discussed. Children with persistent middle ear dysfunction one month after a recurrent episode of acute otitis media are at greater risk for referral to an otolaryngologist.

In Chapter X conclusions are drawn and recommendations are given based on the findings in the preceding chapters.

With regard to the medical management of acute otitis media, the following treatment protocol is recommended:

	first OMA	recurrent OMA
<2 years	analgesic and local decongestant no antibiotic, unless after 3 days irregular course	antibiotic analgesic and local decongestant
≥2 years	analgesic local decongestant fever or earache after 3 days: antibiotic	analgesic local decongestant fever or earache after 3 days: antibiotic

With regard to the monitoring of a patient with an acute otitis media, we recommend re-examining the patient after three days in order to assess the clinical recovery. we also advice re-examining the patient with a recurrent acute otitis media after one month in order to assess the middle ear status.

In the latter examination, the physician fulfils his task to assess the 'otitis-prone' condition of a child by finding:

* an episode of acute otitis media during the first year of life,

and/or

* an abnormal tympanogram one month after a recurrent episode of acute otitis media.

SAMENVATTING

Otitis media acuta, acute middenoorontsteking, is vooral op de kinderleeftijd een veel voorkomende aandoening. Recente registraties tonen in Nederland een incidentie van ongeveer 20 episoden per jaar per 1000 personen. In de leeftijdsklasse van nul tot vier jaar komen in Nederland per 1000 kinderen per jaar ongeveer 200 episoden van otitis media acuta voor. Van alle gevallen van otitis media acuta doet zich ongeveer 80% voor onder de leeftijd van 12 jaar.
Onder gunstige levensomstandigheden en bij een overigens goede gezondheid van de patiënt heeft een acute otitis media in de meeste gevallen (95% van de twee tot 12-jarigen) bij een behandeling met neusdruppels en pijnstillers en zonder antibiotica een goedaardig ofwel regulier beloop, d.w.z. een klinisch herstel (geen oorpijn en of koorts meer) binnen drie dagen en zonder het optreden van complicaties. Volgens de huidige beleidsadviezen in Nederland wordt bij gezonde kinderen in deze leeftijdsklasse pas bij een irregulier beloop, d.w.z. geen klinisch herstel na drie dagen, een antibioticum voorgeschreven.
Hoe dit beloop bij kinderen van zes maanden tot twee jaar is, is in Nederland nog niet eerder onderzocht. Derhalve is voor deze kinderen nog geen wetenschappelijk gefundeerd behandelingsadvies voorhanden.
Bovendien is het van belang te weten of de kinderen met een irregulier beloop vóóraf te onderscheiden zijn van de grote groep kinderen met een regulier beloop. De vraag dringt zich op of de patiëntjes met een irregulier beloop, of een subgroep hiervan, baat zullen hebben bij het direct gebruik van een antibioticum.
Het is bekend dat zich in de populatie kinderen met een otitis media acuta een subgroep onderscheidt, die gekenmerkt wordt door een hoge mate van recidiveren van de aandoening. Kinderen uit deze subgroep worden 'otitis-prone' genoemd en deze conditie is gerelateerd aan het optreden van de eerste episode

van otitis media acuta in het eerste levensjaar. Dit voorspellende kenmerk is echter te weinig specifiek en sensitief. Het is nog niet eerder wetenschappelijk vastgesteld of mogelijk deze 'otitis-prone' kinderen voordeel hebben bij een direct toedienen van een antibioticum.
Internationaal bestaan er grote verschillen in de initiële behandeling van otitis media acuta. Met name in Nederland is al jaren een gecontroleerd afwachtende houding gebruikelijk. Ondanks de gebleken verschillen in beleid is er geen duidelijk verschil in beloop van de aandoening in de verschillende landen geconstateerd.

Er zijn derhalve nog vele controversen en een aantal onbeantwoorde vragen betreffende de behandeling van otitis mdeia acuta. Om die reden is een placebo-gecontroleerde clinical trial uitgevoerd ter beantwoording van deze vragen.
Wat is het klinisch beloop van een recidief otitis media acuta in een populatie overigens gezonde kinderen in de leeftijd van zes maanden tot 12 jaar en wat is de invloed van een behandeling met amoxicilline-clavulaanzuur op het klinisch beloop na drie dagen, het persisteren van effusie en het optreden van een volgend recidief? Tevens werd de interwaarnemerovereenkomst tussen huisarts en KNO-arts bepaald met betrekking tot het stellen van de diagnose otitis media acuta en de otoscopische classificatie naar ernst in stadia. De voorspellende waarde van deze classificatie voor het klinisch beloop werd eveneens bepaald. Het persisteren van een middenoordysfunctie één maand na het instellen van de therapie en mogelijke risicofactoren daarvoor werd bepaald. Het lange termijn beloop, en de invloed hierop van amoxicilline-clavulaanzuur, met aandacht voor nieuw optredende recidieven, overige bovenste luchtweginfecties en persisterende middenoordysfunctie werd onderzocht.

In hoofdstuk II wordt de methodologie van de clinical trial en het onderzoeksprotocol beschreven. Er wordt een overzicht verstrekt van de huidige wetenschappelijke kennis met betrek-

king tot de epidemiologie van de aandoening alsook van de criteria voor de diagnostiek van otitis media acuta.

In hoofdstuk III wordt een literatuuroverzicht gegeven van de microbiologie van otitis media acuta.

In hoofdstuk IV wordt een overzicht gegeven van de 50 engelstalige clinical trials, die getraceerd zijn als gepubliceerde verslagen tussen 1965 en 1989. De studies werden beoordeeld op hun kwaliteit en de validiteit en generaliseerbaarheid van hun resultaten. Dit geschiedde aan de hand van punten, gerelateerd aan studieopzet en -uitvoering in het algemeen, en de aandoening otitis media acuta in het bijzonder. Slechts vier clinical trials bleken zowel placebo-gecontroleerd te zijn, als de toets der kritiek te kunnen weerstaan.

In hoofdstuk V wordt de clinical trial beschreven. Bij een gecontroleerd afwachtende houding en het voorschrijven van analgetica en lokale decongestiva, hebben kinderen met een recidief otitis media acuta een hogere kans op een irregulier beloop dan kinderen met een primaire otitis media acuta. Het behoren tot de leeftijdscategorie zes maanden tot twee jaar is een prognostische factor voor een irregulair beloop (adjusted odds ratio: 5,9).
Het klinisch beloop na drie dagen van een recidief otitis media acuta bij kinderen in de leeftijdscategorie van twee tot 12 jaar wordt niet significant verbeterd door het initieel voorschrijven van amoxicilline-clavulaanzuur. Voor kinderen van zes maanden tot twee jaar oud met een recidief otitis media acuta wordt geconcludeerd dat het beter is om direct een antibioticum voor te schrijven.

In hoofdstuk VI wordt de relatie beschreven tussen de ernst van het otoscopisch ontstekingsbeeld enerzijds en het klinisch beloop na drie dagen anderzijds. De overeenstemming in otoscopische beoordeling van een ontstoken trommelvlies tussen

huisarts en KNO-arts is goed bij kinderen ouder dan twee jaar (Kendall's Tau B: 0,66), en matig bij kinderen tussen zes maanden en twee jaar (Kendall's Tau B: 0,57). De mate van ernst van het otoscopisch ontstekingsbeeld blijkt geen voorspellende waarde te hebben voor het klinisch beloop na drie dagen. De relatie bestaat evenmin na stratificatie voor leeftijdscategorie, voor de aan- of afwezigheid van koorts of voor de therapie. Geconcludeerd wordt dat een stagering van het otoscopisch ontstekingsbeeld geen klinische betekenis heeft.

Gelet op het belang van een goede middenoorfunctie voor de taal- en spraakontwikkeling bij jonge kinderen is het persisteren van effusie na een recidief otitis media acuta bestudeerd. De resultaten worden in hoofdstuk VII weergegeven. Na één maand blijkt nog bij 47,9% van de kinderen een bilaterale middenoordysfunctie te bestaan. Dit percentage is hoger dan bij kinderen met een primaire otitis media acuta. Leeftijd, geslacht, één- of dubbelzijdigheid van de recidief otitis media acuta, antibiotische therapie en het klinisch beloop na drie dagen hebben hierop geen invloed. Alleen het gegeven dat een episode zich in de winter voordoet, blijkt de kans op een middenoordysfunctie te vergroten (p=0,001).

In hoofdstuk VIII worden de gegevens beschreven van het jaar follow-up in de eerstelijn. Hieruit blijkt het percentage 'otitis-prone' kinderen (gedefinieerd als vier of meer episoden per jaar) in Nederland 5,4% van alle kinderen te bedragen. Bij iedere keer dat een kind binnen een jaar een recidief otitis media acuta krijgt, neemt de kans op het krijgen van een volgend recidief toe. Dit fenomeen is onafhankelijk van de leeftijd van het kind.
Het persisteren van een middenoordysfunctie na een recidief otitis media acuta blijkt een risicofactor voor het optreden van een volgend recidief. Amoxicilline-clavulaanzuur blijkt noch het optreden van een volgend recidief te voorkómen of uit te stellen, noch het aantal recidieven in het follow-up jaar

te verminderen.
Het optreden van bovenste luchtweginfecties bij overige kinderen in het gezin heeft geen relatie met het optreden van een recidief otitis media acuta bij de in de clinical trial ingesloten patiënt. Gastheerfactoren lijken van meer belang voor de aanwezigheid in een kind van de 'otitis-prone' conditie.

In hoofdstuk IX worden de gegevens beschreven van het jaar follow-up in de tweedelijn. Het blijken vooral de kinderen met een persisterende middenoordysfunctie na één maand te zijn, die door de huisarts naar de KNO-arts worden verwezen. Het door de KNO-artsen gevoerde beleid wordt beschreven en vergeleken met wat internationaal hieromtrent gebruikelijk is.

Tenslotte wordt, gebaseerd op de resultaten van dit onderzoek en op de huidige stand der wetenschap, een beleidsadvies geformuleerd ten aanzien van otitis media acuta voor de praktizerend arts. Dit advies ziet er in schema als volgt uit:

	primaire OMA	recidief OMA
<2 jaar	analgeticum en lokaal decongestivum geen antibioticum, tenzij na drie dagen irregulier beloop	antibioticum analgeticum lokaal decongestivum
≥2 jaar	analgeticum lokaal decongestivum koorts of oorpijn na drie dagen: antibioticum	analgeticum lokaal decongestivum koorts of oorpijn na drie dagen: antibioticum

Met betrekking tot de follow-up van een patiënt met een otitis media acuta wordt geadviseerd de patiënt na drie dagen terug te bestellen bij een irregulier beloop. Tevens moet voor een

patiënt met een recidiverende otitis media acuta een controle afspraak gemaakt worden na één maand teneinde de middenoorfunctie te bepalen. Dit laatste onderzoek draagt er voor de arts toe bij om de 'otitis-prone' conditie van een kind te bepalen aan de hand van de aanwezigheid van:

* het anamnestisch gegeven van een eerste otitis media acuta gedurende het eerste levensjaar,
* een bilaterale middenoordysfunctie, één maand na een recidief otitis media acuta.

DANKWOORD

Het op zijn plaats krijgen van dit steentje, als bijdrage in het wetenschappelijk fundament van onze samenleving, kostte veel mensen een gezamenlijke hoeveelheid energie, die ik normaliter voldoende acht om bergen te verzetten. Met ieder, die hieraan ook maar een joule bijdroeg, wil ik delen in de voldoening, die de voltooiing van een bouwproces met zich mee brengt. Alle kinderen, die deelnamen aan het onderzoek en hun ouders; alle mensen op het huisartseninstituut; mijn collega-huisartsen en andere teamleden op het gezondheidscentrum; het bestuur van het gezondheidscentrum; alle huisartsen, die hielpen bij de uitvoering van het onderzoek; mijn vrienden: voor jullie bijdragen en steun bedank ik jullie van harte en ben ik ieder van jullie bijzonder erkentelijk. Ik heb bovendien veel van jullie geleerd.

Een aantal mensen hebben in mijn beleving als bouwmeester gefungeerd. Jullie wil ik met name bedanken.

Beste Ruut de Melker, als architect heb je me steeds geïnspireerd en in de gelegenheid gesteld om de werktekeningen verder in te vullen. Niet achter een tekentafel vandaan, maar steeds aanwezig op de bouwplaats. Onvermoeibaar stelde je te allen tijde je ervaring en kennis beschikbaar. Wederom ervaarde ik dat op deze wijze nieuwe gebieden betreden leuk is. Mijn oprechte dank. Ik hoop samen verder te kunnen bouwen.

Beste Franajo Touw, als konstruktietekenaar gaf je me het gevoel ook zonder hulp steeds veilig te kunnen werken. Je leerde me dat het goed is om hoge eisen te stellen aan de grondslagen van de berekeningen. Kwaliteit bepaalt uiteindelijk wat stand houdt. Ondanks dat ik gevoelig ben voor kritiek, was jouw kritisch kommentaar altijd waardevol en ervaarde ik het steeds als konstruktief en plezierig. Daarvoor mijn dank.

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Beste Gert-Jan Hordijk, als hoofdopzichter stelde ik je inbreng van specifieke kennis en ervaring steeds bijzonder op prijs. Bovendien behoedde je pragmatische instelling mij ervoor om luchtkastelen te bouwen. Samenwerking tussen echelons kreeg een nieuwe dimensie. Mijn dank voor je begeleiding.

Mijn dank geldt zeker allen van het secretariaat van de afdeling wetenschappelijk onderzoek van het instituut, met name Ans en Carla. Onder de bezielende leiding van Renée Koek gaven jullie inhoud aan het begrip mede-werkers. Renée, je speelde het klaar om de laatste loodjes, die gehesen moesten worden, stukken lichter te maken. Ik ben daarvoor dankbaar.

Mijn vader zou trots zijn geweest, en tevergeefs zijn best hebben gedaan om dat niet direkt te laten merken. Maar ik weet het, en dat is goed. Moeder, jullie energie zit in dit proefschrift. Bedankt dat ik die door mocht geven.

Lieve Jeanne, de omvang van jouw inbreng is het grootst en ongekend. Wij weten het. Soms doet het uitspreken van dank tekort aan wat gevoeld wordt; zoals nu.
Auke en Sjoerd, jullie bestaan. Ik weet, dat jullie zullen begrijpen, waarom ik jullie op deze plaats daarvoor bedank.

Cees Appelman

DANKWOORD

Dit proefschrift was niet mogelijk geweest zonder de inzet en steun van zeer velen. Ieder die op enigerlei wijze aan dit onderzoek heeft bijgedragen wil ik dan ook oprecht danken. Tot enkele personen dient een bijzonder woord gericht te worden:

Prof.dr. G.J. Hordijk, de deur van Uw werkkamer staat bijna altijd open. Dat dit ook symbolisch is voor Uw toegankelijkheid heb ik vaak mogen ervaren en ik ben U daar zeer dankbaar voor. Uw vermogen de grote lijn en essentie van de materie te zien zijn van essentieel belang geweest. De snelheid waarmee U mijn manuscripten retourneerde, veelal voorzien van gedetailleerd commentaar, stimuleerden steeds om door te gaan.

Prof.dr. R.A. de Melker, van Uw kritische beoordeling van de onderzoeksresultaten en verslaglegging heb ik veel geleerd. Uw enthousiasme was vaak aanstekelijk.

Mevr. prof.dr. F.W.M.M. Touw-Otten, Uw kennis van de onderzoeksmethodologie en het vermogen dat op een eenvoudige medicus-practicus over te brengen zorgden ervoor dat ik door vele bomen toch steeds het bos bleef zien.

J.C. Mol, beste Koos, jij hebt mee aan de wieg van dit onderzoek gestaan en bent als zodanig van groot belang geweest. Toen later enige 'bijvoeding' van node bleek heb jij daarvoor je KNO-praktijk in Amersfoort opengesteld.

De overige Amersfoortse KNO-artsen, C.C. Leibbrandt, G. Pluimers en H. Venker, dank ik eveneens voor hun medewerking bij de uitvoering van het onderzoek.

Mevr. drs. I. van der Tweel, beste Ingeborg, een deel van de statistische bewerkingen van dit onderzoek is door jou uitgevoerd. De sfeer bij de bespreking van de resultaten was

altijd prettig.

Mevr. drs. N. Smyth Van Weesep, beste Nancy, je hebt het hele Engelse manuscript op meer dan professionele wijze gecorrigeerd en ons aldus behoed voor veel 'broken English'.

Bernard van der Laan, onze vriendschap is voor mij op vele momenten van grote waarde. Jouw toewijding bij uitvoering en afronding van je eigen promotieonderzoek was voor mij vaak stimulerend.

Maarten Majoor, je oprechte belangstelling voor de voortgang van dit onderzoek heb ik altijd zeer gewaardeerd. Je humor zorgt ervoor dat de sfeer altijd goed is.

Lieve Yvonne, dat de vrouw van een promovendus offers brengt is bekend. De unieke manier waarop je dat hebt gedaan, mij steeds de ruimte gevend, ook op momenten dat jij die had moeten krijgen, heeft voor mij één ding nog eens bevestigd: ik ben een gelukkig man.

Tot slot wil ik mijn vader memoreren. Graag had ik hem dit proefschrift overhandigd, nauwkeurig en kritisch had hij het ontleed. Hij blijft een voorbeeld voor mij.

Hans Claessen

CURRICULUM VITAE

Cees Appelman werd op 27 september 1946 geboren in Midden-Beemster. In 1965 behaalde hij het diploma H.B.S.-B aan het St. Bonifatiuslyceum te Utrecht. In aansluiting hierop studeerde hij geneeskunde aan de Rijksuniversiteit Utrecht. De studie werd in 1973 afgesloten met het behalen van het artsexamen. Vervolgens voltooide hij in 1974 aan dezelfde universiteit de huisartsopleiding.
Na de vervulling van zijn militaire dienstplicht als reserve-eerste-luitenant-arts besteedde hij het merendeel van zijn tijd aan de oprichting van het Wijkgezondheidscentrum Lunetten te Utrecht, waar hij vanaf april 1978 tot op heden voor halve dagen als huisarts praktiseert.
In de andere helft van zijn werktijd droeg hij in zijn funktie als directeur van het S.E.R.C. tot in 1986 bij aan de organisatie en evaluatie van het proef-bevolkingsonderzoek op cervixcarcinoom. In februari 1986 werd hij aangesteld als universitair docent bij het Universitair Huisarts Instituut te Utrecht. De Nederlandse Organisatie voor Wetenschappelijk Onderzoek stelde hem in deze funktie in de gelegenheid de opleiding te volgen tot huisarts-onderzoeker. Binnen deze aanstelling vond het onderzoek plaats, dat tot dit proefschrift leidde. Vanaf 1 april 1992 is hij aangesteld bij het Universitair Huisarts Instituut te Maastricht als toegevoegd onderzoeker om binnen het Stimuleringsprogramma Geneeskundig Onderzoek de Kaderopleiding Huisartsgeneeskunde te volgen.

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In de andere helft van zijn werktijd droeg hij in zijn funktie als directeur van het B.E.R.C. tot in 1986 bij aan de organisatie en evaluatie van het proef-bevolkingsonderzoek op cervixcarcinoom. In februari 1986 werd hij aangesteld als universitair docent bij het Universitair Huisarts Instituut te Utrecht. De Nederlandse Organisatie voor Wetenschappelijk Onderzoek stelde hem in deze funktie in de gelegenheid de opleiding te volgen tot huisarts-onderzoeker. Binnen deze aanstelling vond het onderzoek plaats, dat tot dit proefschrift leidde. Vanaf 1 april 1992 is hij aangesteld bij het Universitair Huisarts Instituut te Maastricht als toegevoegd onderzoeker om binnen het Stimuleringsprogramma Geneeskundig Onderzoek de Kaderopleiding Huisartsgeneeskunde te volgen.

CURRICULUM VITAE

Johannus Quirinus Petrus Jacobus Claessen werd geboren op 30 maart 1960 te Amsterdam. In 1978 behaalde hij het diploma Gymnasium-ß aan het Collegium Marianum te Venlo. In datzelfde jaar begon hij met de studie geneeskunde aan de Rijksuniversiteit Utrecht, waar het artsexamen in 1986 werd behaald.
Van mei 1986 tot oktober 1987 vervulde hij de militaire dienstplicht als reserve-eerste-luitenant-arts op de afdeling KNO van het Militair Hospitaal "Dr. A. Mathijssen" te Utrecht. Van oktober 1987 tot juli 1988 was hij werkzaam als arts-assistent chirurgie in het St. Laurentius Ziekenhuis te Roermond.
In juli 1988 begon hij als AGNIO op de afdeling Keel-, Neus- en Oorheelkunde van het Academisch Ziekenhuis Utrecht, waar hij per 1 oktober 1988 de opleiding tot keel-, neus- en oorarts startte (opleiders: Prof. Dr. E.H. Huizing en Prof. Dr. G.J. Hordijk).
Gedurende de opleidingstijd heeft hij in samenwerking met C.L.M. Appelman, huisarts, aan het onderzoek gewerkt dat heeft geresulteerd in dit proefschrift.
De auteur is getrouwd met Yvonne Louise Marie de Rooij.

STELLINGEN

behorend bij het proefschrift

RECURRENT ACUTE OTITIS MEDIA

1. De schaarste aan placebo-gecontroleerd onderzoek naar de beste behandeling voor otitis media acuta is in scherpe tegenstelling met de behoefte eraan.

2. Stadiumindeling naar ernst van het otoscopisch beeld van een otitis media acuta heeft geen voorspellende waarde voor het klinisch beloop.

3. Een maand na een recidief otitis media acuta dient een kind door middel van tympanometrie te worden gecontroleerd op het persisteren van middenoordysfunctie.

4. Behandelingsprotocollen voortvloeiend uit patiëntgebonden onderzoek hebben zeer grote waarde, maar mogen nooit ertoe leiden te allen tijde volgens "de Regels" te behandelen. Steeds dient te worden beoordeeld of bij de individuele patiënt een afwijkende therapie toch de voorkeur verdient.

5. "If the yield of panendoscopy is only 1% to 2% for synchronous tumors, the justification for performing this time-consuming procedure has to be questioned constantly'.
   GJ Hordijk et al. Otolaryngol Head Neck Surg 1989; 101: 426-428.

6. Een osteomyelitis van het os frontale kan door gecombineerd gebruik van CT-scan, Tc-99 MDP botscan en Gallium-67 citraat scan nauwkeurig worden opgespoord en vervolgd.

7. Computertomografisch onderzoek van de neusbijholten zonder coronale snedes is onvolledig.

8. Stemvorkproeven blijven van grote waarde bij de diagnostiek van slechthorendheid.

9. 'Bij een patiënt met onbegrepen, recidiverende adenoïdhypertrofie dient een infectie met het HIV in de differentiaaldiagnose betrokken te worden'.
JQPJ Claessen et al. Ned Tijdschr Geneeskd 1991; 12: 525-527.

10. Het is onjuist te concluderen dat het lage ziekteverzuim onder arts-assistenten bewijst dat matige honorering en hoge werkdruk geen verhoogd ziekterisico geven.

11. Bij een auto leidt het monteren van de juiste lichtmetalen velgen door verlaging van het ongeveerde gewicht tot een verbetering van het weggedrag.

12. De relatie die er in sommige klinieken lijkt te bestaan tussen het werken aan een promotieonderzoek en aan nageslacht is merkwaardig en verdient nadere studie.

13. Geld maakt niet gelukkig, met de rente ervan kan dat heel anders liggen.

14. Bij een dubbelpromotie doet elk van beide promovendi eerder het dubbele dan de helft, in tegenstelling tot de algemene opvatting.

Hans Claessen

Utrecht, 26 mei 1992

STELLINGEN

behorend bij het proefschrift

RECURRENT ACUTE OTITIS MEDIA

1. Indien de Nederlandse huisarts met behulp van anamnese en lichamelijk onderzoek de diagnose otitis media acuta stelt, blijkt deze diagnose nagenoeg altijd korrekt te zijn.
2. De objectieve vaststelling van de aanwezigheid van effusie in het middenoor, als noodzakelijk diagnostisch kriterium voor otitis media acuta, in sommige andere landen als voorwaarde voor de diagnose-stelling gehanteerd, kan in Nederland nauwelijks iets aan de diagnostische zekerheid van otitis media acuta toevoegen.
3. Bij overigens gezonde kinderen voegt een antibioticum in het klinisch herstel van de ziekte alleen iets toe aan de werking van het natuurlijk aanwezige eigen afweersysteem, indien het kind jonger is dan twee jaar en een recidief otitis media acuta heeft.
4. Op het persisteren van effusie na een otitis media acuta en het optreden van een eventuele volgende episode heeft een antibioticum, gegeven bij deze otitis media acuta gedurende zeven dagen, geen effekt.
5. Het percentage kinderen, dat verhoogd vatbaar is voor het krijgen van otitis media acuta (vier of meer episoden per jaar) en derhalve speciale aandacht behoeft, bedraagt in Nederland ongeveer 5,4% van de kinderen.
6. Het opvolgen door de huisarts van het advies van cytologen om bij afwezigheid van endocervicale cellen in een cervixuitstrijk de uitstrijk na één jaar te herhalen is een slecht en niet-wetenschappelijk kompromis tussen de herhalingstermijnen 'zes weken' en 'drie jaar', dat tot onmacht bij de huisarts en onrust bij de patiënte leidt.
7. Controversen tussen wetenschapsbeoefenaars van verschillende nationaliteit over de waarde van onderzoeksresultaten worden soms in belangrijke mate veroorzaakt door een gebrek aan kennis omtrent elkaars kultuur, waardoor de interpretatie van de studie-resultaten verschilt, en niet door een gebrek aan validiteit van het onderzoek, zoals dan in de diskussie vaak wordt gesteld.

8. Als de voorgestelde wijziging van de wet op de lijkbezorging ertoe kan leiden, dat eveneens inzake een directe levensbeëindiging zonder toestemming van de patiënt, er minder getoetst zal worden door de samenleving, i.c. de rechter, dan is dit niet gewenst.

9. Waar als beoogde rem op de kostentoename in de ontwikkeling van sommige alternatieven door kostenverzekeraars voor het "plan Simons", de huisartsgeneeskundige zorg buiten het basisverzekeringspakket wordt gedacht, en de tweedelijn vrij toegankelijk wordt, zullen dergelijke alternatieven daarentegen een accelererend effekt op de kostenstijging van de gezondheidszorg hebben.

10. Dat kennis niet automatisch tot gedragsverandering leidt blijkt wederom uit het feit dat in het proefschrift, waarbij deze stellingen zijn gevoegd, soms toch nog melding wordt gemaakt van p-waarden in plaats van betrouwbaarheidsintervallen.

11. De aankondiging op 8 april jongstleden door de secretaris-generaal van de Verenigde Naties, Boutros Ghali, om de aanwezigheid van de VN-vredesmacht in Cyprus waarschijnlijk niet langer te handhaven, is de voorbode van een blijk van Westers opportunisme waar het gaat om een inkonsekwente houding inzake de onrechtmatige Turkse bezetting sinds 1974 van een deel van Cyprus.

12. Het feit dat het Algemeen Burgerlijk Pensioenfonds het huwelijk nog steeds als enige samenlevingsvorm beschouwt in zijn reglement, toont aan dat de naam van dit pensioenfonds eens te meer juist is.

13. Vele wegen leiden naar Rome.
(naar een oud Nederlands spreekwoord)

14. Het verdient aanbeveling om aan onderzoekers, die gezamenlijk een onderzoek uitvoeren, eisen te stellen met betrekking tot de kompatibiliteit van hun hard- en software.

Cees Appelman

Utrecht, 26 mei 1992