OTITIS MEDIA IN CHILDREN:
detection of effusion and influence on hearing

PETRI KOIVUNEN
Department of Otorhinolaryngology

OULU 1999
OTITIS MEDIA IN CHILDREN:
detection of effusion and influence on hearing

Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Auditorium 10 of the University Hospital of Oulu, on May 14th, 1999, at 12 noon.
To my Parents
Abstract

This study was undertaken to improve the diagnosis of otitis media and to investigate possible hearing loss caused by middle ear effusion (MEE) in small children.

Temporal development of AOM was assessed from 250 episodes in 184 children. Sixty-three per cent of cases of AOM occurred during the first week after the onset of URI, peaking on days 2 to 5. The onset of AOM in children with a history of recurrent episodes of AOM did not differ from that in those who had experienced only a few episodes of AOM. No individual tendency was noticed among children suffering more than one AOM episode during follow-up.

Studies on symptomatology and the temporal development of acute otitis media (AOM) during upper respiratory tract infection (URI) were based on three-month follow-up of 857 children. Symptoms of URI only were compared with symptoms of URI complicated by AOM in the same child in 138 children. The most important symptom associated with AOM was earache, with a relative risk of 21.3. Sore throat, night restlessness and fever at days 3-6 were also significantly associated with AOM, with relative risks of 3.2, 2.6 and 1.8, respectively. In 44 children under two years of age, earache, conjunctival symptoms and cloudy rhinitis were significantly associated with AOM.

The accuracy of minitypanometry in detecting MEE was evaluated in 162 children. The finding was compared with the amount of effusion found in myringotomy. Minitypanometry proved to be an accurate method to detect MEE in young children, the sensitivity and specificity values being 79 % and 93 % in cooperative children but it had no value in non-cooperative children. Minitypanometric examination could be performed successfully with good cooperation in 87 % of a total of 206 children in paediatric outpatient clinic.

Impaired mobility of the tympanic membrane (TM) was the best sign of MEE in pneumatic otoscopy of 76 children, with sensitivity and specificity values of 75 % and 90 %, respectively.

The influence of nitrous oxide (N₂O) on MEE was tested by weighting the effusion found in myringotomy during general anaesthesia with and without N₂O in 39 and 37 children, respectively. The mean weight of the effusion in the oxygen-air group did not differ from the weight in the N₂O group, and thus peroperative findings in myringotomy are reliable.

To assess the influence of the quantity and quality of MEE on hearing in small children, transient evoked otacoustic emission (TEOAE) was performed under general anaesthesia before myringotomy in 185 ears of 102 children. Reduced TEOAEs indicating hearing loss were found in 83 % of the ears with mucoid effusion and in 56 % of the ears with non-mucoid effusion, the difference being statistically significant (p<0.01). A significant negative correlation between the reproducibility of TEOAE responses and the amount of effusion was found (Spearman rank correlation coefficient r=-0.589, p<0.001). Findings in minitypanometry correlated with the responses of TEOAE.

Although parents are able to predict AOM quite reliably, various symptoms and the duration of URI seems to be of little value in helping the diagnosis of AOM. Detection of effusion in OM may be improved by minitypanometry in cooperative children. Any kind of effusion may cause hearing loss in small children, which must be considered when treating OM.

Keywords: Otitis media, symptoms, temporal development, hearing loss
Acknowledgements

This study was carried out in the Department of Otolaryngology, Oulu University Hospital, in co-operation with the Department of Paediatrics during the years 1995-1998.

I want to express my sincere gratitude to Professor Juhani Nuutinen, MD, Head of the Department of Otolaryngology, for his encouragement during this research and also for his support in my clinical work. His constructive criticism as a supervisor, which is based on a wide experience of a scientific and clinical career, has deepened my understanding about scientific work in otolaryngology. I am also very much obliged to the former Head of the Department of Otolaryngology, Professor Kalevi Jokinen, MD, who facilitated my first steps in the field of scientific work.

My best thanks and respect are due to my supervisor and teacher, Docent Jukka Luotonen, MD. His support and help at all times during the study have been invaluable. As an excellent organiser, he made it possible to carry out this research without interfering too much with clinical work. I have always received excellent help for whatever scientific or clinical problem I have presented to him.

I am deeply grateful for having had the privilege to do my research under the supervision of Professor Matti Uhari, MD. His intelligence, enthusiasm and endless ideas during these years have made a lasting impression on me. In addition to doing scientific work, I have tried to learn some of his ways of independent thinking in research.

I wish to thank the official referees of this thesis, Professor Olli Ruuskanen, MD, and Docent Markku Sipilä, MD, for their careful and constructive criticism.

I am very grateful to Docent Olli-Pekka Alho, MD, who has been a great support for me during this study and also during my residency. He has also given me a lot of practical advice during the research. My warm thanks go to Kyösti Laitakari, MD, whose unique knowledge in the field of audiology made it possible to perform the series V.

My sincere thanks are due to Tero Kontio, MD, and Marjo Niemelä, MD, who have served as an example for me in research work. The collaboration with them has not only been productive, but also pleasant. I also wish to thank Tytti Pokka, BSc, for her skilful statistical work in the series III and IV. I want to thank Aarno Partanen, MD, for his valuable help in the series IV.
Being an otolaryngologist is not only research work. I am most grateful to Heikki Löppönen, MD, Kalevi Hyrynkangas, MD, and Tapio Pirilä, MD, for sharing some of their wide knowledge and experience in the field of otolaryngologic surgery.

Apart from being of continuous assistance in my research, the staff of the Department of Otolaryngology have offered me a very pleasant atmosphere to work in, for which I am very grateful. Especially, I want to thank Ms. Irja Jouhten for her technical help with the series I, II and V, and Ms. Raili Puhakka for her practical help with the thesis.

Since the beginning of my medical studies, I have been proud of being a member of ‘Humerus club’, which has offered me a possibility also to follow the development of other specialities in medicine. With these twelve athletics, we have shared the successes and failures in medicine and in life during numerous sport competition events in 14 years.

I want to thank surgeon Jukka Salminen, MD, whose very special attitude to work and life has provided me much support and pleasure during these years of research and also served as an example for me. We have shared the same problems when doing our research, and he has shown how to take a right attitude towards them.

The friendship with Timo Koivisto, MD, and Juha Välimäki, MD, has made my work with this thesis much easier. Their unrealistic optimism regarding my survey has been very encouraging.

I most sincerely thank to my parents, Sirpa and Seppo, for their encouragement during my life. They deserve the dedication of this thesis.

Without my wife Riitta, these years would have been much harder. I have always received endless encouragement despite the shortage of time for being together. Even though we have spent most of our little spare time with research work, our love and friendship have still deepened. At the final stage of this thesis, our daughter Sini has reminded me of what the really important things in life are.

This research was financially supported by the Korvatautien Tutkimussäätiö Foundation and the Orion-Farmos company.

Oulu, April 1999

Petri Koivunen
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM</td>
<td>acute otitis media</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>ET</td>
<td>Eustachian tube</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>MEE</td>
<td>middle ear effusion</td>
</tr>
<tr>
<td>N₂O</td>
<td>nitrous oxide</td>
</tr>
<tr>
<td>OAE</td>
<td>otoacoustic emission</td>
</tr>
<tr>
<td>OM</td>
<td>otitis media</td>
</tr>
<tr>
<td>OME</td>
<td>otitis media with effusion</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
<tr>
<td>SA</td>
<td>static admittance</td>
</tr>
<tr>
<td>SOM</td>
<td>secretory otitis media</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>TEOAE</td>
<td>transient evoked otoacoustic emission</td>
</tr>
<tr>
<td>TM</td>
<td>tympanic membrane</td>
</tr>
<tr>
<td>TPP</td>
<td>tympanic peak pressure</td>
</tr>
<tr>
<td>TR</td>
<td>tympanometric gradient</td>
</tr>
<tr>
<td>URI</td>
<td>upper respiratory tract infection</td>
</tr>
</tbody>
</table>
List of original papers

The thesis is based on the following reports, which are referred to in the text by Roman numerals (I-V), and on certain previously unpublished data.


Contents

Abstract
Acknowledgements
Abbreviations
List of original papers

1. Introduction ........................................................................ 15

2. Review of the literature ...................................................... 16
   2.1. Acute otitis media ............................................................ 16
       2.1.1. Terminology ...................................................... 16
       2.1.2. Epidemiology .................................................... 16
       2.1.3. Pathogenesis ..................................................... 17
       2.1.4. Microbial aetiology ............................................. 19
       2.1.5. Risk factors ...................................................... 20
       2.1.6. Symptoms and temporal development ...................... 22
       2.1.7. Treatment of acute otitis media ................................ 23
   2.2. Diagnosis of otitis media ................................................. 24
       2.2.1. Pneumatic otoscopy ............................................. 25
       2.2.2. Tympanometry .................................................... 25
   2.3. Consequences of otitis media .......................................... 28
       2.3.1. Infectious complications ...................................... 28
       2.3.2. Duration of effusion .......................................... 28
       2.3.3. Influence on hearing .......................................... 29
           2.3.3.1. Measured by conventional methods ................. 29
           2.3.3.2. Measured by otoacoustic emission ................. 30
       2.3.4. Late sequelae of otitis media .................................. 31
   3. Purpose of the study .......................................................... 34

   4. Patients and methods ....................................................... 35
      4.1. Temporal development of acute otitis media (I) ............... 35
      4.2. Symptoms of acute otitis media (II) ............................ 36
      4.3. Pneumatic otoscopy in the detection of middle ear effusion (previously unpublished data) ........................................ 36
      4.4. Minitympanometry in the diagnosis of otitis media (III) .... 37
4.5. The effect of nitrous oxide on middle ear effusion (IV) .......................... 37
4.6. Hearing loss in otitis media measured by otoacoustic emission (V) ........ 38
4.7. Statistical analysis .................................................................................. 39
  4.7.1. Series I and II .................................................................................. 39
  4.7.2. Series III, IV and previously previously unpublished data ................ 39
  4.7.3. Series V .......................................................................................... 39
4.8. Ethical aspects ......................................................................................... 40
5. Results .......................................................................................................... 41
  5.1. Temporal development of acute otitis media during upper respiratory
      tract infection (I) ................................................................................... 41
  5.2. Symptoms associated with acute otitis media (II) ................................. 41
  5.3. The accuracy of parents prediction of their child’s possible AOM
      and the predictive value of symptoms (II) ............................................ 42
  5.4. Accuracy of pneumatic otoscopy and the value of various signs of tympanic
      membrane in detecting middle ear effusion (previously unpublished data) ... 44
  5.5. Success rate and the time required to perform the minitympanometric
      examination (III) .................................................................................. 44
  5.6. Accuracy of minitympanometry in the detection of middle ear effusion in
      cooperative and non-cooperative children (III) ....................................... 44
  5.7. The influence of nitrous oxide on middle ear effusion (IV) .................... 46
  5.8. Effect of middle ear effusion on hearing when measured
      by otoacoustic emission (V) ................................................................. 48
  5.9. Correlation of responses in otoacoustic emission measurement
      with findings in minitympanometry (V) ............................................... 48
6. Discussion ...................................................................................................... 50
  6.1. Symptoms and temporal development of acute otitis media .................. 50
  6.2. Accuracy of pneumatic otoscopy and tympanic membrane signs
      in the detection of middle ear effusion ................................................... 52
  6.3. Minitympanometry in the detection of middle ear effusion .................... 52
  6.4. The influence of nitrous oxide on middle ear effusion ............................ 53
  6.5. Hearing loss attributable to middle ear effusion ..................................... 54
7. Conclusions ................................................................................................. 57
8. References .................................................................................................... 58
1. Introduction

Acute otitis media (AOM) is one of the most common diseases in children. Almost every child experiences at least one episode by the age of three and the mean time spent with middle ear effusion (MEE) during the first two years of life is one to two months a year. About half a million episodes appear in Finland every year leading to a cost of 700 million FIM. Because of the growing incidence of antibiotic-resistant bacteria, possibilities to decrease the use of antimicrobials in the treatment of AOM has been considered.

Accurate diagnosis of OM is a cornerstone of treatment, but it is not always easy to perform, especially in small children. Minitympanometry might improve the accuracy of diagnosis in clinical studies and in primary care, but the usefulness of the device is unclear. Parental suspicion of possible AOM during upper respiratory tract infection (URI) is based on the assumption that some symptoms of their child are related to AOM. However, the ability of the parents to predict AOM in their child has not been evaluated. Knowledge of the temporal development of AOM and symptoms of the child with AOM would help to instruct parents when to seek medical advice.

There is growing evidence of adverse long-term consequences of otitis media (OM), which have been related to fluctuating conductive hearing loss caused by MEE. Children who experience several OM episodes under three years of age are at risk of long-term adverse consequences of speech and language development. Unfortunately, small children are likely to suffer from recurrent episodes of AOM, and prolonged effusion and treatment failures after AOM appear especially in children under two years of age. The influence of the type and amount of MEE on hearing in small children and infants has not been determined.
2. Review of the literature

2.1. Acute otitis media

2.1.1. Terminology

Otitis media is a general term covering various conditions of an inflammatory process in the middle ear (1). The presence of MEE, of any kind, can be considered as a sign of middle ear inflammation. It can proceed from an acute to a chronic form with reversible or irreversible pathology. AOM is defined as rapid onset of signs and symptoms of middle ear inflammation, usually with signs of URI, together with clinical evidence of MEE. Synonyms such as acute suppurative otitis media and purulent otitis media are commonly used. Acute onset of purulent discharge through the perforation of tympanic membrane (TM) or ventilation tube is also considered as AOM. The presence of MEE after an episode of AOM without continuing acute infectious symptoms can be described as residual effusion. MEE that persists without acute signs and symptoms refers to otitis media with effusion (OME), which some authors consider as chronic when it persists for more than 12 to 16 weeks (1-4). Various synonyms for OME, such as glue ear, serous otitis media and mucoid otitis media, refer to the type of MEE. OME can also develop without a preceding episode of AOM. Chronic suppurative otitis media refers to a chronic discharge from the middle ear through the ventilation tube, or perforation of the TM.

2.1.2. Epidemiology

AOM is closely related to viral respiratory infections and it is one of the most common diseases in childhood. Approximately every fifth upper respiratory tract infection is complicated by AOM (5,6). The incidence of AOM is highest among children under two years of age and it gradually diminishes with age, the peak incidence being between the ages of 6 to 12 months (5,7-9). In a prospective cohort study of 498 children in the area of greater Boston, the annual incidences of at least one episode of AOM in the first, second and third year were 62 %, 59 % and 40 %, respectively (9). In a Finnish cohort study of 2512 chil-
children, the cumulative incidence of children who experienced at least one episode of AOM was 42% during the first year of life and 71% by the age of two (8). An even higher frequency of middle ear disease has been reported in a prospective study from the USA, where 79% and 91% of the 2253 children experienced at least one episode of MEE before the ages of one and two, respectively (10). Small differences in these studies may be partly due to variable numbers of drop outs, differences in diagnostic criteria or variation in microbiological aetiology. The incidence rates of recurrent AOM in various studies are summarized in table 1.

Table 1. Incidence of recurrent AOM episodes in different studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipilä et al. 1987 (7)</td>
<td>≥3 AOM before age of 18 mo</td>
<td>1642</td>
<td>30</td>
</tr>
<tr>
<td>Teele et al. 1989 (9)</td>
<td>≥6 AOM before age of 3 y</td>
<td>498</td>
<td>16</td>
</tr>
<tr>
<td>Harsten et al. 1989 (11)</td>
<td>≥6 AOM in 12 mo period before age of 36 mo</td>
<td>113</td>
<td>12</td>
</tr>
<tr>
<td>Ingvarsson et al. 1990 (12)</td>
<td>≥4 AOM before age of 4 y</td>
<td>2978</td>
<td>18</td>
</tr>
<tr>
<td>Duncan et al. 1993 (13)</td>
<td>≥3 AOM in 6 mo or 4 AOM before age of 12 mo</td>
<td>1220</td>
<td>17</td>
</tr>
<tr>
<td>Alho 1997 (14)</td>
<td>≥3 AOM in 6 mo period in children aged under 24 mo</td>
<td>2411</td>
<td>15</td>
</tr>
</tbody>
</table>

AOM, acute otitis media; y, years; mo, months; n, number of children in cohort

The incidence of AOM appears to have increased in the past few decades. Schappert found about 2.5 times more clinic visits with a principal diagnosis of OM in the United States during 1990 than during 1975 (15). The incidence of recurrent OM among pre-school children has also increased from 18.7% in 1981 to 26% in 1988 in the United States (16). The same tendency has been found in Finland, where the total number AOM episodes was estimated to be 200 000 in 1982 and 500 000 in 1997 (17,18).

### 2.1.3. Pathogenesis

The pathogenesis of OM is multifactorial and includes host factors, anatomical factors, environmental factors, infection and inflammation. Abnormal function of the Eustachian tube (ET), first suggested more than 100 years ago, is probably the most important factor in the development of AOM. OM can be attributable to loss of protective function of the ET, impairment of pressure regulation and/or impairment of clearance of the tube and middle ear (19). As a consequence of an inflammatory process which is usually caused by viral respiratory infection, the patient develops congestion of the mucosa in the upper respiratory tract, which results in obstruction of the ET (20). This leads to negative middle ear pressure, and if it continues, it is followed by transportation of potential pathogens from the nasopharynx to the middle ear cavity. Because of obstruction of the ET, the clearance of secretion is impaired and it accumulates in the middle ear resulting in OM (20). Infants and children with shorter, relatively wider and more flexible ET, are at a greater risk of insufflate nasopharyngeal secretions to the middle ear.
A relationship between abnormal function of the ET and AOM has been documented in several studies. Buchman et al. inoculated influenzae A viruses into the noses of 27 adults and subsequently 59% of subjects developed negative middle ear pressure and 25% developed AOM (21). Similar results have been obtained by using rhinovirus (22). Negative middle ear pressure occurring during the first two days after an onset of URI has also been detected by Sanyal et al. in a prospective study of 28 pre-school children (23). Moody et al. followed 20 children in winter time and reported that children who developed MEE during a common cold had negative middle ear pressure more often and the pressure returned to normal more slowly than in controls without MEE (24). Ciliary ultrastructural changes in human nasal mucosal epithelium have been detected during the common cold (25). Similar changes most probably occur in the ET as well. Nuutinen et al. reported mucociliary transport to be totally absent in chronic OM and in untreated secretory OM. The mucociliary transport function returned to normal when the ear was clinically healed (26). Functional abnormality of the ET associated with OM was demonstrated by Stenström et al., who used a pressure chamber to test ET function. They found significantly poorer function in otitis prone children than in controls (27). Active muscular opening function of the ET has also been demonstrated to deteriorate during URI (28).

Several inflammatory mediators, such as leukotriens and cytokines are released in viral respiratory infection (29). Jung et al. investigated arachidonic acid metabolites in MEE and concluded that they are important mediators in the pathogenesis of OM (30). In addition to the inflammatory changes causing interference in ET function, viral infection damages mucosal cells and leads to increased bacterial adherence to pharyngeal cells, which has been reported at least with adenovirus, influenzae A virus and rhinovirus (23,31,32,33). Nasopharyngeal normal flora plays an important role in the development of OM. Bacteria rapidly colonize the nasopharynx of infants soon after birth and colonization remains relatively consistent among healthy children. In a Swedish study 62% of children carried S. pneumoniae, M. catarrhalis or H. influenzae at the age of 10 months, but even higher rates have been reported (34,35). Each child has at least one pathogen at the age of two, but the number of pathogens gradually decreases with age and only 40% of children have pathogens in their nasopharynx at the age of 11 to 14 years (36). Children with early nasopharyngeal colonization by S. pneumoniae, M. catarrhalis and H. influenzae have been shown to be at greater risk of developing OM (37). A correlation between nasopharyngeal flora and OM has been shown in a study by Faden et al., who followed 70 children with OM and 40 healthy controls from birth to three years of age (38). They found a significant increase in carriage rates of pathogenic bacteria during episodes of AOM. At the same time the carriage rate of non-pathogens, in particular Streptococcus viridans, declined. Similar results have later been obtained by Bernstein et al. (39). Pneumococcal infections are usually attributable to a newly acquired strain and are seldom associated with prolonged carriage. Acquisition of a new type peaks in winter months and it is usually associated with viral URI (35). Even though the bacterial strain found in MEE in children with AOM can usually also be detected in the nasopharynx, the specificity of nasopharyngeal culture is too low to guide antimicrobial treatment in AOM (38,40).
2.1.4. Microbial aetiology

The association between virus infection and AOM was first described by Berglund et al., who recovered respiratory syncytial virus from middle ear aspirates of two children with AOM (41). The temporal association between a viral URI and AOM has been well documented in a 14-year prospective study (5). The correlation between respiratory virus infections and AOM has been clearly demonstrated in Finnish studies where respiratory syncytial virus and rhinovirus has been particularly associated with AOM (42-44). Direct evidence of viral infection in the middle ear obtained by cultures or by detection of viral antigens in MEE have been found in 15-24 % of patients with AOM (44-48). In these studies several types of viruses have been found in MEE. Respiratory syncytial virus was the principal virus causing AOM in the study of 456 children (49). It was found in 74 % of MEE samples in 65 children infected by this virus, whereas parainfluenza viruses were detected in 52 % and influenza viruses in 42 % of middle ear samples when these viruses were the causative organisms of URI (49). Using the reverse transcriptase polymerase chain reaction (PCR), viral RNA of rhinovirus, respiratory syncytial virus or coronavirus has been found in 48 % of all MEE samples and also in 57 % of bacteria-negative samples (50). The most important viruses associated with AOM in this study were rhinovirus and respiratory syncytial virus.

Concurrent viral infection in the middle ear may worsen the outcome of antibiotic treatment of bacterial AOM. In a study by Chonmaitree, the proportion of patients who did not respond to antibiotic treatment of AOM was 50 % in patients with both viruses and bacteria found in MEE compared with 13 % in the group with bacteria alone (51). This is supported by some other studies (44,45). The worse outcome may partly depend on the type of virus present in MEE. At least rhinovirus has been associated with a poor bacteriological response to treatment (52). Bacteria and viruses together have an additive effect on histamine concentration in MEE and the concentration is higher in patients with persistent otitis than in controls with a good response to treatment. Thus, increased inflammation of the middle ear may be associated with poorer outcome of antimicrobial treatment of AOM (53). However, there are also studies where no differences in the clinical course after antibiotic treatment have been found between patients with and without coexisting viral infection verified in MEE (50).

Although there is growing evidence of a viral aetiology in AOM, with or without concomitant bacterial infection, it is still considered mostly to be a bacterial disease. About one third of conventionally cultured effusions are sterile, but when also detecting S. pneumoniae capsular polysaccharide antigens, evidence of bacteria is found in one third of the culture-negative samples (54). Furthermore, using meticulous bacteriological techniques, evidence of pathogenic bacteria has been found in 90 % of patients with AOM (55). When using the PCR technique, Post et al. found 77.3 % of 97 specimens from children with OME to be positive for at least one of the three commonest bacterial pathogens tested (56). Another study showed a 1.5 fold increase in the proportion of positive samples of S. pneumoniae in MEE when using PCR compared with conventional bacterial culture in 135 children with AOM (57). Pathogens have also been found in 84 % of MEE samples from children with OME when using multiplex PCR, which may implicate inflammation in the middle ear caused by bacterial remnants (58). Because PCR can also detect non-viable pathogens, findings using the PCR technique may be clinically unimportant. The reliability of a
PCR-based assay system in detecting causative pathogens in AOM has been demonstrated in an animal model. Non-viable bacteria did not persist in the MEE and were not detectable by PCR, whereas viable bacteria, even when treated with antimicrobial agents, remained in MEE for weeks and were detected by PCR (59).

The most common bacteria responsible for AOM have been *S. pneumoniae* in 27-52 %, *H. influenzae* in 16-52 % and *M. catarrhalis* in 2-15 % of episodes. The proportion of these bacteria has been relative constant in recent years (1,60). The most notable changes in data collected from 1980-1989 in 2807 children in the United States were an increase in the prevalence of *S. pneumoniae* and a rise in the beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* (60). Other pathogens include *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Klebsiella*, *Escherichia coli* and as a new pathogen *Alloicoccus otitidis*, all at a proportion of a few per cent (1,61,62).

According to recent studies it can be estimated that viable bacteria or traces of bacterial pathogens can be found in about 70-90 % of AOM episodes. Evidence of viral infection in the middle ear, with or without concomitant bacterial infection, can be found in about 20-40 % of cases. Bacteria-negative AOM episodes may be caused by respiratory viral pathogens, for example by respiratory syncytial virus and rhinovirus.

### 2.1.5. Risk factors

Even though risk factors often have confounding interrelations to each other several contributing factors to AOM have been found. Young age is the most important risk factor for AOM (8,9). Young age at the first episode is also inversely associated with persistent MEE and recurrent episodes of AOM (9,11,63,64). Our knowledge of anatomical and functional factors concerning the eustachian tube and nasopharyngeal colonization in infants support these findings (1,38).

Among the strongest risk factors of AOM is day-care in nurseries (65-71). The adverse effect of day-care has been suggested to be most evident during the first two years of life (71,72). The relative risk almost doubles among children attending day-care in nurseries compared with care at home (73). The number of children in a day-care setting is also an important determinant for early AOM, and the risk has reported to be greater in large day-care centres compared with family day-care (68,74). Tainio et al. found daily contact with five or more children to be related to AOM with a relative risk of 2.1 (67). Family day-care was significantly associated with AOM in a meta-analysis (73). Wald et al. reported an increased rate of ventilation tube placement as a result of OM among children in day-care in nurseries compared with children in home care: 21 % and 3 % respectively (72). In addition the re-intubation rate is about three-fold among children in day-care compared with those at home (75). The same tendency has been found in Finland, where the number of adenotomies and tympanostomies increased significantly after local authorities were obliged to offer day-care nursery to all children under three years of age (76).

The most probable explanation for the increased risk of AOM episodes in day-care is increased susceptibility to respiratory infections transmitted by other children. This is supported by Collet et al. who found children admitted to day-care to have twice the risk of having a common cold in comparison with children who remained at home (71). The signif-
icance of transmission of respiratory pathogens in a nursery was enhanced by the result of an intervention study, where the authors were able to reduce the number of respiratory infections and AOM to one third by improving hygienic practice (77). Day-care attendance is also associated with the development of OME (78).

The number of siblings seems to be associated with the occurrence of AOM although this has not been found in all studies (9,66,68,69,74,79). In a meta-analysis, AOM was significantly related to one or more siblings with a risk ratio of 1.92 (73). Sibling’s day-care outside the home increases contacts and the transmission of respiratory pathogens and was the most important determinant for early AOM in one prospective study (80). A sibling’s history of recurrent episodes of AOM may reflect a similar genetic predisposition, i.e. ET function, or a larger amount of transmission of respiratory pathogens, or both, so it is not surprising that a positive family history of AOM is one of the most important risk factors for AOM with a risk ratio of 2.63 (73).

Most studies concerning the association between breast feeding and OM have found a protective effect of prolonged breast feeding against recurrent episodes of AOM and the time spent with MEE (69,66,79). Teele et al. prospectively followed 638 children and found breast feeding for less than three months to be associated with an increased number of AOM episodes in the first year of life (9). Saarinen followed 256 infants for three years and reported an inverse association between duration of breast feeding and incidence of AOM and the protective effect of at least six months of breast feeding lasted up to three years of age (81). The protective effect in other two studies have lasted less than one year (65,68). In a 1220-infant cohort study from the USA, children breast-fed for 4 months or more experienced half the number of AOM episodes compared with those not breast-fed during the 12 months of follow-up. The number of recurrent AOM episodes also declined (13). Similar results have been obtained in Sweden, where none of 24 exclusive breast fed children experienced any AOM episodes during 12 months follow-up (82).

Studies of breast feeding have several confounding factors such as the interrelationship with other risk factors and the adverse effect of cow’s milk or formula rather than the protective effect of human milk. Different feeding positions may also explain the findings. A supine feeding position has been associated with earlier onset of chronic OME (65). The beneficial effect of human milk was partly demonstrated in a study by Paradise and Elster, where open cleft palate children were fed breast milk and formula by using the same kind of artificial feeder (83). A significant protective effect of breast milk was found indicating that the quality of milk is more significant than the mode of feeding.

Exposure to environmental tobacco smoke increases the risk of lower respiratory illness in the first years of life (84-86). Similarly it increases the time spent with MEE. (65,66,87-90). Possible mechanisms behind the adverse effect are goblet cell hyperplasia, mucus hypersecretion in the respiratory tract and decreased mucociliary transport (87,91). Maternal smoking seems to be a greater risk as regards recurrent AOM than paternal smoking (85,92). In a meta-analysis from the USA, passive smoking caused by parents increased morbidity in children, with a risk ratio of 1.19 (86). The authors also calculated that 340 000 – 2 million AOM episodes and 5200 to 165 000 tympanostomies are attributable to environmental smoke.

Some well documented risk factors include race, some congenital disorders and immunological disorders (1,93-95). The relative risk estimate as regards use of a pacifier among day-care children has been found to be 1.43 (96). An association of recurrent AOM with
nasopharyngeal dimensions in children has also been reported (97). In a questionnaire study covering 14,000 infants, a prone sleeping position was found to be a risk factor for ear-related symptoms (98). Several other risk factors, such as low socioeconomic status, atopy, allergy and low birth weight, have been presented as risk factors for AOM, but there is still some discrepancy concerning the association of these factors with middle ear diseases (1).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Studies included [references]</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family history of AOM</td>
<td>[10, 21, 22]</td>
<td>1,240</td>
</tr>
<tr>
<td>Day care outside home</td>
<td>[9, 11, 12, 14, 17, 18]</td>
<td>1,072</td>
</tr>
<tr>
<td>Parental smoking</td>
<td>[17, 18, 22]</td>
<td>1,784</td>
</tr>
<tr>
<td>Family day care vs. home care</td>
<td>[9, 11, 12, 17, 16]</td>
<td>1,030</td>
</tr>
<tr>
<td>At least one sibling</td>
<td>[17, 22]</td>
<td>1,344</td>
</tr>
<tr>
<td>Day care center vs. family care</td>
<td>[9, 11, 12, 17, 16]</td>
<td>850</td>
</tr>
<tr>
<td>Day care center (yes/no)</td>
<td>[9, 11, 12, 17, 18, 19]</td>
<td>1,918</td>
</tr>
<tr>
<td>Use of a pacifier</td>
<td>[9, 28]</td>
<td>4,110</td>
</tr>
<tr>
<td>Breast-feeding &gt;3 mo</td>
<td>[12, 13, 17, 22, 23, 27]</td>
<td>2,549</td>
</tr>
<tr>
<td>Breast-feeding &gt;6 mo</td>
<td>[12, 13, 17, 26, 22, 25, 27]</td>
<td>3,384</td>
</tr>
<tr>
<td>Breast-feeding (yes/no)</td>
<td>[15, 16, 17, 22, 23]</td>
<td>2,193</td>
</tr>
</tbody>
</table>

Fig. 1. Pooled risk ratios from 18 studies analyzed in a meta-analysis of the risk factors for acute otitis media (AOM). AOM was classified as yed or no. (Figure 1 from Uhari et al. Clin Infect Dis 1996;22:1079-1083)

2.1.6. Symptoms and temporal development

Considering how common AOM is, surprisingly few analyses have been reported concerning the significance of those symptoms which predict the occurrence of AOM and its temporal development. The symptoms of concomitant viral upper respiratory tract infection confound the symptoms of AOM and therefore many non-specific symptoms, such as night restlessness, poor appetite, vomiting, diarrhea, loss of appetite and abdominal pain have been claimed to be associated with AOM (1, 4, 99). Rhinitis, cough and earache were the symptoms which increased the risk of AOM compared with age-matched controls in a study of 197 hospitalized children with AOM (100). All three variables correctly predicted AOM in 63% of cases. Usually only ear-related symptoms have been constantly related to AOM and they exist in 54-75% of cases. The association of other symptoms suggested to
correlate with AOM, such as fever, rhinitis and restless sleeping, is still controversial (101–104).

The most common reason to seek medical advice for children during URI is the assumption of AOM. Prolongation of certain symptoms of URI and parents’ suspicion of AOM are important reasons which lead to over-diagnosis of AOM (105). However, there are only a few studies specifically addressing the issue. This aspect is difficult to evaluate and the surveys are therefore easily biased. Detection bias occurs if the children have not been examined during every episode of URI. Diagnosis of AOM may be inaccurate if there are several investigators in the study or if no objective method is used. Controlling possible interindividual variation cannot be ensured when comparing symptoms in children with and without AOM.

Heikkinen and co-workers evaluated the temporal development of AOM and found that 54 % of episodes were diagnosed during the first 4 days and 75 % during the first week after the onset of URI (106). Children experienced three or more AOM episodes had similar pattern in developing AOM than children without previous episodes in one study (107). The mean duration of preceding symptoms before the diagnosis of AOM has been reported to be 3.9-5.9 days (107-108). Specific knowledge of the temporal development of AOM would help in advising parents when they should contact a physician during an URI in order to diagnose and treat possible AOM. In previous literature, individual tendencies as regards the temporal development of AOM have not been evaluated.

2.1.7. Treatment of acute otitis media

Since penicillin and sulphonamides were introduced for treatment of AOM, the nature of management of OM has changed (109). Complications of suppurative OM, most frequently acute mastoiditis, and the incidence of operations because of chronic OM have declined dramatically, which is partly due to improved welfare and hygiene in Western countries (109,110). The aetiology of AOM has also altered; about thirty years ago beta-haemolytic streptococci were the most important pathogen (109). Despite these facts, an increased proportion of antibiotic-resistant bacteria and obscurity in placebo-controlled studies concerning the efficacy of treatment have aroused debate about treatment policies in AOM (111-114).

The goal in the management of AOM is to relieve the symptoms, accelerate the resolution of MEE in order to eliminate hearing loss caused by it and to prevent sequelae. Because bacteria play a major role in the pathogenesis of OM, antibiotics have been indicated in the treatment. Several studies have been conducted in order to clarify whether antimicrobials are beneficial in the management of AOM. A recent meta-analysis of six placebo-controlled studies indicated that the early use of antibiotics provides only modest benefit in AOM, mainly pain relief on days 2-7 (115). Antibiotics had no effect on resolution of MEE at one month, but there was a statistically non-significant tendency towards benefit at three months as measured by tympanometry. The authors concluded that one child out of seventeen benefitted from antibiotic treatment (115). In contrary, in a meta-analysis of 5400 children in 33 randomized trials, an improvement of 13.7 % (95 % confidence interval (CI), 8.2 % to 19.2 %) was found as regards antibiotic therapy in the resolution of MEE within 7 to
14 days after the therapy started (116). Spontaneous resolution of effusion was 81% and the authors calculated that one out of seven children benefits from active treatment. In a study from Pittsburgh, where myringotomy was performed to ensure the diagnosis, antibiotic treatment brought 46.9% effusion-free ears compared with 62.5% in the placebo-treated group two weeks after initialization of treatment in 1049 episodes (117). In a survey of the microbiological efficacy of antibacterial drugs in AOM, clinical success was achieved in 93% of cases where the bacterial pathogen was eradicated compared with 62% of cases where eradication failed (118). Patients younger than 24 months are at the highest risk of treatment failure and also of persistent MEE after AOM (64, 117, 119, 120).

Antibiotics used in the treatment of AOM should be effective against the three most common middle ear pathogens, S. pneumoniae, H. influenzae and M. catarrhalis. Despite the growing proportion of Beta-lactamase production by these pathogens, penicillin-V and amoxyccillin are still recommended as first line antibiotics together with sulphonamide-trimethoprim by many authors and also in Finland (121-124). The conventional duration of antimicrobial course for AOM has been 7 to 10 days. In a meta-analysis of the optimal duration of an antibiotic course, a five days regimen was found to be as effective as seven days or even longer (125). However, Cohen et al. conducted a randomized, double-blind survey among 194 children with AOM, whose mean age was 13.3 months. A five-day regimen of amoxyccillin/clavulanate was not equivalent to a 10-day regimen and especially among children cared for outside their homes, a 10-day course was more effective than a five-day regimen when assessed 12 to 14 days after the outset of treatment (126).

Studies of the value of myringotomy in the treatment of OM have been controversial, but according to the result of recent studies it has not improved the outcome of AOM in uncomplicated cases (112, 117, 127-129). However, in the present era of growing resistance of bacteria to antimicrobial agents, myringotomy should be performed probably more often in order to detect the causative organism of AOM at least in treatment failures. For the same reason, a more aggressive strategy as regards surgical prevention has been recommended instead of the widespread use of prophylactic antibiotic treatment (130, 131). Adjuvant therapies, such as use of decongestants and antihistamine have not been shown to be of any benefit in the treatment of AOM (132, 133).

### 2.2. Diagnosis of otitis media

Differentiation between viral and bacterial AOM could help in targeting antibiotic treatment, but this seems to be impossible without a sample from the middle ear effusion (108). Tejani et al. demonstrated that higher levels of serum C-reactive protein are associated with bacterial AOM, but the sensitivity is so poor that it has no clinical use (134). Serum interleukin-6 levels have been reported to be significantly higher in bacterial AOM, but it was almost entirely attributable to pneumococcal infection. Overall sensitivity and specificity values were 61% and 27%, respectively (135).

Remarkable uncertainty in the diagnosis of AOM was found in a questionnaire study among physicians who had treated a total of 3660 children with AOM (99). In the age groups of 0-12 months and 13 to 30 months, the doctors were uncertain of the diagnosis in 42% and 34% of the cases, respectively (99). Furthermore, in a review article of pertinent
literature concerning studies about OM, clinical diagnostic criteria of AOM were described in only 26 of 43 studies and 18 different sets of criteria were used in these 26 surveys (136). In the same study a questionnaire was sent to 165 paediatricians, which resulted in 147 different sets of diagnostic criteria (136). Thus, there seems to be tremendous diversity rather than agreement in the diagnosis of OM, which also makes it difficult to compare the numerous studies in the field and hampers the discussion about the efficacy of treatment of AOM and the discrepancy concerning late consequences of OM.

2.2.1. Pneumatic otoscopy

The diagnosis of OM requires detection of MEE (4), which is not easy to verify by pneumatic otoscope, even by an experienced examiner. The appearance of the TM is only of limited diagnostic value. A red, cloudy or yellow TM was found in only 46 %, 52 % and 24 %, respectively, of 528 ears of 363 children with AOM (108). In the same study, fluid level was detected in 33 % of ears with AOM. However, red TM is often used as one of the most important signs in otoscopy indicating AOM (99,136) Karma et al. evaluated different otoscopic findings in 11 804 ear-related visits to an otolaryngologist and a paediatrician. The result of myringotomy was used as a reference method and it was performed whenever MEE was suspected. A red TM was found in 17.5-26.8 % of AOM episodes and an abnormal position was detected in 60.7-67.7 % of cases. In ears with MEE without acute symptoms these figures were much lower. A cloudy TM was present in 67.1-92.9 % of all cases when MEE was found. Only impaired motility was acceptably specific in diagnosing effusion. It was found in 93.7-98.3 % of ears when effusion was present, but also in 9.6-28.9 % of cases when effusion was not found in myringotomy (137).

When pneumatic otoscopy is performed and the findings are compared with those in myringotomy, the sensitivity and specificity have been 81-94 % and 58-89 %, respectively (138-141). However, the applicability of these studies to primary care is somewhat restricted because the examinations were performed by experienced otoscopists and also the devices would be different in primary care. It can be assumed that these figures are beyond the overall accuracy of diagnosis of MEE when pneumatic otoscopy is used. Otoscopic examination without testing the mobility of the TM has only limited value in the diagnosis of OM (137,141).

2.2.2. Tympanometry

Tympanometry is a measurement of acoustic immittance of the ear canal and middle ear. Acoustic immittance is a general term used to refer either to acoustic impedance or acoustic admittance measurements. At present most of the devices are based on admittance measurement. Acoustic admittance is the ease with which acoustic energy is transferred from one system to another, which is the opposite of acoustic impedance. If the air in the ear canal is easily set into a vibration, the admittance is high. If the air is difficult to set into a vibration, the admittance of the system is low. Middle ear pathologies that increase the stiffness of the TM, such as negative middle ear pressure and MEE, have a great effect...
on the transmission of low frequency signals. Tympanometry is the measurement of acoustic admittance as a function of ear canal pressure and the resulting graph is a tympanogram. Positive or negative pressure introduced to the sealed ear canal decreases the admittance of the air in the ear canal by stiffening the TM. The effect of air pressure on acoustic admittance measured in the ear canal is systematically altered by the middle ear disease (142).

Four tympanometric variables have been used to detect middle ear disease. Static admittance (SA), i.e. the ease with which acoustic energy flows into the middle ear, is an estimate of acoustic admittance. The term compliance is also used as a synonym for SA. Equivalent ear canal volume is a measure of the ear canal volume in front of the measurement probe. Tympanometric peak pressure (TPP) is the position of the tympanometric peak, i.e. height of SA, on the pressure axis. Tympanometric gradient and width describe the shape of the tympanogram. Tympanometric width is calculated as an ear canal pressure range corresponding to a 50 % reduction in SA and it is reported in daPa. Tympanometric gradient is defined as the change in admittance between the peak value and the mean admittance value (142,143).

The classification mostly used in clinical practice is based on studies by Margolis et al. and Jerger (143,144). In children the tympanogram is classified as abnormal when SA is < 0.2 mmho (B curve) and/or if the TPP is < -139 or > +11 daPa. An A curve (SA ≥ 0.2, TPP > -139 daPa) is interpreted as normal. When the pressure is < -139 daPa and the SA ≥ 0.2 mmho it is determined as C curve indicating negative middle ear pressure. It can further be divided to C1 and C2 curves, and the cut-off point is -300 daPa. Normal tympanometric width ranges from 50 to 150 daPa (143,144). Depending on instrumentation, some authors have used slight modifications of these classifications.

Fig. 2. Three tympanograms; B curve, C1 curve and A curve.

The sensitivity of tympanometry in the detection of middle ear fluid against the gold standard of the presence or absence of MEE, has varied between 58-93 % and the specificity between 71-93 % (139,140,145-147). Orchik et al. classified the amount of MEE found in myringotomy in four categories; none, minimal, moderate and impaction. They reported that in 89 % of ears with a B tympanogram at least a moderate amount of effusion was found, but 33 % of ears with a type A tympanogram also showed a notable amount of effu-
sion in myringotomy (148). The predictive value of a C curve was uninformative. Nozza et al. developed diagnostic criteria for a device they used and reported sensitivity of 83 % and specificity of 87 % at best, when combining SA and the tympanometric gradient (149). When combining tympanometry and pneumatic otoscopy, sensitivity increases to 90-98 % and specificity to 80-93 % (138,139,141).

Tympanometric results have been shown to correlate with conductive hearing loss caused by MEE in young children in some studies. A type B tympanogram suggests a pure tone air conduction threshold greater than 25 dB with a sensitivity of 91-93 % and a specificity of 71-76 % in 3-10-year-old children (150,151). An even better result of tympanometric screening has been reported by Haapaniemi, who stated that TPP>150 daPa is even better than 15 dB hearing screening in the detection of MEE in 7-14-year-old children (152). However, the correlation of tympanometric findings to hearing level in children under three years of age has not been determined.

Most of the previous studies concerning the reliability of tympanometry have been carried out with clinic tympanometers, which are impractical in out-patient use. Minitympanometry is portable tympanometry that has been developed for use in primary care. It has five parts: pressure transducer, pump, loudspeaker, microphone and microcomputer. A 226 Hz probe tone is introduced into a sealed ear canal. A microphone records the sound pressure in the ear canal. The sound level is maintained at a constant 85 dB SPL (Sound Pressure Level) throughout the test. When the amount of sound energy absorbed by the middle ear increases, the voltage to the loudspeaker increases, thus maintaining the constant SPL. The voltage required to maintain the probe tone at 85 dB SPL is proportional to the acoustic admittance of the ear. Air pressure in the ear canal is changed throughout the test by the pump mechanism, and the acoustic admittance is displayed as a function of the ear canal volume (142).

There is still some disagreement about the accuracy of minitympanometry in detecting MEE, and in particular the specificity has been relatively poor. When clinic tympanometry serves as a reference instrument, the sensitivity and specificity have been 96 % and 81 %, respectively (153). When minitympanometry is compared with the gold standard, its sensitivity and specificity values have varied between 90-94 % and 48–63 % in pre-school children, respectively (138,153). In a Finnish out-patient clinic study, false negative findings were found with minitympanometry in 3 % and false positive findings in 7 % of children, when compared with pneumatic otoscopy (154). Interobserver validity of minitympanometry has been shown to be high, up to 95 % (155).

Previous studies have been mainly carried out with older children, which decreases the applicability to primary care. Although cooperation of the children at the time of tympanometric examination probably affects the accuracy of tympanometry, it has not been mentioned in all studies. In addition, differences in quality and quantity of MEE may affect the accuracy of tympanometry. Children at the age of highest risk of AOM have been examined in only a few studies.

In most of the previous studies concerning the accuracy of tympanometry, myringotomies have been performed under general anaesthesia and one explanation offered for the relatively poor specificity values has been the displacement of MEE into the ET by anaesthesia gases (138,146,147,156-158). It is well documented that anaesthesia gases, especially nitrous oxide (N₂O), increase middle ear pressure (159-161). Gates and Cooper also found rising middle ear pressure, but they concluded that it was due to assisted mask venti-
lation (162). However, Levy et al. in a well-planned study demonstrated direct gas diffusion from blood into the middle ear. They tracheotomized 4 guinea pigs and sealed the proximal part of the trachea (163). Freon-22 breathed through the distal part of the trachea was found in each middle ear appearing there through diffusion from the blood. Similarly, N2O should diffuse from the blood into the middle ear cavity, and the middle ear mucosa was suggested to play an active role in a gas composite exchanging (163). This is also supported by the result of another study, where significant changes of N2O concentration across the middle ear mucosa were found during general anaesthesia (164). Disagreement still exists about the effect of increased middle ear pressure on MEE.

2.3. Consequences of otitis media

2.3.1. Infectious complications

Severe infectious complications as sequelae of AOM, such as labyrinthitis, petrositis, intracranial infections and abscesses are uncommon nowadays in Western countries (1). Since the pre-antibiotic era, the incidence of acute mastoiditis, which is the most common complication of AOM, has declined dramatically (165). Previously streptococci were the typical bacteria detected in acute mastoiditis but in a recent analysis of 57 cases, S. pneumoniae was the most common causative pathogen (165,166). A conservative approach using intravenous antibiotics and a drainage procedure seems to be equally effective as surgical therapy in the management of acute mastoiditis (166). Complications such as subperiostal abscess, meningitis and facial palsy developed in 23 % of patients with acute mastoiditis in the 124 patients with acute mastoiditis (167). The high proportion of patients who present with complications of mastoiditis may reflect the masking effect of antibiotics or a delay in diagnosis. In developing countries mastoiditis still occurs in 0.19 % to 0.74 % of schoolchildren (168). The incidence of facial palsy as a complication of AOM also diminished after the introduction of antibiotics, from 5/1000 to 5/100 000 (169). In an analysis of 23 patients complete remission was seen in all but one case (169). van Buchem reported that withholding initial antibiotics in AOM treatment in the Netherlands has not been shown to increase the incidence of complications of AOM (112). However, a conservative approach and withholding of antibiotics in the treatment of AOM has increased the occurrence of acute mastoiditis in Germany (170).

2.3.2. Duration of effusion

Because a tendency for spontaneous recovery and the appearance of asymptomatic episodes in MEE, exact figures for the time spent with effusion after AOM is difficult to evaluate. In ten placebo-controlled studies, the spontaneous cure rate was 14 % to 88 % (119). When using tympanometry in screening for the presence of middle ear fluid, pathological findings indicating effusion have been detected in about 7-20 % of 2 to 3-year-old Danish children, depending on the season of the year (171,172). A tendency of spontaneous reso-
lution has also been demonstrated in screening studies (171-173). After an episode of AOM, MEE persists for more than four weeks in about 40% of children (129,174). In children aged under and over two years of age, effusion was still found in 57% and 46% of placebo-treated children six weeks after the onset of AOM in 527 episodes, respectively (117). In a study of 498 children from greater Boston, the authors estimated that the mean time between diagnosis and resolution of effusion is 23 days in actively treated children (9).

Children less than 24 months of age have a 3.8 times higher risk of persistence of effusion after AOM than older children, which may be a consequence of a similar pathophysiology as that predisposing them to AOM (64). A previous episode of AOM is also a strong risk factor, odds ratio 11.9, for chronic MEE (175). The risk disappears after a period of three months without OM. In a survey of 95 infants followed up to three years of age, the mean duration of bilateral MEE at each episode in groups with low and high AOM incidence was 6 and 10 weeks, respectively (176). Thus duration of effusion is associated with recurrent AOM.

The average time spent with MEE in all children during the first three years of life, which is the most critical age regarding language development, is considerable. In the cohort from greater Boston, the total time spent with MEE during the first, second and third year of life was estimated to be 29, 27 and 18 days, respectively (177). Friel-Patti and Finitzo reported an even higher duration in children aged 6-18 months. The mean time spent with MEE was 62 days per year (178), which was about the same as in a study by Roland et al (179). Recently, Paradise et al. reported the mean cumulative proportion of days with MEE to be 19% in the first year and 15.6% in the second year in a cohort of 2253 infants. About 45% of urban children suffered persistent MEE for three months in the first year of life (10).

### 2.3.3. Influence on hearing

#### 2.3.3.1. Measured by conventional methods

Adverse long-term developmental effects of OM have been considered to be a consequence of hearing loss caused by MEE (178). Because of the lack of cooperation in small children, only few investigators have evaluated hearing impairment caused by AOM in children under three years of age. Olmstead et al. found hearing loss more than 15 dB in 67% of children aged 2.5 to 12 years in an initial audiogram following the diagnosis of AOM (180). In a study comparing different treatment modalities in AOM, 31% of the patients showed an air-bone gap of more than 20 dB in 2- to 12-year-old children one month after diagnosis (112).

Hearing loss in OME has been evaluated in several studies. In children under 15 years of age, the mean hearing level of speech frequencies was 27.6 dB, and in 38% of the patients hearing loss was more than 30 dB (181). In a study by Fria et al., the authors used behavioural observation audiometer, incorporating conditioned responses to an animated toy in 222 infants aged 7-22 months, and pure tone audiometer in 540 children aged 2 to 11 years to examine hearing levels in OME (182). MEE was associated with an average hearing level
of approximately 27 dB at 500, 1000 and 4000 Hz. 30 % of the older children had a pure tone average of 30 dB or more, the range varying from 0 to 50 dB. In the group of infants with bilateral OME, the mean speech awareness threshold was 24 -26 dB (182). Cohen and Sade found similar hearing thresholds in cases of secretory OM in 222 children (183). Hearing loss caused by chronic MEE has also been evaluated by the auditory brain stem response. The mean hearing threshold was 32 dB in 328 ears in children between the ages of 6 to 18 months (179). Hearing loss seems to depend both on the quantity and the quality of effusion (184,185).

2.3.3.2. Measured by otoacoustic emission

To obtain objective and ear-specific data in young children concerning possible hearing loss caused by MEE, the only applicable methods are measurements of auditory brain stem responses and otoacoustic emissions (OAEs). Even though auditory brain stem responses have been claimed to be useful in evaluating hearing in infants with MEE, the long time required for the examination has limited its use (186). Otoacoustic emissions are sounds measured in the external ear canal that are a reflection of an active process occurring in the outer hair cells in a healthy inner ear (187). They consist of the backward leakage of the energy of the basilar membrane travelling wave. This leakage is caused by spatial irregularity within the rows of outer hair cells. The phenomenon can be measured in almost all closed ear canals with normal middle ear and cochlear function (188). Because the cochlea is frequency-specific in its response, frequency-specific information can also be obtained by measuring OAE (188). There are two classes of OAE: spontaneous and evoked. Spontaneous emissions can be measured in the external ear canal without external sound stimulation. They are present in about 60 % of persons with normal hearing. Evoked OAEs are elicited by external sound stimulation. They can further be divided into stimulus-frequency, distortion-product and transient evoked otoacoustic emissions (TEOAEs). According to Probst and Harris, TEOAEs are preferable for screening purposes, whereas distortion-product otoacoustic emissions may be more valuable for monitoring cochlear changes clinically (189). TEOAEs are elicited by brief acoustic stimuli such as clicks or tonebursts and they can be detected in essentially all normally hearing ears in sealed ear canals (190). Because MEE causes stiffening of the TM and ossicular chain, it reduces transmission of acoustic stimulation level and also the backward transmission of OAE, the latter being particularly affected (188). Changes in middle ear pressure also alter the responses of TEOAE (191-193).

When comparing the results of TEOAE measurement with audiometric findings, it has been stated that when the overall hearing is better than 20 dB, TEOAEs are present in more than 90 % of ears. When hearing loss is more than 20 dB, TEOAE responses decrease sharply, being absent when the hearing level is 30-40 dB or poorer (194). Other authors have also concluded that when the sensorineural hearing level exceeds 20-30 dB, TEOAEs are usually not measurable (188,189,195,196).

In previous studies the effect of MEE on responses in TEOAE measurement has been variable. Owens et al. recorded TEOAEs in children with chronic MEE diagnosed by B tympanogram and otoscopy and whose average hearing loss was 25 dB. None of the 20 ears
with effusion demonstrated normal TEOAEs (197). In contrast, Amedee found measurable TEOAEs in 50% of 60 ears with MEE in 30 children aged 23 - 88 months (198). None of the patients with mucoid effusion showed responses in this study. The author concluded that the presence or absence of emissions was primarily a function of the type of middle ear fluid (198). When comparing TEOAE with Play audiometry at the 20 dB level, TEOAE has been demonstrated to be sensitive method in detecting conductive impairment (199). This is in agreement with Hall et al., who stated that TEOAE can be recorded in middle ear disease only when hearing thresholds are 30 dB or better (195). Nozza et al. found measurement of TEOAE to be a reliable method in screening for hearing impairment and middle ear disorders (200). Thus, TEOAE measurement seems to be an accurate method in detecting conductive hearing loss induced by MEE in small children and infants.

2.3.4. Late sequelae of otitis media

Development of the phonological system is dependent on the child’s repeated experience with spoken language. Phonetic prototypes are necessary for language perception preceding speech comprehension (201). The latter half of the infant’s first year is a critical period in learning language and during this period infants begin to acquire a vocabulary (202). The fundamental task of language acquisition and segmentation of words from fluent speech can be accomplished by 8-month-old infants, based on statistical relationships between neighbouring sounds (203). In addition 8-month-old infants are beginning to engage in long-term storage of words that occur frequently in speech, which is an important prerequisite for learning language (202). The critical period for phonology has been found to be in the second half of the first year of life, for syntax it is up to the end of 4th year of life and for semantics up to the end of the 15th –16th year of life (204). Since a fluctuating hearing ability increases the variation of perceived sound patterns even more than a constant hearing loss and thus impairs the recognition of words in infancy, a fluctuating hearing loss during the sensitive period may be even more hazardous to language development than a stable, mild hearing impairment (205).

In 1969 Holm and Kunze reported that a fluctuating hearing loss accompanying chronic OM before the age of two causes delay in speech and language development at the age of 5 to 9, measured by various tests (206). One of the first prospective studies in 1988 revealed a significant association between the time spent with MEE and language development (207). Teele et al. followed 207 children from birth to the age of seven, at which age they assessed intelligence, academic achievement, speech and language (177). Confounding variables were controlled by multivariate analysis and they found that the time spent with MEE during the first three years of life was inversely associated with ability in speech, language and school performance in reading and mathematics. No association was found between OM suffered during years 4-7 and performance at the age of seven (177).

In a study of 394 children, retrospective data were collected from parents by questionnaire to obtain a history of OM (208). The validity of retrospective data from a random sample was checked by comparison with medical records, and the information given by the parents was found to be accurate. Multiple regression analysis adjusted for confounding variables showed that children with more than four otitis episodes before the age of three years
performed significantly less well in the reading comprehension test at the age of nine, and the adverse effect was stronger among girls than in boys. Reading comprehension test result correlated with the teacher’s grading of the student’s reading (208). When teachers evaluated the performance of 1708 children at school at the age of seven and the result was compared with otitis history, recurrent OM episodes before the age of three were associated with lower performance in various mathematical skills (RR 1.2 –1.4, 95% CI 1.0 to 1.7) and classroom concentration among girls (RR 1.4, 95%, CI 1.1 to 1.4) (209). The boys with recurrent otitis episodes performed poorly in reading (RR 1.3, 95 % CI 1.0-1.6) and oral performance (RR 1.2, 95% CI 1.1 to 1.4) (209).

Most of the studies evaluating the association between hearing and developmental disorders have been based on epidemiological evidence and not on serial hearing measurements, which would more reliably show the relation between fluctuating hearing loss and late sequelae of OM. This restriction has been overcome in a survey by Friel-Patti et al., where auditory brain stem responses were recorded in order to evaluate hearing levels in 14 otitis prone and 14 non-otitis prone children at the ages of 6, 12 and 18 months (205). Language development was assessed at the age of 24 months. In the otitis-prone group 71.5 % of children showed language delay, with 42.9 % delayed greater than 6 months and it was related to conductive hearing loss. In the control group 21.4 % of children suffered from language delay (205). Similar risk factors for OM and for delayed developmental disorders may have confounded the results in some studies, even though multivariate regression analysis were performed. The fact that there are only minor differences in risk factors for OM among healthy siblings has been utilized in a study by Sak and Ruben, who compared 18 children with a history of recurrent MEE with their effusion-free siblings. They found significant associations between verbal ability, auditory decoding and spelling skills, and recurrent MEE (210). Otitis-prone children are particularly considered to produce consonants less accurately than their counterparts with little or no history of OM (211). There are also reports which indicate that OM is associated with behavioural problems (212,213).

On the other hand, there are several studies which have failed to demonstrate any relationship between early OM and cognitive, language and psychosocial development. In a prospective study of 88 children, a modest association between time spent with MEE and low measures of language and cognitive skills was found at the age of two years (214). The authors explained the result by the finding that children with more OME lived in less caring environments. However, the total time with MEE in this study was 82.5 % between 6 and 14 months, which could have caused bias in the control group. Some investigators have included only socially disadvantaged children (215,216), or evaluated AOM occurring in children older than three years (217), or in children with repaired palatal clefts (218). All of these factors may bring about the result of the study towards non-significancy. Because of the time-consuming tests required to evaluate cognitive abilities, language and reading, study population tend to be small, which can also make the result non-significant (219). The heterogeneous tests and differences in language in various countries also hamper the comparability of studies. Other confounding factors may be difficulties in the diagnosis of MEE, interaction between risk factors and limitations in research designs (220).

There is also some evidence that OM in childhood is associated with permanent high frequency hearing loss (221,222), which seems to be mainly of the conductive type (223). Neither recurrent AOM or its treatment seem to cause permanent sensorineural hearing loss in speech frequencies (224).
Despite the lack of agreement about the late developmental consequences of childhood recurrent OM, in most of the studies at least some tendency towards an adverse effect of OM has been detected. Thus, a symposium of developmental implications of early life OM concluded that a child with OME should at least be provided with an optimal listening and language-learning environment (225).
3. Purpose of the study

The purpose of the present study was:

1. To determine the temporal development of AOM.
2. To evaluate how the symptoms of the child and parental suspicion of AOM predict the existence of AOM.
3. To assess which signs are accurate in diagnosing middle ear effusion by pneumatic otoscopy.
4. To find out if diagnostic accuracy in OM can be improved with minitympanometry and to assess whether there is an association between the tympanogram and the amount of MEE.
5. To evaluate if N₂O in general anaesthesia has an effect on middle ear pressure and the amount of MEE.
6. To evaluate the hearing loss in OM measured by TEOAE.

The overall aim of the study was to improve accuracy in the diagnosis of MEE and to evaluate hearing loss resulting from it.
4. Patients and methods

4.1. Temporal development of acute otitis media (I)

A total of 857 previously healthy day-care children aged 0.6-6.9 years (mean 3.7 years) were enrolled from 34 day-care nurseries. The parents were asked to register all the symptoms, especially fever, cough, rhinitis (clear, cloudy, obstructive), earache, sore throat, vomiting, diarrhoea, night restlessness, irritability, poor appetite and conjunctival symptoms of their child during the study period. When a child had any of the following acute symptoms: rhinitis, cough, sore throat or conjunctivitis, the child was considered to have URI. The symptoms were registered on symptom sheets that were collected monthly. During visits to the clinic, the parents were also asked whether they suspected that their child had AOM or not.

At the beginning of the study, all the children were screened for MEE by hand-held (Micro Tymp® Welch Allyn) minitympanometry and, if the finding was abnormal, by pneumatic otoscopy. Children were included in the study only after complete resolution of MEE. When a child had any symptoms suggestive of URI, the parents were asked to bring him/her to the outpatient department within 3 days of the beginning of the episode, and if AOM was not diagnosed, once a week until the symptoms disappeared. Whenever the child had earache or a sore throat or if the parents suspected AOM, they were asked to bring their child to the clinic the same day. During the visit, a trained nurse performed a minitympanometric examination. Tympanometry was repeated at least three times before an abnormal tympanogram was accepted. The tympanogram was classified as abnormal if SA was < 0.2 mmho (B curve) or if TPP was < -139 (C curve) or > +11 daPa (positive curve) together with SA over 0.2 mmho. An A curve (SA ≥ 0.2 mmho, TPP -139 - +11 daPa) was interpreted as normal. Pneumatic otoscopy was always performed when the finding in tympanometry was interpreted as abnormal, or the examination was not considered reliable, or if the child had a sore throat or earache (or if the parents suspected it), or if there was discharge from the ear. The otoscopic criteria for the diagnosis of AOM were discharge from the ear, an air-fluid level behind the TM or a cloudy or red TM together with impaired mobility accompanied by the symptoms of URI. At least three asymptomatic days between any given URI and AOM episodes were required before they were registered as separate events. The disappearance of possible previous middle ear effusion had also to be verified before registering a
new episode of AOM. AOM was treated with amoxycillin (40 mg/kg) for 7 days whenever there was no contraindication for this medication.

Children who had had at least one episode of respiratory tract infection with AOM during a three-month follow-up period were included in the analysis of temporal development of AOM. The time lag preceding the diagnosis of AOM after the beginning of URI was registered, and the onset of earache was calculated from the symptom diary. A possible individual tendency to develop AOM with a consistent pattern was analyzed among the children who had had more than one episode of AOM. The hypothesis that children with a history of recurrent episodes of AOM have a different pattern in developing AOM compared with children who have had only few attacks was tested by comparing the temporal development of AOM between these two groups. The children who had undergone operative treatment because of recurrent AOM or who had had more than five episodes of AOM before entering the study were classified as having recurrent episodes of AOM. The possible effects of gender and age on the developmental pattern of AOM was also analyzed.

Because the children were not examined daily during their URI, we carried out two further analyses to assess the possible delay in the diagnosis of AOM. The developmental pattern of AOM was compared between the children whose diagnosis of AOM was based on discharge from a ventilatory tube or from a spontaneous perforation, and all the other children with a diagnosis of AOM. We also compared the time lag between developing AOM after the onset of URI in children with and without earache.

4.2. Symptoms of acute otitis media (II)

The population in series II was the same as in series I. Only the first attack of AOM during each URI episode was included in the analyses. Children who had persistent symptoms of URI for more than 30 days were excluded from the analyses. Only those children who had had respiratory infections both with and without AOM during the follow-up period were included in series II. The symptoms during an episode of AOM were compared with the symptoms during an episode without AOM. Calculations involving parental suspicion of AOM were carried out for the whole study population, with a total of 345 episodes of AOM.

4.3. Pneumatic otoscopy in the detection of middle ear effusion
(previously unpublished data)

A total of 76 children referred for adenoidectomy and/or tympanostomy tube placement in the Department of Otolaryngology of Oulu University Hospital were included in the study. Thirty-nine (51 %) of the patients were boys and the ages ranged from 7 months to 9 years (mean 2.5 years). The previous otological history was obtained by parental interviews. All the children were examined preoperatively by using pneumatic otoscopy by the same otolaryngologist and the appearance, position and mobility of the TM was registered. Myrin-
gotomy was performed on each ear and the presence of effusion was registered. Signs and motility of the TM were registered and compared with the absence or presence of MEE.

4.4. Minitympanometry in the diagnosis of otitis media (III)

Two different sets of patients were enrolled to the series III. The first set consisted of children brought to the Out-patient Emergency Department of Paediatrics, University Hospital of Oulu, with any sign or symptom of infection. A trained nurse performed minitympanometric examination (MicroTymp® Welch-Allyn) in a total of 206 children, 130 boys and 76 girls, whose mean age was 4.7 years, ranging from one month to 16 years. The success rate and the time needed to perform minitympanometric examination on each ear were recorded.

The second set of patients consisted of 162 consecutive children (68 girls and 94 boys) referred for adenoidectomy and/or tympanostomy tube placement in the Department of Otolaryngology, University Hospital of Oulu. The ages of the children varied from 7 months to 8 years (median 34 months). The patients had earlier experienced an average of 8.5 episodes of OM (range 1 to 25). Informed consent was obtained from all the parents. Ten ears out of 324 were excluded because of perforation or tympanostomy tubes. Minitympanometric examination was performed on each ear, and it was repeated if a type B tympanogram was obtained. The child was classified as non-cooperative if he or she was crying or resisted the tympanometric examination. The tympanometric findings were compared with the results of myringotomy performed on each ear under general anaesthesia. The quality of the MEE was classified by the operating surgeon as serous or mucoid.

The tympanograms were classified as type A when the SA was ≥ 0.2 mmho and the TPP -200 - -100 daPa, type B when the SA was < 0.2 mmho, and type C when the TPP was ≤ -200 daPa and the SA ≥ 0.2 mmho. Measures of the curves were interpreted separately by the authors, and in cases of disagreement, a consensus was reached through a group conference.

4.5. The effect of nitrous oxide on middle ear effusion (IV)

The study population in series IV was the same as in the study on pneumatic otoscopy (previously unpublished data, 4.3). Tympanometry (MicroTymp® Welch-Allyn) was performed on each ear before the operation by the same otolaryngologist. Four ears out of 152 were excluded because of a perforation or a tympanostomy tube. The examination was repeated during an anaesthesia before myringotomy. Myringotomy was performed on each ear by another surgeon, who was unaware of the result of the preoperative tympanometry. The presence of possible effusion was registered and the effusion was aspirated. The suction tips were weighed before and after the aspiration of MEE and the weight of the effusion was calculated. The quality of the MEE was visually classified as serous or mucoid by the operating surgeon. The tympanograms were classified as type A, when compliance was ≥ 0.3 mmho and the TPP > -100 daPa, type B, when SA was < 0.3 mmho, and type C when TPP was < -100 daPa and SA 0.3 mmho. The curves were interpreted
separately by the authors, and in cases of disagreement, a consensus was reached in a group conference.

Anaesthesia was induced with fentanyl (1-2 μg/kg) followed by thiopenthal sodium. Sixty-four of the patients were relaxed with succinylcholine and endotracheally intubated when adenoidectomy was performed. Tympanostomy only was performed on 12 children and anaesthesia was maintained by mask ventilation under spontaneous breathing. The first 39 children were ventilated with a mixture of 30 % oxygen and 70 % N₂O with 0.5 -1.0 % isoflurane (N₂O group). The following 37 children were ventilated with a mixture of oxygen and air at an oxygen fraction of 0.3 with 0.5-2.0 % isoflurane (oxygen-air group).

The N₂O and oxygen-air groups were similar with respect to age. The number of previous AOM episodes was also similar in the N₂O (mean 10 episodes) and the oxygen-air groups (mean 8 episodes). Preoperative tympanogram findings were also similar in the two groups.

4.6. Hearing loss in otitis media measured by otoacoustic emission (V)

All the children referred to the Department of Otorhinolaryngology of the University of Oulu for adenoidectomy and/or ventilation tube placement because of chronic MEE or recurrent otitis media episodes between January 1 and April 30, 1998, were regarded as candidates for the study. After informed consent had been obtained from the parents, a minitympanometric examination with a hand-held device (MicroTymp® Welch Allyn) was performed by a trained nurse on each ear after the child had been given premedication for the operation. If the first tympanogram was classified as B curve, the examination was repeated at least three times before the finding was classified as reliable.

The minitympanometric findings were classified as in series II. B and C2 curves were interpreted as abnormal and C and A curves as normal tympanograms. Only the children who were cooperative at the time of the minitympanometric examination were included in the study (102 children).

TEOAEs were measured using the Quickscreen mode of a computer-based ILO 88 Analyzer (Otodynamics Ltd., Hatfield, England) under general anaesthesia before myringotomy. Before the measurement, the external ear canal was cleaned. The stimuli consisted of a standard set of non-linear clicks with an intensity of 95 dB peak equivalent sound pressure. Alternate responses were stored and averaged in two separate buffers, A and B. The correlation between the two averages determined the reproducibility of TEOAE, which was calculated by the device and expressed as a percentage.

TEOAEs were considered to be present when the amplitude of the response was at least 3 dB above the noise level and at least halfway across each of the test frequency bands of 1 to 2, 2 to 3 and 3 to 4 kHz. When only one or two of the test frequency bands were present, TEOAEs were classified as being partially present. The TEOAE measurement was considered technically unreliable when the stimulus level in the closed ear canal was less than 71 dB. The higher the reproducibility, the more identical waves A and B appear, which indicates the presence of TEOAE.
4.7. Statistical analysis

4.7.1. Series I and II

Statistical analyses were performed by using SPSS version 7.0. McNemar’s test was used to test differences between symptoms during episodes with and without AOM. Relative risk (RR) and 95% CI were calculated for each symptom. The sensitivity and specificity of parental suspicion concerning their child’s possible AOM were calculated. The ability to predict AOM by means of various symptoms was analyzed using a logistic regression model where AOM was the dependent variable and symptoms were covariants. The duration of symptoms of URI in different groups with and without AOM was compared by using the Mann-Whitney U-test.

4.7.2. Series III, IV and previously unpublished data

Differences between the N₂O and the oxygen-air groups were tested with a two-tailed t-test for continuous variables, and a binomial test was used for the non-parametric variables. 95% confidence intervals were calculated accordingly. The sensitivity and specificity of the results of pneumatic otoscopy and the finding of a B curve in minitympanometry were assessed by using the presence or absence of middle ear effusion in myringotomy as a gold standard. The Spearman rank correlation coefficient was calculated between the SA of minitympanometry and the net weight of MEE in the cooperative group. Differences between the mean weights of effusion in ears with different types of tympanograms were first tested in one-way analysis of variance, and if the difference was significant, the analysis was continued with a t-test. The sensitivity and specificity values of different pneumatic otoscopic signs predicting acute otitis media were also calculated.

\[
\text{Sensitivity: Probability that the diagnostic test result will be positive when the disease is present} = \frac{\text{true positive results}}{\text{total patients with disease}} \\
\text{Specificity: Probability that the diagnostic test result will be negative when the disease is not present} = \frac{\text{true negative results}}{\text{total patients without disease}}
\]

4.7.3. Series V

Differences between the mean weight of effusion in the presence and absence of TEOAE were calculated by one-way analysis of variance. The Chi-square test was used to analyze the difference between mucoid and non-mucoid effusion associated with responses in TEOAE measurement. The Spearman rank correlation coefficient was calculated between the reproducibility of TEOAE and the weight of MEE.
4.8. Ethical aspects

All the studies were approved by the ethics committee of Oulu University Hospital. Informed consent was obtained from the parents. Myringotomies performed in this research were of normal diagnostic practice in children undergoing adenotomy or tympanostomy. Measuring TEOAEs in children during general anaesthesia is a non-invasive examination.
5. Results

5.1. Temporal development of acute otitis media during upper respiratory tract infection (I)

A total of 250 episodes of AOM were diagnosed in 184 children (mean age 3.0 years) during three months of follow-up. Sixty-three per cent of cases of AOM complicating URI occurred during the first week, peaking on days 2 to 5. Eighty-nine percent of all episodes occurred by the end of the second week after the onset of URI (Figure 3).

The onset of AOM in children with a history of recurrent episodes of AOM did not differ from those who had experienced only a few episodes of AOM. Nor did gender or age affect the onset of AOM. Sixty-one children had more than one occurrence of AOM in two distinct URI episodes. The temporal development of AOM during the first event did not correlate with the time lag during the second event, which was interpreted as lack of an individual tendency in the temporal development of AOM.

The 127 children with earache showed a similar time in developing AOM as children without ear-related symptoms, and also fifteen children whose diagnosis was based on discharge through ventilation tube had a similar time lag in diagnosis of AOM as other children who were diagnosed by pneumatic otoscopy. The mean duration of symptoms of URI in the subgroups with and without AOM was similar in this study, where AOM was treated effectively.

5.2. Symptoms associated with acute otitis media (II)

A total of 138 children experienced at least one episode of URI with or without AOM. The most important symptom associated with AOM was earache with a relative risk of 21.3. However, 41 % of children with AOM did not have ear-related symptoms and 15 % had earache but AOM was not diagnosed. Sore throat, night restlessness and fever were also significantly associated with AOM, with relative risks of 3.2, 2.6 and 1.8, respectively. Eight per cent of the children with AOM suffered fever more often at days 3-6 than chil-
children with URI alone (Table 2). Non-specific symptoms such as cough, poor appetite and gastrointestinal symptoms were not related to AOM.

In the total of 44 children younger than two years, only earache suspected by parents (RR= 8.5), conjunctival symptoms (p=0.016) and cloudy rhinitis (RR=3.2) correlated to AOM. In the 94 children of two years or older the value of earache was emphasized, the risk ratio being 47. Sore throat was also significantly associated with AOM, with risk ratio of 3.3. Other symptoms with positive association were night restlessness and irritability (Table 2).

5.3. The accuracy of parents prediction of their child’s possible AOM and the predictive value of symptoms (II)

The parents correctly predicted their child’s AOM in 71 % of cases. The sensitivity and specificity of their suspicion were 71 % and 80 %. The corresponding figures for children younger and older than two years were 75/75 % and 69/82 %, respectively. The best combination of symptoms, assessed by logistic regression analysis, was earache together with night restlessness which predicted AOM correctly in 71 % of cases.
Table 2. Symptoms in 138 children who had upper respiratory infection (URI) both with and without acute otitis media (AOM). Relative risks (RRs), 95% confidence intervals (CIs) and P-values*.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All (n = 138)</th>
<th>Children &lt; 2 Years (n = 44)</th>
<th>Children ≥ 2 Years (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOM (%)</td>
<td>URI (%)</td>
<td>RR (CI)</td>
</tr>
<tr>
<td>Earache</td>
<td>82 (59)</td>
<td>21 (15)</td>
<td>21.3 (7.0-106)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>19 (14)</td>
<td>8 (6)</td>
<td>3.2 (1.1-11)</td>
</tr>
<tr>
<td>Night restlessness</td>
<td>33 (31)</td>
<td>20 (14)</td>
<td>2.6 (1.1-6.9)</td>
</tr>
<tr>
<td>Fever</td>
<td>58 (42)</td>
<td>39 (28)</td>
<td>1.8 (1.1-3.2)</td>
</tr>
<tr>
<td>Conjunctival symptom</td>
<td>20 (15)</td>
<td>10 (7)</td>
<td>2.4 (1.0-6.9)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clear</td>
<td>70 (51)</td>
<td>70 (51)</td>
<td>1.5 (0.9-2.7)</td>
</tr>
<tr>
<td>cloudy</td>
<td>69 (50)</td>
<td>57 (42)</td>
<td>1.5 (0.9-2.5)</td>
</tr>
<tr>
<td>obstructive</td>
<td>57 (42)</td>
<td>48 (35)</td>
<td>1.4 (0.8-2.4)</td>
</tr>
<tr>
<td>Irritability</td>
<td>54 (39)</td>
<td>40 (30)</td>
<td>1.7 (1.0-3.2)</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>30 (22)</td>
<td>23 (17)</td>
<td>1.5 (0.7-3.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>102 (74)</td>
<td>95 (69)</td>
<td>1.3 (0.7-2.5)</td>
</tr>
<tr>
<td>Gastrointestinal (diarrhoea, vomiting or pain)</td>
<td>11 (8)</td>
<td>12 (9)</td>
<td>1.0 (0.3-2.5)</td>
</tr>
</tbody>
</table>

* McNemar’s test ** Not possible to calculate since there were no URI children with this symptom
5.4. Accuracy of pneumatic otoscopy and the value of various signs of tympanic membrane in detecting middle ear effusion (previously unpublished data)

Most of the TM signs in pneumatic otoscopy had limited value in the detection of MEE. Only impaired mobility of the TM had a moderate sensitivity value (Table 3). When the different signs were combined into an overall subjective judgement, however, an acceptable sensitivity (81 %) and specificity (86 %) were obtained (Table 3).

<table>
<thead>
<tr>
<th>Signs in pneumatic otoscopy</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red or opaque TM</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>Bulging or retracted TM</td>
<td>56</td>
<td>93</td>
</tr>
<tr>
<td>Impaired mobility of the TM</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Air-fluid level</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Overall judgement</td>
<td>81</td>
<td>86</td>
</tr>
</tbody>
</table>

5.5. Success rate and the time required to perform the minitympanometric examination (III)

Minitympanometric examination was performed successfully in 179 children (86.9 %) and failed in at least one ear in 27 children of the outpatient children. The patients who did not cooperate were significantly younger than those who allowed the nurse to examine their ears (mean 1.5 years vs. 5.8 years, p<0.0001). The mean time needed for tympanometry was 2.1 minutes (range 0.5 to 10 minutes).

5.6. Accuracy of minitympanometry in the detection of middle ear effusion in cooperative and non-cooperative children (III)

The tympanometric examination could be performed with good cooperation on 183 ears of 162 children, whereas in 131 examinations the child was not cooperative at the time of the examination among children referred for adenoidectomy and/or tympanostomy. Ten ears were excluded because of perforation or tympanostomy tubes. The mean age of the children was 40 months (median 35 months) in the cooperative group and 23 months (median 19 months) in the non-cooperative group.

The sensitivity and specificity values of the B curve in detecting MEE by tympanometry were 79 % and 93 % in the cooperative group. In the non-cooperative group sensitivity was 71 %, but specificity only 38 % (Table 4). Sensitivity and specificity of minitympanometry in the children under 24 months were 78 % and 91 %, and in children older than 24 months...
they were 79% and 94%, respectively. The proportion of unsuccessful examinations was much smaller in the cooperative group (Table 4). The net weight of the fluid varied from 5 to 695 mg with a mean of 59 mg. Most of the false A curves (A curve in ear with effusion found in myringotomy) were associated with only insubstantial amounts of effusion (Figure 4). SA had a significant negative correlation with the weight of the middle ear fluid in the cooperative group (Spearman rank correlation $r=-0.66$, $P<0.001$).

MEE was present in myringotomy in 30% of the ears. Mucoid effusion was more common than serous (59% versus 33%). The quality of effusion did not affect the findings in minitympanometry.

![Weight of middle ear fluid](image)

**Fig. 4.** The weight of the middle ear fluid of the cooperative patients classified according to the findings in minitympanometry.
Table 4. Preoperative tympanometric findings compared with the presence and the mean weight (mg) of middle ear fluid obtained in myringotomy in 314 ears of 162 children classified by the child’s cooperation at the time of the tympanometric examination. Ten ears were excluded because of perforation or tympanostomy tubes.

<table>
<thead>
<tr>
<th>Finding in myringotomy</th>
<th>Cooperative*</th>
<th>Non-cooperative**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Fluid absent</td>
<td>106</td>
<td>9</td>
</tr>
<tr>
<td>Fluid present</td>
<td>7</td>
<td>42</td>
</tr>
<tr>
<td>Weight (SD)</td>
<td>79 (49)</td>
<td>213 (117)</td>
</tr>
</tbody>
</table>

The sensitivity and specificity in the cooperative group were 79 % and 93 %, respectively. In the non cooperative group, sensitivity was 71 % and specificity 38 %. When calculating these figures, the A and C curves were summed. * Unsuccessful or unclear: 3. ** Unsuccessful or unclear: 70

5.7. The influence of nitrous oxide on middle ear effusion (IV)

The number of ears where effusion was found was similar in the N₂O and the oxygen-air groups. The mean weight of effusion in the oxygen-air group did not exceed the weight in the N₂O group. Instead a non-significant tendency towards more effusion in the nitrous oxide group was noticed. The mean weights of effusion in the N₂O and oxygen-air groups were 66.4 mg and 49.0 mg, respectively (difference is 17 mg, 95 % CI –21.1-56.0, p=0.383). (Figure 5)

The increment of middle ear pressure was indirectly demonstrated by a change in tympanograms from A curve to B curve in the N₂O group. Eighteen of the 20 type A preoperative tympanograms changed to type B tympanograms during N₂O anaesthesia. In the oxygen-air group, only 4 of the 16 type A tympanograms changed to type B peroperatively. The result was similar in the spontaneous mask ventilation group. (Table 5)
Fig. 5. Weight of middle ear effusion in 148 ears according to the use of nitrous oxide (N₂O). Nitrous oxide was used in group A and it was not used in group B. Intratracheal intubation ●, mask ventilation ▲.

Table 5. Pre- and peroperative tympanometric findings in 76 children (148 ears) under anaesthesia with and without nitrous oxide (N₂O).

<table>
<thead>
<tr>
<th>Anaesthesia</th>
<th>Preoperative</th>
<th></th>
<th>Peroperative</th>
<th></th>
<th>Number of ears with effusion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>U*</td>
<td>A</td>
</tr>
<tr>
<td>With N₂O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mask ventilation</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Intratracheal intubation</td>
<td>17</td>
<td>29</td>
<td>16</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>36</td>
<td>4</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Without N₂O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mask ventilation</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Intratracheal intubation</td>
<td>16</td>
<td>26</td>
<td>6</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>30</td>
<td>6</td>
<td>16</td>
<td>29</td>
</tr>
</tbody>
</table>

*=unsuccessful
5.8. Effect of middle ear effusion on hearing when measured by otoacoustic emission (V)

TEOAE could be measured technically reliably in 185 ears of 102 children. Among the 67 ears with effusion, no responses were obtained in 31 (45 %) ears and in 19 (28 %) ears responses were measured in all the three frequency bands. In 19 (28 %) ears with effusion, responses were recorded in one or two frequency bands. Among 116 ears with no effusion, in only 3 (3 %) ears were no responses obtained (Table 6). Reduced TEOAEs were found in 83 % of the ears with mucoid effusion and in 56 % of the ears with non-mucoid effusion, the difference being statistically significant (p<0.01) (Table 6). Responses were significantly dependent on the amount of MEE. There was a significant difference between the mean weight of effusion in the ears with no responses and the ears with responses in all three frequency bands (p<0.001). Significant negative correlation between the reproducibility of TEOAE responses and the amount of effusion was also found (Spearman rank correlation coefficient, r=-0.589, p<0.001) (Table 6).

5.9. Correlation of responses in otoacoustic emission measurement with findings in minitympanometry (V)

The minitympanometric examination could be performed reliably in 136 ears of 102 children, and the finding could be compared with those of TEOAE measurement in 124 ears in 98 children. Among the 89 ears with normal tympanograms, 65 (73 %) showed responses in all three frequency bands, while no responses were obtained in 6 (7 %) ears. Among the 35 abnormal tympanograms, reduced responses in the TEOAE measurement were present in 25 (71 %) ears. There was a significant association (p<0.01) between the weight of MEE found in myringotomy and the type of tympanogram (Table 7).

Table 6. Mean weight (mg) of effusion compared with responses in transient evoked otoacoustic emission (TEOAE) measurement in 185 ears where TEOAE could be measured reliably in the study population of 102 children operated upon because of otitis media.

<table>
<thead>
<tr>
<th>TEOAE responses</th>
<th>No effusion</th>
<th>Mucoid**</th>
<th>Non-mucoid**</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>No responses</td>
<td>3</td>
<td>24</td>
<td>191</td>
<td>89</td>
</tr>
<tr>
<td>Response in one frequency band</td>
<td>3</td>
<td>5</td>
<td>104</td>
<td>101</td>
</tr>
<tr>
<td>Responses in two frequency bands</td>
<td>13</td>
<td>6</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Responses in three frequency bands</td>
<td>97</td>
<td>7</td>
<td>75</td>
<td>120</td>
</tr>
<tr>
<td>Overall</td>
<td>116</td>
<td>42</td>
<td>138</td>
<td>109</td>
</tr>
</tbody>
</table>

*Significant (p<0.001) difference between groups, except between the groups of responses in two and three frequency bands. **Significant (p<0.01) difference in reduced TEOAE between mucoid and non-mucoid effusion.
Table 7. Mean weight (mg) of middle ear effusion classified by responses in transient evoked otoacoustic emission (TEOAE) measurement compared with normal (A curve and C1 curve) and abnormal (B curve and C2 curve) minitympanometric findings in 124 ears where a minitympanometric examination and a TEOAE measurement could be performed reliably in a study population of 102 children operated upon because of otitis media.

<table>
<thead>
<tr>
<th>TEOAE responses</th>
<th>Minitympanometric findings</th>
<th>Normal*</th>
<th>Abnormal*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>No responses</td>
<td>6</td>
<td>105</td>
<td>88</td>
</tr>
<tr>
<td>Response in one frequency band</td>
<td>3</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Responses in two frequency bands</td>
<td>15</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Responses in three frequency bands</td>
<td>65</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Overall</td>
<td>89</td>
<td>13</td>
<td>37</td>
</tr>
</tbody>
</table>

*Significant (p<0.01) difference between the weights of middle ear fluid
6. Discussion

6.1. Symptoms and temporal development of acute otitis media

Our study design concerning symptoms of AOM had some advantages compared with previous studies. The diagnosis of AOM was confirmed by both minitympanometry and pneumatic otoscopy, and in most cases by the same physician. To control possible bias of parents seeking medical help and variations in children’s reactions to different pathogens during URI, we examined the children during each episode of URI and compared the symptoms of URI with and without AOM in the same child. Symptoms of concomitant URI always confuse assessment of the specific symptoms of AOM, which may explain the variation of results in previous studies concerning the issue.

The most important symptom related to AOM in our study was earache, with a relative risk of 21.3, which is in agreement with the result of other studies (100-104). The result is not surprising because of an ongoing inflammation and infectious process in the middle ear during AOM. Assessment of possible earache in a small infant may be difficult and therefore parents may also regard restless sleeping, crying, irritability and rubbing of the ear as earache, which probably partly explains the variation of frequency figures in previous studies.

Our finding that sore throat and fever are significantly correlated to AOM, which is not supported by all studies (102), is in agreement with our understanding of the pathophysiology of AOM. Inflammation of the nasopharynx caused by viral infection may well result in a feeling of sore throat in children. The fever profile, with a greater proportion of febrile AOM children on days 2-9 is suggestive of the development of a bacterial complication of the viral disease, which agrees with the present opinion of AOM being a bacterial disease (1). The finding is also in accordance with the results of a clinical trial on AOM, where antimicrobials were found to significantly reduce fever compared with placebo (129). The association of conjunctival symptoms and cloudy rhinitis with AOM in children less than 2 years olds in this study, could be indicative of bacterial infection at all these sites, which is supported by the result of some previous studies where usually non-typeable H. influenzae has been found in conjunctival, nasal and middle ear cultures (226,227). We found no asso-
ciation between AOM and gastrointestinal symptoms, cough and poor appetite, as suggested earlier (1,99).

Even though earache was the most important symptom related to AOM, as many as 41% of the children with AOM did not have any ear-related symptoms. This is also in agreement with previous studies where the sensitivity of earache has been as low as 60% (100-102). Fifteen percent of children had earache but were found not to have AOM. Thus, AOM cannot be reliably differentiated from URI on the basis of symptoms, while even the best combinations of symptoms can predict AOM correctly in only about 71% of cases in children over and under two years.

Despite wide variation in the symptoms, the parents could predict if their child had AOM with relatively good accuracy, the sensitivity and specificity being 71% and 80%, respectively. These figures were surprisingly similar in both age groups despite the differences in the combinations of symptoms predicting AOM in these age groups. Thus parental suspicion of AOM cannot be ignored, whatever the symptoms are. The finding is also epidemiologically important, suggesting that data showing an increasing incidence of AOM based on the number of clinic visits are reliable and do not merely reflect changes in the habits of parents in seeking medical advice (15).

Variability of time in the development of AOM during URI in children and even variation in the same child is easily understood, when considering the multifactorial aetiology of the pathophysiology of AOM. Patency of the ET, severity of inflammation, function of the immunological system and virulence of causative pathogens are major aspects of the progress of AOM (1). The children in our study developed AOM during URI somewhat later than in a study of Heikkinen et al., who found 54% of AOM episodes to appear in the first four days and 75% in the first week after the onset of URI (106). In both studies the peak incidence of AOM was during the second to fifth days, which is in accordance with the finding that negative middle ear pressure manifests within the first few days after the start of URI in pre-school children (23,25). In a study by Sanyal et al. 97% of the children developed negative middle ear pressure during the first four days after the onset of URI (23). However, they also found great variation in the development of effusion, being up to 28 days.

The value of duration of URI in the diagnosis of AOM is limited. In our study, the cumulative incidence of AOM was 41% in the first four days but as many as 40% of AOM episodes developed later than one week after the onset of URI. If the parents had visited a physician only during the first two days of URI, more than 80% of the AOM episodes would have been missed. Furthermore, AOM develops irregularly even in the same child, and the temporal development of AOM in children with multiple episodes is not different from those with only a few episodes.

Prolonged symptoms and parental expectation are two reasons bringing about overtreatment of AOM (105). Even though there are some symptoms significantly associated with AOM, the duration of URI is of no help in making correct diagnosis. According to the criteria, AOM is defined as detection of effusion in middle ear together with symptoms of URI (4). Differentiation of AOM and OME can be impossible in some cases with recurrent URI with residual AOM effusion. There are no definitive symptoms or limit in the temporal development of URI which would suggest one or the other. Appearance of TM is also of limited value in distinguishing AOM from OME. However, performing tympanostomy in either case would not be overtreatment.
6.2. Accuracy of pneumatic otoscopy and tympanic membrane signs in the detection of middle ear effusion

Impaired motility of the TM had acceptable sensitivity and specificity values in detecting MEE, which agrees with results published by Karma et al. (137). The appearance of the TM had no value in our series, which is supported by the results of some studies (108,228), but not all (99,139). Karma et al. found cloudiness to be a good sign in predicting MEE, but they performed myringotomy only when they suspected AOM, which impairs the accuracy of diagnosis (137). Even the position of the TM appears to be of limited value in the diagnosis of MEE, because of its poor sensitivity. Deciding on a diagnosis of OM should always be based on detection of middle ear fluid, which is only achieved by assessing the mobility of the TM when using otoscopy. This would simplify the diagnostic uncertainty and the wide variation in diagnostic criteria demonstrated previously (99,136).

Our study population comprised of children who did not have ongoing URI, and thus AOM was not suspected. However, according to the definition of AOM, i.e. effusion appearing in the middle ear during URI, the cornerstone of diagnosis is detection of MEE. We were able to confirm that accurate diagnosis of OM by otoscopy is impossible without assessment of the mobility of the TM. Thus, performing otoscopy instead of pneumatic otoscopy is of very limited value in the diagnosis of OM, a fact which is supported by the results of earlier studies (145).

The sensitivity (81 %) and specificity (86 %) values achieved in this study are acceptably high considering that the children had suffered from several episodes of AOM and most of the children were under three years old, which impairs cooperation. In previous studies in which pneumatic otoscopy has been used in the diagnosis of AOM, the sensitivity and specificity have been 81-94 % and 74-89 %, respectively (138, 140,141). These values have been achieved by experienced otoscopists, which means that accurate diagnosis of OM is not easy to achieve. Declining frequency in carrying out myringotomy has also worsened the feedback of physicians’ diagnoses of OM.

According to a review article on OM, failure to distinguish AOM from OME is a common reason for the overuse of antibiotics (229). The author claimed that the signs of acute infection, i.e. red, yellow, grey or thickened TM, can be detected and are distinctive of AOM. A discolored TM of normal thickness and position together with decreased mobility would suggest OME (229). However, these signs have been considered to be unacceptably inaccurate method in previous studies on the diagnosis of AOM (108,137), and in our study also the appearance of the TM as regards detection of effusion was worthless. Thus, distinguishing AOM from OME on the base of the TM signs may be difficult.

6.3. Minitympanometry in the detection of middle ear effusion

We found minitympanometry to be a method well comparable to pneumatic otoscopy performed by an experienced otoscopist in detecting middle ear fluid when performed in cooperative children, which is in accordance with the results of previous surveys (138,140,141). An objective method could increase accuracy in the diagnosis of OM in primary care, where the diagnostic criteria of AOM show great variation (136). In the rare
cases of an incorrect A curve against the gold standard, the amount of fluid is insubstantial with no effect on hearing (V). The significant negative correlation between SA and the weight of MEE agrees with our result in series V, where the amount of fluid correlated to hearing loss measured by OAE (V). The clinical utility of SA has not been widely accepted, probably due to a lack of norms and standardized measurement procedures, as suggested in some previous reports (142,143). The amount of fluid in ears with type C1 tympanograms appeared to be roughly the same as in ears with type A tympanograms. Our opinion is that, in clinical practice, A and C1 tympanograms can be grouped together and interpreted as normal findings in minitympanometry. Similar suggestions have been made earlier, even though there is no general agreement on the significance of a type C tympanogram (140,153).

The great weight variation of MEE found in our study (5 mg-695 mg) partly accounts for the discrepancy in previous studies concerning the sensitivity and specificity of tympanometry, because tympanometry appears to display a normal A curve in cases of small amounts of MEE (139,140,145-147,150). Disregard of the child’s cooperation or crying and differences in interpretation may also explain the variation in specificity values of tympanometry in previous studies (145).

According to our results, minitympanometry may improve diagnostic accuracy in cases of AOM. Although minitympanometry has no value in the detection of MEE in non-cooperative children, the proportion of cooperative children among group of unselected patients in a paediatric outpatient clinic in our series was sufficiently high (87 %) to justify the use of the device in primary care. This is supported by the results of two previous studies in which clinical tympanometry and pneumatic otoscopy have been served as a reference methods (154,155). Performing minitympanometry in the age group of under two years, which is also the critical period as regards the late sequelae of OM, is less often successful than in older children.

Previously the validity of minitympanometry and pneumatic otoscopy have been compared in only one study, and the authors found the latter to be slightly more accurate (138). The sensitivity and specificity values achieved in minitympanometry and pneumatic otoscopy in this study were calculated from different populations, and non-cooperative children were also included to the analysis of pneumatic otoscopy. Thus, comparability of the figures is somewhat limited. However, both of these methods are sufficiently accurate in the diagnosis of AOM.

### 6.4. The influence of nitrous oxide on middle ear effusion

The amount of MEE was not influenced by N₂O used during general anaesthesia. The result was similar among the children in the mask ventilation group and in the tracheal intubation group, which indirectly supports a previous finding that gas diffusion into the middle ear occurs through the blood circulation (163). A negative effect of N₂O on MEE is supported by some authors, even though they did not measure the amount of effusion and the conclusions were based only on tympanometric findings (159,230). We were able to confirm indirectly a finding, that N₂O anaesthesia raises the pressure in the middle ear (159,161,163,164). The previously reported discrepancy concerning sensitivity and espe-
cially specificity values of tympanometry in detecting MEE seems not to be attributable to
displacement of MEE to the ET by way of increased middle ear pressure caused by N₂O (138,146,156-158). Thus, there must be other reasons for the diversity of the results, such as cooperation of the children, variation in the amount of effusion, interpretation of tympanograms and variations in study populations. The scale used in minitympanometry is not wide enough to measure the actual pressure during N₂O anaesthesia, which has been reported to vary from 230 to 420 mmH₂O (160). Drake-Lee and Casey showed that wide-range tympanometry predicted the findings at myringotomy even during N₂O anaesthesia (231). However, minitympanometry is of no value in detecting effusion peroperatively when N₂O is used.

The suspicion, that increased middle ear pressure forces some middle ear fluid to be
expelled through the ET is groundless. Thus, the operative surgeon can rely on the finding
during myringotomy when deciding whether to insert a ventilation tube or not. Our result
enables comparing preoperative findings of the detection of MEE by various diagnostic
tools with the result of myringotomy performed under general anaesthesia.

### 6.5. Hearing loss attributable to middle ear effusion

One of the limitations in studies concerning the association between OM and development-
al impairment later in life has been lack of evidence of hearing loss during OM (23). We
were able to confirm by objective measurement that OM of any kind in small children and
infants causes significant hearing loss, about 30 dB, in speech frequencies in 45 % of
cases, detected by absence of TEOAEs. In addition, reduced TEOAEs were obtained in 28
% of ears with effusion. The result is well in agreement with some previous studies where
the average hearing loss has been about 30 dB in small children (179,182). Unlike these
studies, we performed myringotomy immediately after the hearing measurement in order
to confirm the diagnosis and to evaluate the quality and quantity of effusion.

Children with severe hearing loss receive inconsistent auditory signals, which results in
inaccurate encoding of the information into the database from which language develops.
Thus rehabilitation of children with profound hearing loss is indicated, at least when hearing
loss exceeds 30 dB in speech frequencies. Language acquisition and segmentation of words
are accomplished in infancy by reference to the statistical relationship between neighbour-
ing speech sounds (203). It is logical to assume, that fluctuating hearing loss caused by OM
episodes can interfere with this statistical relationship and thus impair the learning of the
language. Moreover, as early as 8 months, which is also the time period of the highest inci-
dence of AOM episodes, children are beginning to engage in long-term storage of words
(202). The adverse effect of OM on later development has been related to OM episodes experi-
enced under three years of age (177,208,209). Children under three years are susceptible
to OM and they have a much higher risk of persistence of effusion after AOM (5,7,8,64).
Furthermore, previous studies have shown that the time spent with MEE can be 20 % dur-
ing the first year and 17 % during the second year and about 45 % of urban children suffer
consistent MEE for more than three months of the first year of their life (10). Combining
these facts with the results in our study, which demonstrate that OM with effusion usually
causes considerable hearing loss in small children, the diagnosis and treatment of OM cannot be ignored.

The magnitude of conductive hearing loss caused by MEE is dependent on both the quality and quantity of effusion, the latter being more important. This has not been previously documented in children. In experimental works only the amount of effusion has affected the hearing threshold (184, 185). The result agrees with our knowledge of the importance of the mobility of the TM in conducting sound waves into the inner ear. Previously, the effect of MEE on the responses in TEOAE measurement has been examined in only few studies, where the authors have found TEOAEs to be absent in 50 - 92 % of ears containing effusion (198). In one study the result of measurement of TEOAE in ears with MEE has been suspected to be dependent of the type of MEE, even though the amount of effusion was not measured (198). The great variation in the amount of effusion, 5 to 695 mg in series IV, may explain the variation of results in TEOAE measurement in previous series. This is supported by our finding of significant negative correlation between the amount of MEE and the reproducibility of TEOAE measurement.

The effect of MEE on hearing during AOM has not been previously studied in small children. We consider that non-mucoid effusion, i.e. serous effusion, better reflects the situation in AOM. It was found to impair the responses in TEOAE measurement in 52 % of cases. Thus, repeated episodes of AOM may cause a fluctuating hearing loss of more than 20-30 dB, which agrees with the result of a study by van Buchem et al. where even one month after AOM, an air/bone gap of more than 20 dB was detected in older children (112).

The value of minitympanometry in assisting detection of MEE was confirmed in the series V. We found a good correlation between the type of tympanogram and the hearing level estimated by TEOAE. There was also a significant difference in the amount of MEE in relation to the different types of tympanogram. Our finding, that conductive hearing loss caused by MEE is related to minitympanometric findings is supported by most of the previous studies conducted with older children (150-152). Only Fria et al. failed to support the relationship, which is somewhat puzzling (182). Ignoring the cooperation of the children may be an explanation for the discrepancy.

Our result showing that small amounts of MEE did not affect the TEOAE responses, facilitates the follow-up of OME and prevents possible overtreatment. Even experienced otoscopyists do not achieve better sensitivity than about 90 %, which is also the case with tympanometry. However, the hearing impairment is usually less than 20-30 dB in these cases. Thus, if small amounts of effusion are missed in pneumatic otoscopy or in minitympanometric examination, there is probably no significant hearing loss. Similarly when there is uncertainty about the possible effusion in a follow-up visit regarding OM, only re-examination is needed.

Acute otitis media is a very common problem in childhood; about every fifth child suffers from recurrent AOM, and the incidence appears to be increasing (5, 15). To prevent long-term adverse effects of OM and also to avoid overtreatment with multiple antibiotic courses, diagnostic accuracy must be emphasized among physicians dealing with OM. Selecting appropriate patients for interventions in the prevention of OM is also very important, but it is not easy to carry out as shown in a study by Alho et al. (232). Future studies may give insight regarding the ongoing discussion concerning the relationship between early-life OM and developmental impairment in children. However, there is convincing evidence of the effects of all kinds of MEE on hearing and it is reasonable to conclude that
recurrent fluctuating hearing loss during the sensitive period of language development cannot be an optimal condition for any child. It can interfere with language acquisition and learning competence, which may be permanent in some children. This should guide physicians towards active diagnosis, treatment and prevention of OM and a child’s hearing and developmental status should always be taken into account in decisions regarding middle ear diseases.
7. Conclusions

1. Even though most AOM episodes develop during the first five days, a considerable proportion of cases appear later than one week after the onset of URI. The variation in temporal development of AOM is further emphasized by the finding that there was no individual tendency in time lag of AOM.

2. Ear-related symptoms are most strongly associated with AOM, and sore throat and fever to a much lesser extent. It appears, that various symptoms and the duration of URI are of little value in helping the diagnosis of AOM. However, parental suspicion of AOM in their child should not be ignored.

3. Carrying out otoscopy without assessing the mobility of the TM leads to an unacceptably low accuracy in diagnosis of OM. Impaired mobility of the TM is the most accurate mark in the prediction of MEE, but other TM signs are inaccurate.

4. Minitympanometry is a method well comparable to pneumatic otoscopy performed by an experienced otoscopist in detecting middle ear fluid when carried out with a cooperative child. An association between amount of MEE and finding in minitympanometry was found.

5. Nitrous oxide increases middle ear pressure in general anaesthesia. However, it has no influence on the amount of MEE. Validity tests of diagnostic devices used in the detection of MEE can be performed during general anaesthesia with N₂O.

6. Both the quantity and quality of MEE have an influence on hearing thresholds measured by TEOAE. Thus, repeated episodes of OM may cause fluctuating hearing loss of more than 20-30 dB, which can be consider to be a risk factor for development requiring normal hearing.
8. References


62


