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Tympanometry in Diagnosis and Follow-up of Otitis Media in Children less than Two Years of Age

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Cover
"It is so easy, even children are able to do it!"

To children

-they deserve the right for correct diagnoses

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1 SUMMARY

The burden of ear infections is heavy for families, health care personnel and society as well for children. The diagnostics of otitis media are complicated, especially in infants. Otoscopic examination is subjective. Furthermore, a large proportion of otitis media is diagnosed in busy emergency care departments at inconvenient hours. The uncertainty in the diagnostics may result in overdiagnosis and unnecessary treatment. Increased antimicrobial consumption may aggravate the bacterial drug resistance situation.

In this study, the application of tympanometry to diagnosis and follow-up of otitis media in open care was evaluated. In the Finnish Otitis Media Studies conducted by the National Public Health Institute, tympanometry has been routinely used in diagnostics of respiratory infections in children less than two years of age. Longitudinal follow-up of study children from 2 to 24 months of age combined with detailed documentation of the findings has enabled a large-scale assessment of tympanometry.

Specifically, a high concordance in interpretation of graphical tympanograms was achieved among the study physicians. The diagnostic validity was high even in infants, the age group where conventional diagnostic methods are especially questionable. In the classification method employed, a high specificity was achieved with moderate sensitivity. The positive predictive value, suitable for clinical decision-making, was excellent. Furthermore, normative values were determined; a clear need of age-specific norms for the development of refined diagnostics was confirmed. Tympanometry was found to be valuable in the assessment of risk of developing otitis media during respiratory infection. A negative middle ear pressure finding increased the risk of subsequent ear disease within three weeks. The occurrence of otitis media in children with negative middle ear pressure was lower than previously reported. However, if otitis media was diagnosed concomitantly with negative middle ear pressure, the bacterial culture of the middle ear sample was predominantly negative.

Tympanometry is a suitable aid in increasing the accuracy of diagnosis for ear infections. Considerable value is expected especially in the examination of young children. Tympanometry might be useful even in decreasing antimicrobial consumption by decreasing false diagnoses of acute otitis media and by identifying infections suitable for expectant follow-up without antimicrobial treatment.

2 TIIVISTELMÄ

Äkillinen välikorvatulehdus on merkittävä kansanterveydellinen ongelma yleisyytensä ja vaatimiensa hoitoresurssien vuoksi. Korvatulehdusten diagnostiikka on ongelmallista. Kohteena ovat pienet lapset, joiden tutkiminen saattaa olla hankalaa. Tärykalvon tarkastelu perustuu subjektiiviseen arviointiin. Lisäksi tutkimus joudutaan usein suorittamaan kiireisillä päivystysvastaanotoilla epämukavina työaikoina. Epävarmuus korvatulehdusdiagnostiikassa johtaa herkästi taudin ylidiagnostisointiin ja turhiin hoitoihin. Runsas antibioottien käyttö johtaa puolestaan bakteerien vastustuskyvyn lisääntymiseen.

Tässä tutkimuksessa selvitettiin tympanometrian soveltuvuutta avohoidon korvatulehdus-diagnostiikan ja seurannan apuvälineeksi. Kansanterveyslaitoksen korvatulehdustutki-muksissa tympanometriaa on käytetty alle 2-vuotiaiden lasten hengitystieinfektioiden yhteydessä. Tarkka lasten hengitystietulehdusten pitkittäisseuranta sekä löydösten yksityiskohtainen dokumentointi mahdollisti laaja-alaisen arvioinnin tympanometrian osalta.

Graafisten tympanometriatulosten tulkinta todettiin yhdenmukaiseksi useiden lääkärien tulkitessa tympanogrammikäyriä. Tympanometrian diagnostinen osuvuus todettiin tarkaksi alle 1-vuotiailla lapsilla, joilla perinteinen diagnostiikka on hankalinta. Tutkimuksen herkkyys todettiin kohtalaiseksi. Poikkeavan tuloksen positiivinen ennustearvo taudin suhteen oli erinomainen. Laajasta tutkimusaineistosta määritettiin normaaliarvot alle 2-vuotiaille lapsille. Todettiin selkeä ikäriippuvaisten normaaliarvojen tarve diagnostiikkaa kehitettäessä. Tympa-nometriasta todettiin olevan apua arvioitaessa välikorvatulehduksen ilmenemisen riskiä: voimakas välikorvan alipaine hengitystietulehduksen aikana lisäsi välikorvatulehduksen ilmaantuvuutta kolmen viikon sisällä. Tutkimuksessa todettiin välikorvan voimakkaan alipai-neen liittyvän hengitystietulehdukseen ilman välikorvatulehdusta huomattavasti useammin kuin aikaisemmissa tutkimuksissa. Mikäli välikorvatulehdus todettiin alipaineisessa korvassa, oli välikorvan bakteeriviljelylöydös useammin negatiivinen kuin ilman tätä löydöstä.

Tympanometria on käyttökelpoinen apuväline korvatulehdusdiagnostiikan tarkentamiseen avohoidossa. Erityisesti pienten lasten tutkimisessa laitteesta on saatavissa selkeä apu. Tympanometriasta saattaa olla apua myös antibioottihoidon vähentämisessä: väärien positiivisten diagnoosien väheneminen sekä antibioottihoidon välttäminen tapauksissa, joissa bakteeritulehdusta ei todennäköisesti ole.

3 TABLE OF CONTENTS

4 LIST OF ORIGINAL PAPERS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals. In addition, unpublished data are presented.

I Arto Palmu, Heikki Puhakka, Tapani Rahko, Aino K Takala. Interrater agreement in tympanometry in infants. Scand Aud 2000; 29:260-265.

II Arto Palmu, Heikki Puhakka, Tapani Rahko, Aino K Takala. Diagnostic value of tympanometry in infants in clinical practice. Int J Ped ORL 1999; 49: 207-213.

III Arto Palmu, Heikki Puhakka, Heini Huhtala, Aino K Takala, Terhi Kilpi. Normative values for tympanometry in 7- and 24-month old children. Audiology 2001; 40:178-184.

IV Arto Palmu, Heikki Puhakka, Tapani Rahko, Aino K Takala, Terhi Kilpi. Predicting the development and outcome of otitis media by tympanometry. Int J Ped ORL, in press.

V Arto Palmu, Ritva Syrjänen, Terhi Kilpi, Heikki Pursiainen, Heikki Puhakka, Tapani Rahko, Elja Herva, Aino K Takala. Negative pressure tympanograms in children less than two years of age - different bacterial findings in otitis media by tympanometric results. Int J Ped ORL 2001; 61:61-69.

5 ABBREVIATIONS

AOM	acute otitis media
CI	confidence interval
daPa	decapascal
ECV	ear canal volume
FinOM Cohort Study	Finnish Otitis Media Cohort Study
FinOM Vaccine Trial	Finnish Otitis Media Vaccine Trial
KTL	National Public Health Institute, Finland
MEE	middle ear effusion
MEF	middle ear fluid
NPV	negative predictive value
OM	otitis media
OME	otitis media with effusion
OR	odds ratio
PncCRM	a pneumococcal conjugate vaccine, capsular polysaccharides conjugated to CRM197 protein
PncOMPC	a pneumococcal conjugate vaccine, capsular polysaccharides conjugated to OMPC protein
PPV	positive predictive value
SAA	static acoustic admittance
SPL	sound pressure level
TM	tympanic membrane
TPP	tympanometric peak pressure
TW	tympanometric width

6 INTRODUCTION

MOTTO: "THE TREATMENT DECISION IS EASY WHEN YOU HAVE A DEFINITIVE DIAGNOSIS"

Otitis media (OM) is a frequent occurrence in children, especially among those less than two years of age. The treatment of otitis media requires extensive resources (Freid et al. 1998) and additional caring for the sick child leading to both direct and indirect costs of considerable magnitude (Gates 1996, Niemelä et al. 1999, Capra et al. 2000). Otitis media is the most common indication for antibiotic treatment in children (Wang et al. 1999). Furthermore, otitis media is the most common indication for surgical procedures in children in USA (Owings and Kozak 1998). Despite high morbidity, otitis media has negligible mortality in developed countries. However, long-term sequelae in terms of delayed speech and language development and cognitive development (Teele et al. 1990, Teele 1994, Luotonen et al. 1996) may cause poor success in school and, eventually, in life generally.

A physician's diagnostic examination for the assessment of otitis media usually includes a short interview of the parents and (pneumatic) otoscopy. Commonly, the consultations occur outside office hours in busy on-call practices, necessitating rapid examination. Symptoms of children with otitis media are unspecific, especially in young children. Furthermore, infants are not able to express their symptoms adequately; consequently the parental interpretation may be incorrect. Thus, visual otoscopical assessment of the tympanic membrane has been the mainstay of OM diagnostics. However, otoscopical verification of the diagnosis is difficult in young children and physicians commonly feel uncertain about the diagnosis (Froom et al. 1990). Despite the shortcomings of the basic tools a high level of diagnostic accuracy should be achieved. Poor sensitivity of the diagnostics and the consequent omission of adequate treatment may lead to acute complications or prolonged episodes of otitis media, prolonged episodes of hearing impairment and consequent effects on cognitive and linguistic development. Poor specificity, on the other hand, may lead to unnecessary treatment, groundless additional concern for the parents, higher costs and increased side effects. The most frightening consequence of unnecessary treatment with antibiotics is the increased antibiotic resistance of the bacteria. Moreover, the antimicrobial treatment of otitis media is highly controversial due to its good prognosis even without treatment (Rosenfeld 1996). A reduction of antibiotic use for the treatment of acute otitis media (AOM) has been suggested

and used especially in the Netherlands (van Buchem et al. 1985, Froom et al. 1997), but elsewhere antibiotic treatment of acute otitis media is considered worthwhile (Rosenfeld 1996). More widespread reduction in antibiotic consumption could be achieved by the identification of characteristics of otitis media with excellent prognosis. These cases would be the first candidates for withholding antibiotic treatment.

Consequently, more accurate methods for the diagnosis and follow-up of otitis media are needed. Tympanometry has the potential to improve the routine diagnostics of otitis media in open care practice. Tympanometry is an easy, quick and painless non-invasive method to obtain objective quantitative results on the middle ear system.

This study evaluated the accuracy and suitability of tympanometry to open care diagnosis and follow-up of otitis media in children less than two years of age. Specifically, the interpretation of tympanometry, diagnostic accuracy for detection of middle ear fluid, assessment of normal values for the tympanometric variables, and the prognostic value of tympanometry in respiratory infection and otitis media were studied.

7 REVIEW OF THE LITERATURE

7.1 Otitis media in children

7.1.1 Definition of otitis media

Otitis media is an inflammation of the middle ear without reference to etiology or pathogenesis (Bluestone 1999). Several distinct patterns of disease establish the entity of otitis media. Acute myringitis is defined by strong inflammatory signs on the tympanic membrane in the presence or absence of middle ear fluid (Klein et al. 1989). In children less than two years of age, middle ear fluid (MEF) is commonly detected in acute myringitis (Palmu et al. 2001). AOM is manifested by the signs and symptoms of acute illness combined with evidence of acute middle ear disease presenting middle ear fluid. Otitis media with effusion (OME) refers to the presence of middle ear fluid without associated symptoms or signs of acute infection (Berman 1995, Bluestone 1999). OME is common after the acute phase of AOM before the resolution of the disease. If OME is prolonged (>3 months), the term chronic OME is used (previously commonly designated as secretory otitis media). Further classification of otitis media (Bluestone 1999) includes the complications, such as perforation of the tympanic membrane and mastoiditis. Chronic perforation may be associated with or without a middle ear infection; chronic suppurative otitis media is defined by a permanent perforation of the tympanic membrane (TM) with continuous or intermittent discharge. Effusion in the middle ear cleft is almost unexceptionally present in otitis media although the designation "otitis media without effusion" has been used for otitis cases where no fluid has been discovered (Bluestone 1999). However, most commonly the fluid-free stage occurs in the early or the late stages of an otitis media event when signs of inflammation are present in the middle ear and tympanic membrane without concomitant middle ear effusion (MEE).

However, the unequivocal clinical definition of OM is far from straightforward. Diverse definitions for AOM have been previously used in clinical practice and in research (Hayden 1981). Despite the efforts of consensus panels (Klein et al. 1989) there are still multiple different designations and definitions in the literature or clear definitions are lacking. Most commonly the combination of acute symptoms and signs of middle ear inflammation are

required for the diagnosis of AOM (Berman 1995). The definition adopted by the Finnish consensus conference (Karma et al. 1987) was as follows: both acute ear-related symptoms and signs of middle ear fluid must be present. Acute symptoms must include at least one of the following: earache, tugging at of rubbing of the ear, irritability, restless sleep, fever, loss of appetite, other simultaneous respiratory tract infection, or concurrent gastrointestinal symptoms. Special attention has to be paid to differentiate AOM from external otitis, acute myringitis and secretory otitis media (Karma et al. 1987).

The identification of the phase and type of the disease is important in the diagnosis of OM since the treatment depends on the type of the disease (Faden et al. 1998). However, the types of otitis media are difficult to distinguish clinically from each other, and a designation continuum of OM has been presented to describe the situation (Senturia et al. 1980). In the normal pattern, AOM results in the phase of OME before resolution. However, the persistence of MEF is a common complication. Chronic OME is commonly defined by a persistence of more than three months (Bluestone 1999). Furthermore, recurrent AOM (rAOM) commonly interferes with the course of a single episode and makes the assessment of the phase of the disease even more difficult. Donaldson (1987) has presented four typical patterns of otitis media (isolated, recurrent, persistent and relapsing otitis media) in children. The identification of a specific pattern could be useful for selecting appropriate treatment and follow-up (Donaldson 1987).

7.1.2 Epidemiology and risk factors

The incidence of AOM is highest in children aged less than two years of age. Up to 62% of children experience at least one attack of AOM during the first year of life and over 70% have contracted AOM before their second birthday (Sipilä et al. 1987, Teele et al. 1989, Alho et al. 1991). In a recent, large prospective study, up to 91% of children had experienced at least one episode of MEE before their second birthday (Paradise et al. 1997). Recurrent attacks are highly characteristic of AOM. There is clear evidence that the age at which children experience the highest incidence has become younger (Paavolainen 1966, Pukander et al. 1982). Furthermore, there are reports of increased incidence of AOM over the past decades (Klein 1994, Lanphear et al. 1997, Joki-Erkkilä et al. 1998). Currently, otitis media is the most common cause of office visits after the well-child visits in the United States accounting

for 17% of all ambulatory care visits in children under five years of age (Freid et al. 1998). Otitis media is also the most common indication for antibiotic treatment in developed countries (McCaig and Hughes 1995, Rautakorpi et al. 1999, Wang et al. 1999). Additionally, otitis media is the most common indication for surgical operation in children in the USA (Owings and Kozak 1998). Alho et al. (1992) reported a cumulative incidence of 7% for surgical operations in children under two years of age in northern Finland in the eighties. Up to 30% of children under 2 years of age have been reported to have undergone ventilation tube surgery within a one-year follow-up (Myer and France 1997).

In addition to the young age, various other risk factors for AOM have been identified (Uhari et al. 1996, Daly and Giebink 2000). The incidence of AOM peaks at autumn and spring concurrently with the viral respiratory infections (Vesa et al. 2001), which are the most important risk factors. Furthermore, day care outside the home, the presence of siblings, parental smoking, lack of breast-feeding, and pacifier use have been documented as risk factors, but their association with increased risk of a viral respiratory infection reduces their importance as independent risk factors (Pukander et al. 1985, Ståhlberg et al. 1986, Sipilä et al. 1988, Teele et al. 1989, Alho et al. 1990, Niemelä et al. 1995, Paradise et al. 1997).

Strong genetic susceptibility is an important risk factor for otitis media. Influence of hereditary factors is manifested by association with parental and sibling history of AOM (Stenstrom and Ingvarsson 1997), racial differences in OM (Griffith 1979, Wiet 1979, Torzillo et al. 1983), male sex, and results showing high degree of association in monozygotic twins (Kvaerner et al. 1997, Casselbrant et al. 1999).

7.1.3 Etiology and pathogenesis

Both bacteria and viruses have an important role in the etiology of AOM. The most common bacterial pathogens isolated from MEF in children with AOM are *Streptococcus pneumoniae* (26 to 39% of attacks), *Haemophilus influenzae* (12 to 23% of attacks) and *Moraxella catarrhalis* (6 to 23% of attacks) (Howie et al. 1970, Luotonen et al. 1981, Bluestone et al. 1992, Kilpi et al. 2001). Commonly, around 30% of MEF samples yield no bacterial pathogens in culture. The previously common *Streptococcus pyogenes* has become less common over the past decades (Grönroos et al. 1964, Kilpi et al. 2001). Another change in the

bacterial etiology is the increasing occurrence of *M. catarrhalis* especially in the United States and in the Nordic countries, while in some countries, like Spain, *M. catarrhalis* is a rare finding (del Castillo et al. 1996). The most alarming feature in the bacteriological reports has been the increasing proportion of pathogens resistant to antimicrobial agents. The proportion of β-lactamase-producing strains of *H. influenzae* has increased to 25 to 30% and practically all *M. catarrhalis* isolates resist β-lactam antimicrobials (Bluestone et al. 1992). However, the advent and spreading of penicillin-resistant *S. pneumoniae* has raised the most concern (Dagan et al. 1994, Dowell et al. 1999, Dagan 2000) thus further increasing the importance of the prevention of otitis media. Fortunately, Finland has had low resistance rates so far (Kilpi et al. 2001, Pihlajamäki et al. 2001), but the warning signs have to be taken seriously.

Other bacteria, such as gram-negative rods and *Staphylococcus aureus* are occasionally isolated from the MEF during AOM. For routine treatment decisions of AOM, the consideration of these pathogens is not relevant, but their role has to be reassessed if found in bacterial culture. Additionally, *Mycoplasma pneumoniae* has been demonstrated by PCR in MEF (Räty and Kleemola 2000), and *Chlamydia pneumoniae* by PCR (Storgaard et al. 1997) and culture (Block et al. 1997) in MEF. *Alloiococcus otitidis* has been recovered from OME, but not from AOM (Hendolin et al. 1999). The role of these bacteria in the pathogenesis of otitis media awaits further confirmation.

The vast majority of attacks of AOM manifest shortly after the first symptoms of a viral respiratory infection (Heikkinen and Ruuskanen 1994). Various viruses have been demonstrated in the respiratory tract during AOM. Furthermore, viruses have been isolated and demonstrated also in MEF samples. Respiratory syncytial virus, parainfluenza virus, influenza virus and human rhinovirus are the most common viral pathogens discovered from MEF samples (Berglund et al. 1966, Pitkäranta et al. 1998, Heikkinen et al. 1999). The proportion of virus-positive MEF samples has increased as more sensitive PCR methods have been employed (Pitkäranta et al. 1998, Heikkinen 2000).Viral and bacterial coinfections are common, yet pure viral infections have been documented in up to 22% of ears with AOM (Ruuskanen and Heikkinen 1994, Pitkäranta et al. 1998).

The pathogenesis of otitis media is a complex interplay of both bacterial and viral pathogens further interfered by the host response. The first step in the pathogenesis of AOM is the impairment of the Eustachian tube function due to the viral respiratory tract infection

(Bluestone 1996). Consequently, the pressure equilibration of the middle ear is disturbed and negative middle ear pressure can be observed in the initial phase (Sanyal et al. 1980, McBride et al. 1989, Moody et al. 1998). The negative middle ear pressure may lead to capillary transudation of fluid. Additionally, the drainage of the middle ear and protection against organisms and secretions ascending from the nasopharynx is impaired (Bluestone 1996). The impaired function of the Eustachian tube is mediated by increased levels of inflammatory mediators and cytokines present in respiratory infections (Ganbo et al. 1995, Noah et al. 1995) inducing swelling of the inflamed mucosa and impairment in the mucociliary function. The Eustachian tube is short and almost horizontal in position in infants and young children (Bluestone 1996, Suzuki et al. 1998), predisposing to an efflux of nasopharyngeal secretions into the middle ear.

In the nasopharynx, the viral respiratory infection increases the quantity and adherence of the bacterial pathogens colonizing the host (Wadowsky et al. 1995) and higher nasopharyngeal carriage rates of bacterial pathogens have been reported in respiratory infection and in AOM compared to healthy children (Faden et al. 1990, Syrjänen et al. 2001). As the Eustachian tube function is impaired the mucosal secretions are able to ascend and finally bacterial pathogens invade the middle ear. Once entering the middle ear the bacteria, if not prevented by host response, start to multiply. Bacterial and host inflammatory cell products attract leucocytes; the inflammatory cascade procedes and middle ear effusion accumulates. Thus, together with the host response the middle ear pathogens produce the signs and symptoms of a middle ear infection.

7.1.4 Treatment

Antibiotic prescription has been the mainstay of treatment during the antibiotic era. Since the advent of antibiotics, serious complications have become a rarity. Multiple studies have documented the bacterial eradication by various antimicrobials (Klein 1993). However, the correlation between bacteriological and clinical success is not straight-forward (Marchant et al. 1992). In meta-analyses, a modest yet significant effect of antimicrobial treatment in favor of clinical resolution has been confirmed (Rosenfeld et al. 1994, Del Mar et al. 1997). No differences between different antimicrobials were detected (Rosenfeld et al. 1994, Del Mar et al. 1997). A high rate of spontaneous recovery, both microbiologically and clinically, has

raised doubts on the rationality of routine antimicrobial treatment of AOM (Culpepper and Froom 1997).

Consequently, withholding antibiotic treatment has gained increasing popularity, especially in the Netherlands (van Buchem et al. 1981, van Buchem et al. 1985). In other countries, the duration of the treatment regimens has shortened, because equivalent results have been achieved with shorter courses of less than seven days compared to 7 to 10 day courses (Chaput de Saintonge et al. 1982, Ingvarsson and Lundgren 1982, Meistrup-Larsen et al. 1983, Bain et al. 1985, Hoberman et al. 1997, Pichichero and Cohen 1997, Kozyrskyj et al. 1998), although in children younger than 2 years longer courses may be more effective (Hoberman et al. 1997). The major motive for withholding antimicrobial treatment is the concern over increasing antimicrobial resistance and the fear over the paucity of new groups of effective antimicrobial candidates for treating infections caused by multi-resistant pathogens. Additionally, side effects and costs of the treatment would be reduced. However, an increased incidence of acute mastoiditis has been reported, and inadequate antimicrobial treatment has been suggested as one reason (Hoppe et al. 1994, Ghaffar et al. 2001).

Antihistamines and decongestants are commonly used as adjuvant therapy in AOM. However, the studies on their usefulness in hastening recovery have been mainly negative (Meistrup-Larsen et al. 1978, Thomsen et al. 1979, Moran et al. 1982, Bhambhani et al. 1983, Schnore et al. 1986). In the prevention of otitis media or in the treatment of OME, they certainly do not have any effect (Olson et al. 1978, Randall and Hendley 1979, Cantekin et al. 1983, Mandel et al. 1987). Similarly, non-steroidal anti-inflammatory drugs have no effect on the clearance of MEF (Varsano et al. 1989, Bertin et al. 1996), but pain relief was observed in the latter study. However, commonly these medications are requested for symptomatic relief of AOM and the concurrent respiratory viral infection. Prescription of these drugs is usually safe and well tolerated, although potential adverse effects demand notification of caregivers.

The use of myringotomy in the treatment of AOM has become unpopular. The advantages of myringotomy observed in Finnish studies (Puhakka et al. 1979, Qvarnberg 1981) in the reduced duration of MEF have not been repeated in more sophisticated randomized trials (van Buchem et al. 1981, Engelhard et al. 1989, Kaleida et al. 1991). However, the procedures were different: in the Finnish studies careful aspiration of the middle ear fluid was performed after myringotomy while in the remaining studies only a myringotomy incision was made

without aspiration, or else the information on aspiration was lacking in the reports. In the meta-analytic report of the efficacy of antimicrobial drugs for AOM by Rosenfeld et al. (1994) initial tympanocentesis increased the primary control rate (reduction or improvement in symptoms and signs at days 7 to 14) by 6.5%.

7.1.5 Clinical course of acute otitis media

Several different outcomes of AOM are possible after initial antimicrobial treatment (Bluestone 2000). The AOM episode may run a favorable course with rapid disappearance of symptoms and signs of acute infection. However, most commonly the symptoms abate gradually but the MEF is commonly detected for weeks after an attack of AOM (Teele et al. 1980, Marchant et al. 1984, Kaleida et al. 1987, Klein et al. 1992, Mandel et al. 1995). In a favorable case, the middle ear fluid subsides gradually. There is limited data on normalization of the tympanic membrane thickening in otitis media (Berger et al. 1996). Residual thickness of TM may complicate the assessment regarding the presence of MEF before definitive normalization. The most common recommendation is to schedule the follow-up visit for healing of AOM 1 to 3 months after the diagnosis (Bluestone 2000). After one month, majority of ears have cleared MEF (Mandel et al. 1995). Although the resolution continues up to three months, recurrent AOM may interfere with the clinical course.

In a worse case, a treatment failure may be observed with persistent symptoms and signs; even a suppurative complication may develop (Goldstein et al. 1998, Bluestone 2000). The persistence of middle ear effusion is more common in young children less than two years of age (Shurin et al. 1979, Jero et al. 1997) and in ears with a viral co-infection (Arola et al. 1990, Chonmaitree et al. 1992). Furthermore, all these courses of outcome may be interrupted by a recurrent episode with a different clinical course. Even in early recurrences within 30 days, the disease is commonly caused by a new organism different from the initial pathogen (Carlin et al. 1987). Again, the risk of recurrence is highest in children aged younger than two years (Kaleida et al. 1987).

The rate of spontaneous recovery from AOM is high even without antibiotic treatment. In a meta-analysis of antibiotic treatment of AOM, the estimated spontaneous recovery (defined as disappearance of all presenting symptoms within 7 to 14 days) without antibiotic treatment

(placebo or no drug) was 81% (Rosenfeld et al. 1994). In one study, the prevalences of MEF (diagnosed with tympanometry) were similar in the treatment group (37%) and placebo group (35%) after 30 days (Burke et al. 1991). Thus, the majority of ears were free of disease irrespective of treatment.

7.1.6 Conventional diagnostic methods for otitis media

7.1.6.1 Symptoms

Traditionally, the diagnostic instruments for OM have been a short interview for the occurrence of acute symptoms and previous occurrence of disease and (pneumatic) otoscopy. In the case of infants and young children as patients, the examinee is generally unable to express the symptoms. The interpretation of symptoms is difficult even for the parents, becoming more difficult the younger the patient.

By definition, the presence of acute symptoms is necessary for the diagnosis of AOM. However, symptoms are compulsory but not confirmatory for the diagnosis of AOM. Symptoms of the preceding viral respiratory infection are the most common complaints in AOM (Niemelä et al. 1994, Heikkinen and Ruuskanen 1995). Presence of ear pain has the highest association with AOM (Niemelä et al. 1994, Heikkinen and Ruuskanen 1995, Uhari et al. 1995, Kontiokari et al. 1998), but ear pain is frequently caused also by other than ear-related diseases (Ingvarsson 1982, Browning 1990). Also ear pulling as the chief symptom is most commonly due to other reasons than AOM; if presented as an isolated symptom, diagnosis of AOM is highly improbable (Baker 1992). In children less than two years of age, the prediction of AOM by symptoms is more difficult compared with older children (Uhari et al. 1995). Additionally, the sensitivity of earache for diagnosis is low, especially in children less than two years of age (Hayden and Schwartz 1985, Niemelä et al. 1994).

The previous diagnoses and treatment of otitis media are relevant in the determination of the phase and pattern of otitis media (Donaldson 1987, Faden et al. 1998). These are likely to be reliable if there have been previous contacts to the physician and the diagnoses are registered and available. However, in the usual case various clinics have been visited and several physicians have given treatment to the child. This prevents continuity in the treatment of otitis

media. Especially when children followed for prolonged OME acquire acute respiratory symptoms, the discrimination between OME and AOM is difficult. Rigid application of the definitions may lead to overdiagnostics of AOM and unnecessary treatment.

7.1.6.2 Otoscopy

Otoscopy with a hand-held otoscope instrument is the routine method used for visualization of the external ear canal and TM for signs of otitis media in pediatric and general practice. Otorhinolaryngologists routinely use a headlamp or otomicroscope with Siegle's speculum. Diagnostic accuracy of otoscopy can be enhanced by pneumatic otoscopy in AOM (Schwartz et al. 1981), and especially in OME (Pelton 1998). However, the light output of the otoscopes may be inadequate if not properly maintained (Barriga et al. 1986). Furthermore, it is common that old-fashioned otoscopes with unreliable seals are in routine use in general and pediatric practices, even in University hospitals, making reliable diagnosis by pneumatic otoscopy difficult (personal observation).

The studies assessing diagnostic accuracy of pneumatic otoscopy in OME are presented in Table 1. Cloudiness, impaired movement, visible fluid level and a discharging ear are signs predicting MEF, while redness of the tympanic membrane is a considerably poorer sign (Schwartz et al. 1981, Karma et al. 1989). Redness of the TM is commonly seen without OM in children with fever, in crying children, and in ears after manipulation for wax cleansing (Berman 1995). Thus, diagnosis of otitis media should not be solely based on redness of the TM. Otoscopy is a highly subjective technique and thus prone to observer bias and variability in the technique (Gates 1986, Cavanaugh 1989). Extremely low pressures are needed to obtain movement in a normal tympanic membrane (Gates 1986). Again, the accuracy of the otoscopical diagnosis has been poorer in younger children (Gimsing and Bergholtz 1983, Froom et al. 1990). Validation of otoscopical skills (Kaleida and Stool 1992) would be highly useful for all physicians treating children with respiratory infections. However, this kind of formal validation requires considerable time and resources.

In some occurrences, pneumatic otoscopy may be difficult or even impossible to perform. If the child is poorly co-operative or the ear canal is filled with wax which cannot be removed, the otoscopical diagnosis is most likely unreliable. In a study by Schwartz et al. (1983) 57% of the children under one year of age presented with excessive ear wax impeding adequate

visualization, compared to 34% in children aged 13 to 23 months and 19% in children older than 24 months. Additionally, in young infants the position of the tympanic membrane is oblique, complicating visual assessment. And last, the ear canal may be anatomically too narrow to permit enough light to view the tympanic membrane adequately.

Table 1. Diagnostic value of otoscopy for diagnosis of otitis media with effusion compared to myringotomy in children.

First author and year	Age, years	Definition for abnormal finding	Sensitivity*	Specificity*
Paradise (1976)	0.2-5	Investigator's assessment of definite effusion	92%	83%
Cantekin (1980)	0.5-15	Investigator's assessment of definite effusion	A: 94% B: 81%	A: 82%‡ B: 82%
Karma (1989)	0.5-2.5	Impaired mobility	A: 99% B: 94%	A: 90% B: 71%
Mains (1989)	1.7-12	Impaired mobility	A: 88% B: 84%	A: 90% B: 84%
Vaughan-Jones (1992)	Mean 6.2	Investigator's assessment of effusion	90%	75%
Finitzo (1992)	0.5-9	Abnormality in color or TM landmarks and immobility	93%	58%
Nozza (1994)	1-12	Investigator's assessment of effusion	85%	71%

* if multiple otoscopists reported separately, the designations A and B are used.
‡ specificity recalculated, equivocal diagnosis interpreted as no OME.

7.1.6.3 Myringotomy

Myringotomy with aspiration is an objective method for the assessment of middle ear status and the presence of MEF. However, routine use of this procedure has decreased during the past years and decades, especially among pediatricians and general practitioners. In Finland myringotomy was performed in the 1980's in around 40% of AOM episodes (Alho et al. 1992), but already in the beginning of the 1990's in less than 20% of cases (Uhari et al. 1992). Consequently, training in the routine diagnostics of otitis media lacks the golden standard of verification of the disease, as myringotomy is only rarely performed.

Due to shortcomings in the basic tools, modern equipment has been introduced to make the diagnosis more objective and accurate. Tympanometry was introduced in the late 60's (Brooks 1968) and reflectometry in the 80's (Teele and Teele 1984). Tympanometry has a more established role in both research and clinical practice.

7.2 Tympanometry

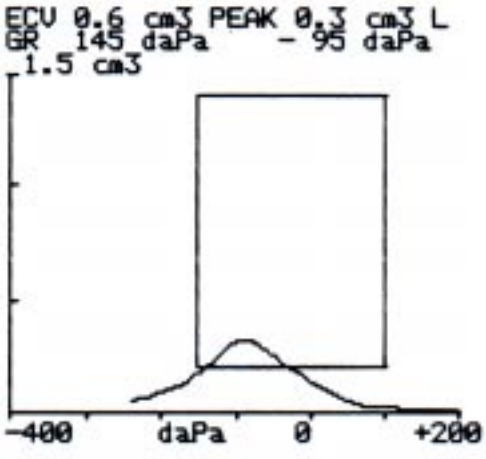
Tympanometry is an application of impedance audiometry, suitable for the diagnosis of middle ear effusion (Margolis et al. 1994), assessment of tympanic membrane perforations (Rock 1991), and for the estimation of middle ear pressure (Terkildsen and Thomsen 1959, Lildholdt et al. 1980).

7.2.1 Physical principles of immittance audiometry

The movement of acoustic energy from one medium to another is affected by the acoustic immittance characteristics of the two structures. In the ear, middle ear structures modify the transmission of acoustic energy from the air of the external ear canal (low resistance medium) into the fluid of the inner ear (high resistance medium). Immittance audiometry refers to the measurement of the transmission of acoustic energy through the middle ear system.

Tympanometry is a special application of immittance audiometry; it is a measurement of acoustic immittance of the middle ear system as a function of the changing external ear canal pressure. The immittance characteristics of the middle ear system change with varying ear canal pressure. These changes are depicted as a tympanogram (Figure 1), a graphical representation of the immittance results at different external ear canal pressures.

Figure 1. Example of a normal tympanogram.



Acoustic immittance is a combined designation including acoustic impedance and acoustic admittance. Acoustic impedance (Z) refers to the resistance of the middle ear system to acoustic energy flow, and acoustic admittance (Y) refers to the ease of flow of acoustic energy into the middle ear (Wiley and Block 1985). These are reciprocals to each other and can be calculated as Y=1/Z.

The acoustic impedance consists of resistance (R) and reactance (X), which in turn has two components: compliant reactance and mass reactance. Reciprocally, the acoustic admittance consists of conductance (G) and susceptance (B). The latter has two components: compliance and mass susceptance (Table 2).

The acoustic impedance components have their mechanical counterparts. The resistance represents the friction of two different particles when moved. The compliant reactance represents the stiffness of a spring when force is applied to compress the spring. The mass reactance represents the inertia of a mass (a particle remains in its present state until sufficient energy is applied to move the particle). Similarly, the acoustic impedance counterparts are dissipation of acoustic energy in fine mesh screens (resistance), volume of air in an open tube (mass reactance) and volume of air in a closed cavity (compliant reactance).

To make it more complex, the reactance components are out-of-phase components and are frequency-dependent. The sinusoidal force of an acoustic tone does not produce an instant increase in reactance but is in different phase, lagging 90 degrees. The compliant and mass reactance are in opposite phase; the predominant component determines the direction of the reactance. The impedance components cannot be simply summed together to get the result; rather the angle has to be taken into account. When these two components are exactly the same but in opposite phases, the total reactance of zero is achieved in a specific frequency, called the resonant frequency of the ear.

However, in low frequencies, like the 226 Hz normally used for conventional tympanometry, the compliance is the major susceptance variable and the mass susceptance has negligible impact. The designation "stiffness-dominated" has been used (Shanks and Shelton 1991). Additionally, the conductance of the ear is lower on low frequencies compared to the compliance. Thus, in ideal circumstances of minimal conductance, the admittance could be expressed as compliance similar to the volume of an air column in a hard-walled cylinder.

In middle ear disorders these immittance variables are subject to change to a various degree and they can be measured by tympanometry. The contrast to a normal finding can be observed most dramatically in a fluid-filled middle-ear cavity when the interface of air-tympanic membrane-air is changed to air-tympanic membrane-fluid in otitis media with effusion.

Table 2. Tabulation of the admittance variables and the corresponding impedance, acustic, and mechanical counterparts (Popelka 1984, Wiley and Block 1985).

Admittance variable and its symbol	Reciprocal variable and its symbol	Impact on low frequency	Acoustic counterpart	Mechanical counterpart
Admittance Y	Impedance Z			
1. Susceptance B	1. Reactance X			
Compliance jB	Compliant reactance -jX	Major	Air in a closed tube	Spring
Mass susceptance -jB	Mass reactance jX	Minor	Air in an open tube	Mass
2. Conductance G	2. Resistance R	Constant	Fine-mesh screen	Friction

7.2.2 Historical perspective

Initially, the interest in measuring the acoustic impedance of the ear was due to the introduction of the telephone and its technical development (Shallop 1976, Thomsen 1999). Metz (Metz 1946) introduced the concept of acoustic impedance to clinical practice in audiology. He used a modified mechanical acoustic impedance bridge to measure impedance on normal and pathological ears.

Terkildsen and Scott Nielsen (1960) developed the electroacoustic bridge, the first commercially available instrument (Madsen Electronics Model Z061) and they also introduced the technique for assessment of middle ear pressure using impedance audiometry, and thus introduced the application of tympanometry (Terkildsen and Thomsen 1959). Zwislocki (1963) introduced the first commercial application of the mechanical acoustic impedance bridge.

Subsequently increasing interest was expressed in acoustic impedance measurements, and reports of tympanometry using mechanical (Feldman 1967) or electroacoustic instruments (Liden et al. 1969, Jerger 1970) were published in the late 60’s and early 70’s. These early instruments measured the acoustic energy and converted it to electrical energy, thus giving results in arbitrary units with variation between instruments. The comparison of these early studies is therefore difficult.

Recently, the instruments have greatly improved, although the basic principle is the same. Currently, electroacoustic admittance meters have an automatic feedback circuit (automatic gain control) to maintain a constant sound pressure level (SPL). These instruments have replaced the electroacoustic impedance bridges and mechanical bridges, giving results of admittance in absolute units which are suitable for comparison and quantitative analysis. The introduction of ANSI standard "Specifications for instruments to measure aural acoustic impedance and admittance (aural acoustic immittance)" in 1987 has brought uniformity to instruments, tympanometric units and calibration (American National Standards Institute 1988). Automated measurements, built-in printers, digital displays, faster pressure sweeps, and hand-held instruments have changed the testing to be quick and easy. The continuous improvement in instrumentation, new indications for the use of tympanometry, the increasing

popularity of testing, and the increasing incidence of otitis media have made research on acoustic immittance, and tympanometry especially, more essential and more voluminous.

7.2.3 Instrumentation

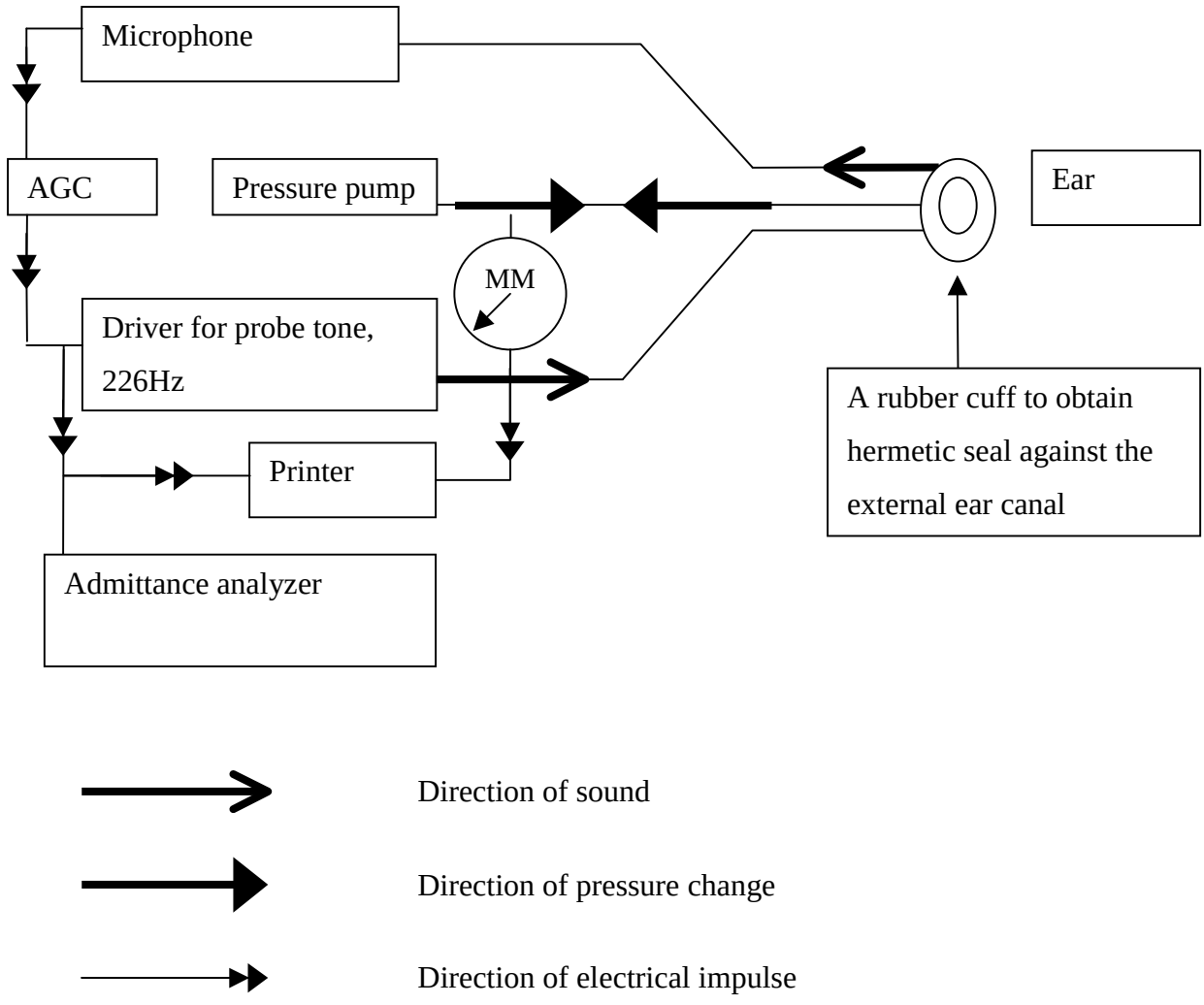
To be able to measure acoustic immittance as a function of ear canal pressure, the tympanometers have a loudspeaker to produce a probe tone, a microphone to record and analyze the reflecting sound, and a pressure pump to change the pressure during the testing (Figure 2). Currently available commercial instruments measure acoustic admittance, instead of acoustic impedance, of the ear canal and the middle ear system.

7.2.3.1 Probe tone and microphone

A constant probe tone, typically 226 Hz, is produced to enter the hermetically-sealed ear canal. The intensity of the probe tone is detected by the microphone. A constant sound pressure level (SPL, usually 85 dB) is maintained by a feedback-system (automatic gain control) of the microphone and the probe tone loudspeaker. As the acoustic immittance characteristics change (during the pressure sweep) the SPL detected by the microphone also changes. Through the feedback-system the probe tone intensity is changed by the loudspeaker voltage. This voltage change is proportional to the acoustic admittance of the ear and is registered and displayed as the admittance value of the respective ear canal pressure.

Other frequencies than 226 Hz have also been used, most commonly 678 or 800 Hz (Liden et al. 1974, Haughton 1977, van Camp et al. 1983). High frequency tympanometry has not been studied and applied to practice as much as low frequency tympanometry. High frequency tympanometry produces a wider variety of tympanometric curves and is more complex to interpret since at higher frequencies both susceptance and conductance have a substantial role (Margolis and Shanks 1985).

Figure 2. Schematic drawing of a tympanometry instrumentation. Open arrows indicate direction of sound, closed arrows indicate direction of pressure change and double arrows indicate electrical impulse. MM, manometer; AGC, automatic gain control.



Multiple-frequency tympanometry is a method of acoustic immittance measurement through a sweep of frequencies, for example from 250 to 2000 Hz. Through multiple-frequency tympanometry it is possible to directly assess the resonant frequency of the middle ear system. The resonant frequency is the probe tone frequency where susceptance becomes zero due to the counteractive forces of its components. A normal value for resonant frequency is around 900 Hz. Below this value the middle ear system is stiffness-controlled and above the normal value mass-controlled according to the more prominent component of the susceptance (Shanks and Shelton 1991). The changes in resonant frequency are used to assess the pathology of the middle ear system, especially those of the ossicular chain.

The most commonly used 226 Hz probe tone has some definitive advantages. The middle ear system is stiffness-dominated (compliance) at this frequency and the effects of mass and friction are minor. Hence interpretation and presentation of the results is simple; the majority of modern instruments display only the compliance of the middle ear. Additionally, the compliance value is directly proportional to the closed air volume, and hence the external ear canal volume (ECV) is obtained by the instrument. In the following sections only low frequency tympanometry (i.e. 226 Hz) is considered.

The probe tone driver is also used for acoustic reflex testing. A standardized sound stimulus of increasing intensity is delivered from the loudspeaker into the middle ear to elicit the reflex. The admittance change produced by the contraction of the stapedius muscle is observed by the instrument.

7.2.3.2 Pressure transducer

The pressure transducer automatically changes the pressure of the sealed external ear canal during the testing procedure. Serial measurements of admittance values in different pressure points are performed. The plot of these admittance values as a function of the pressure is called the tympanogram (Figure 1). The direction, speed and range of the pressure sweep are essential for interpretation of the results (Feldman et al. 1984, Kobayashi et al. 1987, Hergils et al. 1990). Most commonly a positive-to-negative pressure sweep is produced at a fast speed (up to 600 daPa/s) between +200 and -400 daPa relative to the ambient pressure.

7.2.3.3 Clinical test procedure

The probe tip is hermetically sealed against the outer orifice of the patient's external ear canal (Figure 3). The tip size should be selected based on the size of the outer orifice of the ear canal; different tip sizes should be available to obtain a tight seal (Grason Stadler Inc 1995). However, a constant degree of insertion of the probe tip should be used to obtain reliable results for the ECV. Ultrasonography gel can be used for a better seal in problematic cases. The child should be kept calm, preferably in a sitting position on the parent's lap. The recumbent position of the patient may produce a shift of the middle ear pressure to a more positive direction (Daniel et al. 1985). Holding the head gently may be appropriate, but force is not desirable, since if the child is not comfortable he/she will start to resist the procedure. A tight seal is obtained by gently pulling the ear lobe backward to straighten the ear canal. When inserting the probe tip a slight rotation of the probe usually seals the external ear canal efficiently. Using modern quick pressure-sweep equipment, the procedure takes only a few seconds to finish. If acoustic reflex measurement is included, the procedure will take longer, maximally about 15 seconds.

Figure 3. Clinical test procedure in a young child. Gentle hold of the head prevents movement during the procedure.

Movement and crying affects the sensitive recordings and thus interferes with testing. Every effort should be taken to obtain as good co-operation as possible. Tympanometry should be done prior to any part of examination or procedure that might be uncomfortable or frightening for the patient. Also, pneumatic otoscopy is usually better done after tympanometry, since most children resist pneumatic otoscopy to some extent. In case of occluding earwax, the instrument will fail to measure. In these cases, cleansing of the earwax is necessary before the measurement. However, a small amount of earwax does not interfere with the testing, since the instrument requires only an air passage to the tympanic membrane, not a straight visual view of the tympanic membrane.

In infants, the attention of the child should be drawn elsewhere. In older children, usually good co-operation is obtained by letting the child become familiar with the instrument and the sounds it produces. In case of poor co-operation, testing can usually still be performed, but the interpretation may be difficult (Koivunen et al. 1997) and the results may not be valid.

7.2.4 Tympanogram

The normal curve obtained with a low-frequency probe tone usually shows only one peak (Figure 1). The admittance value reaches the maximum in a point of equivalent ambient pressure across the tympanic membrane during the pressure sweep. In case of an ear with middle ear fluid no maximum point is obtained and a flat curve results.

This resulting curve, the tympanogram, has several parameters which can be expressed numerically, from which quantitative values may be obtained (Figure 1). Additionally, many classification schemes have been introduced based on different shapes of the tympanograms (Jerger 1970, Paradise et al. 1976, Orchik et al. 1978, Fiellau-Nikolajsen 1983). However, these different shapes can be commonly defined by the numerical values of the tympanometric variables.

7.2.4.1 Static acoustic admittance

Static acoustic admittance (SAA) is the maximum height of the tympanogram curve. It is expressed as units of mmho (mho is a reciprocal of ohm, the unit of electric impedance;

mmho refers to millimhos). At 226 Hz probe tone frequency, the admittance is in the majority due to the compliance component (Wiley and Block 1985). Consequently, only the compliance component of the admittance is commonly registered and expressed as cubic centimeters (cm^3), to correspond to the air volume with the same value of admittance. Other terms used for this variable in the literature are admittance, compliance and impedance (reciprocal of admittance).

Modern instruments automatically subtract the admittance value of the air volume in the external ear canal in front of the tympanic membrane from the total admittance (admittance at tympanometric peak pressure (TPP) minus admittance at +200 daPa), thus giving static value for the admittance (SAA) as an approximation to the admittance on the lateral surface of the tympanic membrane. Thus the obtained value is directly the admittance attributable to the middle ear system.

High ear canal pressure (+200 daPa) is usually employed as the reference value, although this does not always give the most exact results (Shanks and Lilly 1981). The minimum value of admittance (either at positive or negative pressure) should be subtracted from the maximum admittance at the TPP to get more reliable estimates of SAA and ECV.

Another source of error in correction for the ear canal volume is the change of the ear canal volume during the testing procedure due to movement of the probe tip, tympanic membrane and walls of the ear canal (Shanks and Lilly 1981). Different sweep rates affect the SAA. An increase in sweep rate has been reported to increase SAA (Feldman et al. 1984, Margolis and Heller 1987). The direction of the sweep rate may also change the SAA. It is important to always report the type and speed of pressure sweeps to make the interpretation and comparison of studies easier. Also, repetitive testing increases the SAA values, probably due to the "stretching" effect of the pressure sweep on the elastic characteristics of the middle ear system (Wilson et al. 1984, Karzon 1991, Gaihede and Ovesen 1997). However, SAA values obtained at different sessions have low variability (Wiley and Barrett 1991). Furthermore, quantitative measurement of SAA requires checking of the calibration frequently since atmospheric pressure and altitude affect the results.

SAA receives values between 0 and 3.0 cm^3. Values above 0.2 cm^3 are commonly considered normal. The 90% range of values has been determined by several authors (Margolis and

Heller 1987, Nozza et al. 1992, Silman et al. 1992, Hanks and Rose 1993, Page et al. 1995) in the age group of 3 years of age and above. The mean SAA values have been 0.50 to 0.78 cm^3 in these studies, the lower 90% range values varying from 0.22 to 0.40 cm^3 and higher 90% range values from 0.81 to 1.5 cm^3. Only two studies (Roush et al. 1995, De Chicchis et al. 2000) have previously reported normative values in children less than 2 years of age. The reported SAA values have been lower (means 0.32 to 0.48 cm^3 and 90% range 0.20 to 0.70 cm^3). The SAA values increased with age (Roush et al. 1995, De Chicchis et al. 2000).

Abnormally high values may result from ossicular fractures or other ossicle discontinuation. However, these are uncommon in pediatric routine practice. More commonly high values result from flaccid scarred tympanic membranes (Haapaniemi et al. 1995) or patient movement during the testing procedure. These should be interpreted with caution in relation to the findings in the otoscopical status.

Low values for SAA are most commonly obtained from ears with MEF. A thickened tympanic membrane (Haapaniemi et al. 1995) may also show low admittance curves. In ears with no peak (type B curve) the admittance reaches zero. Ears with TM perforation show also flat tympanograms, but these curves can be distinguished from ears with MEF by the abnormal value for ECV (see below).

7.2.4.2 Tympanometric peak pressure

Tympanometric peak pressure (TPP) refers to the point of maximum admittance on the pressure scale relative to the ambient pressure. TPP is an estimate of the middle ear pressure, since the maximum point of admittance is obtained when the pressure across the TM is zero. Flat tympanograms do not give any result for TPP.

TPP is given in decapascals (daPa) or millimeters of water (mmH_2O) which give roughly equal values (1 daPa=1.02 mmH_2O). The range of values obtained depends on the pressure scale of the instrument, but is most commonly between -400 to +200 daPa. Normal values are between -100 and +50 daPa. Values lower than -100 daPa correspond to a middle ear with decreased pressure and retracted tympanic membrane due to inadequate ventilation through the Eustachian tube (Jerger 1970). Abnormally high values are sometimes seen in the initial

phases of AOM corresponding to the rapid accumulation of middle ear effusion and gas, resulting in high pressure recordings (Paradise et al. 1976, Ostergard and Carter 1981).

TPP is also affected by the direction of the pressure sweep; the peak shifts to the direction of the sweep (Kobayashi et al. 1987, Gaihede et al. 2000). The shift is positively correlated with the sweep rate (Feldman et al. 1984, Kobayashi et al. 1987). However, Feldman (1984) reported that in ears with middle ear pathology the pressure shift was opposite, while there is a recent report of increased shift in ears with OME (Gaihede et al. 2000). Margolis and Heller (1987) did not find any difference between the different speeds of pressure sweeps in children, though a difference was found in adults.

Increased TPP values have been documented in a recumbent position (Daniel et al. 1985, Shinkawa et al. 1987) and under cervical compression (Nakashima 1995). These most probably reflect the increased perilymphatic pressure and the consequent effect on middle ear pressure.

Low TPP has been used as an indicator for the presence of MEF, especially by Dutch researchers (de Melker 1992, Finitzo et al. 1992, Claessen et al. 1994, van Balen and de Melker 1994). However, abnormal TPP alone is a poor indicator for the presence of MEF (Paradise et al. 1976, Fiellau-Nikolajsen 1983). Abnormal TPP has been excluded as a criterion for medical referral from the guideline by the American Speech-Language-Hearing Association (ASHA 1990).

7.2.4.3 Gradient

The steepness of the tympanogram curve was first expressed as gradient. Brooks was the first to introduce the definition of gradient (1968). He calculated the difference in admittance ("gradient difference") between the peak value and the value at a pressure interval of 50 daPa at either side of the peak, giving the gradient in units of cm^3. Subsequently, Paradise and co-workers (1976) defined the gradient as a ratio. For calculation of the gradient, a horizontal line was drawn on the tympanogram where the curve width is 100 daPa. Gradient was then calculated as the ratio of the height of the curve above the horizontal line divided by the height of the whole curve. Sometimes this variable is called "relative gradient"; absolute gradient is a synonym for the gradient difference (Fiellau-Nikolajsen 1983). The ratio method

has been found superior to the difference method (de Jonge 1986), since it has lower correlation with the admittance and is thus an independent variable.

The relative gradient has been used by several investigators (Paradise et al. 1976, Fiellau-Nikolajsen 1983, Feldman et al. 1984, Nozza et al. 1994, Gaihede and Ovesen 1997). In unselected healthy children the 90% range has been 0.25 to 0.60 (Koebsell and Margolis 1986, Nozza et al. 1992). However, values above 0.1 have commonly been considered normal (Fiellau-Nikolajsen 1983, Nozza et al. 1994).

However, the use of this variable has been superseded by tympanometric width (Koebsell and Margolis 1986), which has been selected to be calculated automatically by the modern equipment (Grason-Stadler Inc 1995).

7.2.4.4 Tympanometric width

Tympanometric width (TW) refers to the shape of the tympanogram. TW is calculated as the width of the tympanogram in half the value of the SAA on the pressure scale (de Jonge 1986). It is expressed in units of daPa. In a comparison of different gradient measures, TW was considered the most useful (Koebsell and Margolis 1986). The advantages of the TW measure were low association with SAA, comparatively small variation in normal ears but a large total variation, and independence of sweep speed (Koebsell and Margolis 1986). Normal values (defined as 90% range) for TW are usually 60 to 150 daPa in children (Koebsell and Margolis 1986, Margolis and Heller 1987, Silman et al. 1992, Page et al. 1995). TW has been found useful in the distinction of some borderline tympanograms for the presence of MEF. Low values are given in sharp curves due to flaccid or highly compliant tympanic membranes. High values are obtained from shallow curves from ears with MEF. For flat curves, no values for TW are obtained (the value approaches infinity).

TW has been found to be unaffected by procedural variations in the pressure sweep rate (Margolis and Heller 1987) or repeated measurements (Karzon 1991). The term gradient has been also used for this variable, though it commonly defines another variable for the tympanogram shape (see above).

7.2.4.5 Ear canal volume

Ear canal volume (ECV) refers to the air volume in the external ear canal in front of the probe tip (Rock 1991). ECV is measured at +200 daPa, when the ear canal represents a hard walled cavity, as the acoustic admittance (with 226 Hz probe tone) attributable to the volume of air in the ear canal. ECV is expressed in cm^3. Normal values for children with intact tympanic membranes are usually between 0.4 and 1.0 cm^3 (Margolis and Heller 1987, Shanks et al. 1992). ECV increases slightly with age (Haapaniemi 1996), but it is rather constant in children less than two years of age (Shanks et al. 1992, De Chicchis et al. 2000). Adults usually have values between 0.6-1.5 cm^3 (Margolis and Heller 1987)

Higher values of ECV are obtained from ears with perforation in the tympanic membrane. In these ears the volume of the middle ear cleft and mastoid system are also included in the value of the ECV. In children aged less than 7 years, the best criteria for diagnosis of tympanic membrane perforation was found to be an ECV of at least 1.0 cm^3 or increase of ECV at least 0.4 cm^3 compared to previous measurement (Shanks et al. 1992). By this way the intactness of the tympanic membrane can also be assessed by tympanometry.

Low values for ECV (<0.4 cm^3) are obtained from ears with occluding wax or probe against the ear canal. In such cases testing should be repeated. If ECV does not exceed 0.3 cm^3, all tympanometric results should be interpreted with caution.

7.2.5 Acoustic reflex

The contraction of the stapedius muscle in the middle ear, causing increased stiffening of the ossicular chain and tympanic membrane, can be registered as an admittance change. The contraction is elicited by a sufficiently intense sound stimulus. This test procedure, acoustic reflex, is commonly performed in connection with tympanometry. The result can be expressed as present or absent, but the threshold sound intensity capable of inducing the acoustic reflex may also be expressed.

Usually the acoustic reflex is measured at the tympanometric peak pressure. The sound stimulus is commonly given in multiple frequencies with increasing output from 80 to 105

dB. The testing can be performed ipsilaterally but also contralaterally with a contralateral speaker. The normal values for different frequencies , defined as 90th percentile (=upper limit for 80% range), for pure tone acoustic reflex are 95 to 100 dB contralaterally (Silman and Gelfand 1981). Ipsilateral thresholds are typically 10 dB lower (Brookhouser 1998). In children there is gradual improvement (decrease in the reflex threshold intensity) in the acoustic reflex with increasing age up to the age of ten years (Osterhammel and Osterhammel 1979).

Abnormal results in acoustic reflex may result from various reasons: decreased afferent input due to conductive middle ear disorder; decreased afferent input due to sensorineural disorder; abnormal efferent function due to the brainstem or the facial nerve; failure to detect the admittance change due to middle ear dysfunction (ASHA 1990).

In young children the test is more difficult to perform due to poor co-operation; consequently the absence of reflex is difficult to interpret. In ears with MEF, the additional increase in impedance may be left undetected. Furthermore, in children with sensorineural hearing loss the acoustic reflex is not suitable for screening of OME. Additionally, the reflex may be difficult to elicit even in normal ears, and low middle ear pressure further complicates the testing. Consequently, different instruments have given varying results on repeated measurements (Birch et al. 1986).

The inclusion of acoustic reflex testing results in tympanometry classifications has increased accuracy in some reports (Fiellau-Nikolajsen 1983). However, acoustic reflex testing has also led to high false positive rates (Lous 1983), consequently acoustic reflex testing is not included in the current ASHA guideline (ASHA 1990).

7.2.6 Tympanogram classifications

Different classifications for the tympanogram shapes have been suggested after the introduction of tympanometry into large-scale use. Correlation of specific tympanometric shapes with the middle ear status was initially the basis for these classifications. Here only classifications intended for low-frequency tympanometry (226 Hz) are presented.

7.2.6.1 Jerger 1970

Jerger (1970) introduced the classification of tympanograms into three basic types (A, B and C) and their characteristic clinical counterparts. Type A was most commonly found in healthy and otosclerotic ears characterized by a clear peak around the ambient pressure in the tympanogram. The flat type B tympanogram with no compliance change over the pressure range was associated with ears with middle ear fluid or adhesive otitis media. The type C tympanogram, characterized by a distinct peak at negative pressure area, was most commonly seen in healthy ears with significant negative pressure. This classification of tympanometric configuration (based on presence and location of the peak) has remained as the basis for more sophisticated classifications, although more accurate definitions are now available due to the use of absolute, rather than arbitrary units.

7.2.6.2 Paradise 1976

Soon it became evident that a more refined classification was needed, especially for negative pressure ears and ears with slightly decreased admittance, for better distinction of healthy ears from ears with middle ear disease. Paradise et al. (1976) included gradient (i.e. the steepness of the curve) in a refined classification of the tympanograms to be better able to distinguish ears with middle ear fluid in some controversial curves. Paradise et al. (1976) introduced seven curve types comprised of 15 variants and reported the probability of middle ear fluid in each of these types. This classification system was further validated by Cantekin et al. (1980). Smith et al. (1982) refined the classification regarding positive pressure tympanograms.

7.2.6.3 Orchik 1978

Orchik et al. (1978) modified the Jerger classification by introducing shallow counterparts for A and C tympanograms; As and Cs. These were included in the classification to present curves with a shallow but observable compliance peak (>6 units in the arbitrary relative scale). However, the authors did not find the types As and Cs conclusive for the presence of middle ear fluid (Orchik et al. 1978).

7.2.6.4 Danish classification

Tos (1979) modified the Jerger classification by introducing C1 (TPP -100 to -199 mmH_2O) and C2 (TPP below -200 mmH_2O) curves according to the magnitude of middle ear pressure expressed as the TPP in tympanometry. In his thesis, Fiellau-Nikolajsen (1983) collected the results of studies with tympanometry. He concluded that curves with relative gradient $\leq$0.1 should be regarded as flat (type B) curves, since these curves had the best correlation with the presence of middle ear fluid. Additionally, he introduced acoustic reflex testing to further increase the accuracy of tympanometry. In this classification, flat curves and negative pressure curves (TPP $\leq$-100 H_2O) with absent stapedius reflex were suggestive of middle ear fluid.

However, gradient has not received widespread application in the classification since it is not calculated automatically by modern instruments. Manual calculation is time-consuming and somewhat unreliable.

7.2.7 Diagnostic value of tympanometry

Multiple studies have been performed to assess the diagnostic value of tympanometry in the detection of middle ear effusion. Table 3 summarizes the diagnostic accuracy obtained with several instruments for AOM and Table 4 summarizes the findings in OME.

For the diagnosis of AOM, the sensitivity of type B tympanogram is 63% (weighted average of the studies in Table 3). However, the sensitivity increased to over 80% when high positive pressure tympanograms were also considered indicative of AOM. In these studies, specificity was not determined since only children with AOM confirmed otoscopically were included.

For the diagnosis of OME, the tympanometric variables SAA and TW or gradient have been most commonly employed for definition of the diagnostic schemes. The reported figures for sensitivity and specificity have been around 80%, with marked variation depending on the definition of the positive result indicating MEF in tympanometry (Table 4).

Table 3. Sensitivity of tympanometry using 226 Hz probe tone for diagnosis of acute otitis media in children. Sensitivity values given for type B curve (I) and type B combined with high positive pressure tympanograms (II).

First author and year	Instrument	children/ears, N	Age, years	Sensitivity I	Sensitivity II
Schwartz (1980)	Teledyne 1-D	103/161	0.3-17	75%	80%
Lampe (1981)	NA	32/43	Mean 5.3	38%	85%
Wheeler (1986)	Peters AP 61c	154/438	<12	64%	NA
Babonis (1994)	Welch Allyn microtymp	90/107	0.5-10	66%	84%
Green (1994)	American Electro-medics AE105	117/117	0.5-5	57%	85%
Sakaguchi (1994)	RS 30	144/144	Mean 4.9	56%	NA

NA, not available

Fiellau-Nikolajsen (1983) reported an excellent accuracy of 97% with 96% sensitivity and 98% specificity in a small group of highly selected three-year-old children (N=44) with chronic secretory otitis media (having failed repeatedly in serial tympanometry). The inclusion of C2 curves as indicative of otitis media (Ovesen et al. 1993, van Balen and de Melker 1994) produces extremely low values for specificity.

The inclusion of the acoustic reflex into the classification scheme increased the accuracy in some studies (Fiellau-Nikolajsen 1983, Silman et al. 1992) while in others it did not (Nozza et al. 1994). Additionally, the performance of the acoustic reflex test is more difficult and time-consuming; the test has failed in some subjects due to the lack of co-operation (Nozza et al. 1994). Consequently, some subjects cannot be classified in schemes including acoustic reflex testing.

Table 4. Diagnostic value of tympanometry using 226 Hz probe tone for diagnosis of otitis media with effusion in children.

First author and year	Instrument	Definition for abnormal tympanogram*	OME diagnosis	N, children/ears	Age, years	Sensitivity	Specificity
Paradise (1976)	Madsen ZO-70	EFF, HN-g, TR-g	Myringotomy	96/177	0.6-5	95%	76%
Paradise (1976)	Madsen ZO-70	EFF, HN-g, TR-g	Otoscopy	141/273	0.6-5	74%	93%
Orchik (1978)	NA	Type B curve	Myringotomy	75/142	NA	43%	100%
Fiellau-Nikolajsen (1983)	Madsen ZO-73	Grad≤0.1, or TPP ≤-100 daPa and absent IAR	Myringotomy	44/88	3-4	96%	98%
Toner (1990)	Rexton Tymp82	Type B curve	Myringotomy	121/222	1.5-12	86%	93%
Babonis (1991)	Welch Allyn Microtymp	Type B curve	Myringotomy	120/220	0.5-10	78%	82%
Finitzo (1992)	Maico Impedance Bridge No.610	Type B curve	Myringotomy	86/163	0.5-9	57%	93%
Silman (1992)	Grason-Stadler 1723	ASHA (1990)+absent IAR, or TPP≤-100 daPa and absent IAR	Otoscopy	107/135	3-10	90%	92%
Ovesen (1993)	Madsen ZS 330	B and C2 curves	Myringotomy	220/440	0.8-14.8	94%	53%

Table 4. Continued.

First author and year	Instrument	Definition for abnormal tympanogram*	OME diagnosis	N, children/ears	Age, years	Sensitivity	Specificity
Nozza (1992)	Grason-Stadler GSI33	Grad≤0.1 alone, or Grad≤0.3 and absent IAR	Myringotomy	61/111	1-8	90%	86%
Nozza (1994)	Grason-Stadler GSI33	TW>275	Myringotomy	171/249	1-12	81%	82%
Sassen (1994)†	TYMP-85TT and GSI-27A	Type B curve	Myringotomy	41/67	0.5-2	90%	67%
				221/421	2-11.5	81%	63%
van Balen (1994)	Welch Allyn Microtymp	Type B and C2 curves	Myringotomy	142/284	0.5-12	94%	48%
Koivunen (1997)	Welch Allyn Microtymp	Type B curve	Myringotomy	162/183‡	0.5-8	79%	93%
Watters (1997)	Grason-Stadler GSI33	Type B curve	Myringotomy	501/955	1-15	91%	79%

* Abbreviations for curve types in Paradise's classification: EFF, effusion (roughly corresponding type B curve); HN, high negative (corresponding type C curve); TR, transitional zone curve (compliance decreased); -g, gradient ≤0.15.
Other abbreviations: IAR, ipsilateral acoustic reflex; NA, not available

† Results divided in two age groups: children up to two years of age and children above two years

‡ Ears tested during good co-operation

7.2.7.1 False positive test result

The finding of a flat type B curve in the absence of MEF may result from numerous reasons. The mode of anesthesia, especially the use of nitrous oxide (N_2O), has been reported to affect middle ear pressure (Shaw et al. 1978, Gates and Cooper 1980, Marshall and Cable 1982, Gersdorff 1992, Rees and Freeland 1992, Elam et al. 1998). Some controversy exists over whether nitrous oxide is capable of clearing fluid in the middle ear and thus be responsible for a dry tap at myringotomy. In a Finnish study, no difference was noticed in the weight of the MEF sample after myringotomy between anesthesia with nitrous oxide and without it (Koivunen et al. 1996). However, a change of tympanogram type during anesthesia and negative myringotomies in ears with otitis media has been reported by many authors (Shaw et al. 1978, Gates and Cooper 1980, Marshall and Cable 1982, Gersdorff 1992, Rees and Freeland 1992). Consequently, such false positives, may in some cases be "false" false positives.

However, some uncertainty prevails on the results. The tympanogram sweep range was only +200 to -200 daPa in the study of Rees and Freeland (1992); in the study by Shaw et al. (1978) the range is not reported. Gates and Cooper (1980) found similar results with N_2O and N_2O with halothane. They concluded that the inflation and pressure change of the middle ear was due to assisted mask ventilation. Further, the time interval from assessment of otitis media to the surgery is not always reported in these studies.

An increased proportion of false positive values has been reported to occur in unco-operative children (Koivunen et al. 1997). Crying and movement during the test procedure interferes with the testing and may even prevent the test procedure. Also excess earwax or the wrong test procedure can result in a flat curve due to (partial) blocking of the test probe. Careful testing with repeated measurements usually gives reliable results. Furthermore, as the time required for testing has shortened with modern instruments, the effect of poor co-operation has become less detrimental.

Thickened TM or crust on the TM as a sequelae of an otitis media episode during the healing phase may result in a false positive tympanometric finding after resolution of MEF.

7.2.7.2 False negative test results

False negative results have been obtained in ears with segmental finding in otoscopy (Schwartz and Schwartz 1980) or small amounts of MEF (Fiellau-Nikolajsen 1983, Ovesen et al. 1993). Also, more sophisticated assessment of the quantity of the MEF has shown, that ears with normal tympanograms associated with MEF have only small amounts of effusion (Koivunen et al. 1997). This effect is more clearly seen in AOM with the inclusion of early phases of disease with small amounts of MEF resulting in low sensitivity values (Table 3). The quality of the MEF (serous MEF) was associated with negative pressure curves in an animal study (Giebink et al. 1983), but this finding has not been confirmed in children (Fiellau-Nikolajsen 1983).

Children less than 7 months of age were found to have a high rate of false negatives (Paradise et al. 1976), largely due to compliant ear canals in the young age. However, contradictory results have also been obtained (Groothuis et al. 1979).

7.2.7.3 Multiple simultaneous pathologies

In case of multiple concurrent pathologies, unexpected results can be obtained. For example, an ear with abundant middle ear fluid but a flaccid tympanic membrane may give high-peaked tympanograms (Margolis and Shanks 1985). Vice versa, a stiff middle ear system may show low admittance even in the absence of middle ear fluid.

7.2.8 Tympanometry and hearing loss

The presence of MEF usually produces an average conductive hearing loss of 27 dB in OME (Fria et al. 1985). However, the degree of hearing impairment shows large variation, and not all ears have lowered hearing thresholds (Fria et al. 1985).

The SAA values have been shown to negatively correlate with the amount of MEF, i.e. a high quantity of MEF is associated with low SAA and flat tympanograms (Fiellau-Nikolajsen 1983, Ovesen et al. 1993, Koivunen et al. 1997). Consequently, tympanometry has been found to detect quite accurately the ears with hearing impairment in OME (Ben-David et al.

1981, Dempster and MacKenzie 1991, Kazanas and Maw 1994, MRC Multi-centre Otitis Media Study Group 1999). A type B tympanogram is commonly associated with hearing impairment, while peaked tympanograms indicated normal hearing even in the presence of MEF. Furthermore, in younger children (3 to 5 years of age) tympanometry predicted hearing impairment more accurately (MRC Multi-centre Otitis Media Study Group 1999).

7.2.9 Comparison between otoscopy and tympanometry

The correlation of clinical findings in pneumatic otoscopy with tympanometry results have been evident since the earliest studies (Jerger 1970). This is very logical, since both procedures examine the movement of the tympanic membrane in relation to pressure changes in the external ear canal. This is one of the features which makes tympanometry useful in the education of otoscopical skills, as subjective otoscopical findings can be compared with objective test results.

The performance of tympanometry has been compared with that of otoscopy. Toner and Mains found a similar accuracy between these two methods when compared with myringotomy (1990). Similarly, Nozza et al. found a similar accuracy between tympanometry and a validated otoscopist (1994). Gimsing and Bergholtz (1983) found good agreement between otoscopy and tympanometry in detecting abnormally low middle ear pressure.

However, it has to be noticed that in these studies otoscopy has been performed by experienced specialists and different results could be obtained in general practice. A Danish study group evaluated the change in clinical diagnosis of general practitioners when tympanometry was included in the examination (Johansen et al. 2000). The initial clinical diagnosis, based on otoscopy and history, changed after performance of tympanometry in 26% of the children. An inconclusive initial diagnosis was reported in 4% of children; after tympanometry 81% of these received a definitive diagnosis (Johansen et al. 2000). Furthermore, nearly 20% of children with an initial diagnosis of healthy ears were considered to have otitis media. Vice versa, again nearly 20% of children who had been considered to have otitis were considered normal after tympanometry. However, no attempts to assess the validity of any of the diagnoses was performed. Nevertheless, it was documented that tympanometry can make a difference.

7.2.10 Diagnostic algorithms combining otoscopy and tympanometry

A refinement of diagnostic accuracy has been proposed by combining otoscopical findings with tympanometry and also acoustic reflex. Cantekin et al. achieved a better accuracy (sensitivity 97% and specificity 90%) for an algorithm combining otoscopy, tympanometry and acoustic reflex (1980). However, 29% of ears could not be evaluated due to missing information (mainly due to missing acoustic reflex), and an additional 8% received an equivocal result. Similarly, Nozza et al. (1994) found a slight increase in specificity when tympanometric information was included to otoscopical assessment. Le et al. (1992) reported a four-level profile for OME using otoscopy, SAA and TW to characterize the severity of OME findings. However, use of this profile merely identifies the ears with obscure findings regarding MEF.

A working group of ASHA has developed criteria for screening for hearing impairment and middle ear disorders (ASHA 1990) including otoscopy, tympanometry, questionnaire and audiometry. The purpose of these criteria is to detect children with a risk of hearing impairment and a consequent need of medical referral.

7.2.11 Factors affecting comparability between studies

Comparison of otitis media studies using tympanometry is not always fruitful, as a wide diversity of clinical diagnostic criteria for otitis media have been used (Hayden 1981). In most clinical reports, however, the presence of middle ear fluid verified by myringotomy has been used as the golden standard.

The main factor influencing the results of any study is the study population. In the studies collected in Table 4, children with otologic problems, either chronic secretory otitis media or recurrent AOM, have been examined after referral to a clinic of otolaryngology for surgical intervention. This produces a strong selection bias and the results cannot be interpreted to be valid for the general population (Nozza et al. 1994). The prevalence of the presence of MEF affects substantially the positive and negative predictive values when interpreting the data for clinical routine situations.

Another problem is the wide age range of the study populations (Tables 3 and 4). Otitis media in an infant is probably highly different from that of a school child. Anatomy, Eustachian tube function, symptom presentation and the perception of symptoms, the time pattern of the disease, middle ear findings, predisposition to disease, defense mechanisms, etc. are probably also reflected in the immittance characteristics of the otitis episode.

The golden standard of MEF verification by myringotomy has been performed under general anesthesia using nitrous oxide by inhalation and assisted mask ventilation. Nitrous oxide has been reported to effect the pressure of the middle ear and even presence of MEF in myringotomy. Thus false negative middle ear taps might have been performed due to the mode of anesthesia (Shaw et al. 1978, Gates and Cooper 1980, Marshall and Cable 1982, Gersdorff 1992, Rees and Freeland 1992).

Otitis media is a disease continuum having different phases during the episode. Spontaneous recovery is common; a fluctuating pattern is frequently encountered; and recurrences affect the course of disease (Bluestone 2000). Thus, probably different phases of disease have been examined, and the patient selection may influence the results to a high degree. The degree of parental concern and the availability of treatment facilities and previous experiences also affect the phase when the child is brought to the examination.

Acoustic immittance instruments have improved dramatically. In the beginning, i.e. at the end of the sixties and beginning of the seventies, different probe tone frequencies were used. The interpretation proved to be highly different in high probe tone instruments, which are now getting increasing interest again. However, still most of the literature deals with 226 Hz probe tone instruments.

Similarly, the first instruments expressed immittance in relative, arbitrary units, rather than absolute units valid for comparison between instruments, different places and times. At the end of the seventies, instruments with absolute units became available, leading to the production of the ANSI standard (American National Standards Institute 1988). These instruments could be calibrated objectively to obtain valid results for comparison.

The absolute units made it possible to define the tympanometric curve types exclusively based on the tympanometric variables. However, not all reports give their classification definitions

in absolute units; rather some still use the early classification systems without giving definitive values for the tympanometric variables. Modern instruments also calculate and display the values for the variables. However, in the beginning tympanograms were manually plotted after impedance measurements at selected pressure points (Paradise et al. 1976) and the different variables have been manually calculated or optically derived (Nozza et al. 1994) from the tympanogram curves. Subsequently, automated plotters were attached to the immittance instruments and finally integrated printers have been attached.

However, still many confounding factors are involved. The speed of the pressure sweep has increased substantially. First, manual tympanometry at selected pressure intervals was used (Paradise et al. 1976, Orchik et al. 1978). Subsequently automated pumps became routine, but the sweep rate has increased from a few daPa/s up to 600 daPa/s. Additionally, different sweep directions have also been used, though positive to negative direction has been most commonly used. In some studies unconventional pressure sweep ranges are used, complicating the interpretation of results. For example, if the lower sweep range limit is -200, type C2 is indistinguishable from a type B curve (Rees and Freeland 1992). Due to technical improvements the duration of test procedure has been reduced from 5-15 minutes (Paradise et al. 1976) to only a few seconds with modern instruments (Grason-Stadler Inc 1995).

Unfortunately, not all procedures are explained in enough detail to get an unequivocal view of the method performed. Additionally, it has been shown that different instruments may produce varying results in sequential testing (De Chicchis and Nozza 1996, Gaihede and Marker 1998). Some of these differences were prominent enough to warrant instrument-specific norms (De Chicchis and Nozza 1996).

8 OBJECTIVES OF THE STUDY

The objectives of the present study were:

1. To assess the concordance of interpretation of the tympanograms (I)

2. To determine the diagnostic accuracy of tympanometry in a primary care clinic (II)

3. To assess the normal values for the tympanometric variables in children (III)

4. To determine the prognostic value of tympanometry during respiratory infection and in otitis media (IV)

5. To study the association of negative tympanometric peak pressure with the occurrence of middle ear fluid and the bacterial etiology of otitis media (V)

9 MATERIAL AND METHODS

The material for this series was derived from two longitudinal cohort studies (the Finnish Otitis Media (FinOM) studies), in which children were prospectively followed in special study clinics from 2 to 24 months of age. Full-time study physicians and study nurses especially educated for the purpose carried out the clinical follow-up of the study children. Both studies were conducted by the National Public Health Institute (KTL), Helsinki, Finland.

9.1 Finnish Otitis Media Cohort Study

The FinOM Cohort Study was conducted as a pilot study for the succeeding vaccine trial. The objective of the Cohort Study was to assess the nasopharyngeal carriage and subsequent disease (especially AOM) due to *Streptococcus pneumoniae* (Kilpi et al. 2001). The more practical objective was to prepare, finalize and test the procedures and protocols for the FinOM Vaccine Trial.

The Cohort study was conducted in one clinic in the Hervanta area of the city of Tampere in southern Finland from April 1994 to July 1997. Totally, 329 children were recruited to the study. All children 2 months of age were eligible for the study if they were current residents in the study area, if at least one parent/guardian could speak Finnish, and if their general health allowed participation in the follow-up. The children were recruited after an informed parental consent.

The study follow-up included ten prescheduled healthy visits, as well as additional sick visits due to respiratory infections and control visits for the healing of otitis media 3 to 5 weeks after a diagnosis of otitis media. The parents were encouraged to bring the child to the study clinic for a sick visit, to be examined by the physician, whenever the child had symptoms of respiratory infection and especially if the parents suspected AOM.

A total of 281 children were followed through the entire follow-up until 24 months of age. The most common reason for discontinuation was relocation of the family (N=19), followed by withdrawal of the informed consent (N=16).

Totally 2920 visits (1996 sick visits, 653 follow-up visits for OM and 271 close-out visits at 24 months of age) during which tympanometry was scheduled were conducted. Of the 5840 ear examinations at the visits, 4062 ears had available tympanometry data (ears with perforations and failed tympanometry excluded) and were selected for further analysis. However, 151 (4%) of the ears lacked a definitive middle ear diagnosis and were not included in the analyses. The tympanometric data derived from these visits were utilized for papers IV and V. Additionally, unpublished data concerning the diagnostic value of tympanometry are presented.

9.2 The Finnish Otitis Media Vaccine Trial

The primary objective of the FinOM Vaccine Trial was to assess the efficacy of two pneumococcal conjugate vaccines (PncCRM and PncOMPC) for prevention of AOM (Eskola et al. 2001). The Vaccine trial was a randomized controlled double-blind trial. Hepatitis B virus vaccine served as the control. The children were enrolled at 2 months of age and were given intramuscular injections of the study vaccine at 2, 4, 6 and 12 months of age.

The trial was conducted in the cities of Tampere and Nokia and the municipality of Kangasala from December 1995 through April 1999. Altogether 2497 children were recruited to 8 study clinics. Before 24 months of age 87 children discontinued the follow-up. The two most common causes for discontinuation were withdrawal of the consent (N= 37) and moving out from the study area (N=33).

In the Vaccine trial, altogether over 13000 sick visits, over 5000 follow-up visits, 2476 scheduled healthy visits and 2414 close-out visits at 24 months of age were conducted. For papers I and II, a sample of 242 tympanograms from 121 consecutive visits of 58 infants aged one year or less at one study clinic (managed by the author) was analyzed. For paper I, all study physicians (N=10) and an audiologist from the university hospital interpreted the tympanograms independently. For the analysis of paper II, type B tympanograms were considered indicative of MEF. The golden standard diagnosis for the presence of MEF was obtained from pneumatic otoscopy and myringotomy if performed. For paper III, all scheduled 7- and 24-month healthy visits were utilized. Tympanometric recordings of healthy otoscopically normal ears with intact tympanic membranes were selected for analysis.

9.3 Pneumatic otoscopy and diagnosis of acute otitis media

Similar clinical procedures were followed in both FinOM studies. A careful physical examination was performed, including pneumatic otoscopy (Welch Allyn 20200 Otoscope, Welch Allyn, Skaneateles Falls, NY, USA) for diagnosis of otitis media. The diagnosis of AOM was based on at least one clinical acute symptom (ear ache, ear pulling, ear discharge not due to external otitis, irritability, poor sleeping, fever, cough, rhinorrhea, gastrointestinal symptoms or other respiratory symptoms) combined with an abnormal finding in pneumatic otoscopy suggesting MEF. The otoscopical findings suggesting AOM were cloudiness, bulging or decreased mobility of the tympanic membrane, or visible fluid in the middle ear. Asymptomatic otitis media with effusion (OME) was diagnosed by the same otoscopic criteria with no symptoms. The diagnosis of AOM was verified by myringotomy with aspiration in 88% of ears in the Cohort Study and 93% of ears in the Vaccine Trial. Local anesthesia with phenol on a cotton tip was used and the MEF was suctioned to a sterile glass tip. The resulting MEF sample was further prepared for bacterial culture.

9.4 Tympanometry

Tympanometry (GSI 38 Autotymp, Grason-Stadler, Milford, NH, USA, Figure 4) was performed routinely by the study physicians during all visits to aid in the diagnosis of otitis media. The tympanometer used a 226 Hz probe frequency with positive-to-negative pressure sweep and a rate of 600 daPa/s except near the tympanogram peak, where the sweep rate slowed to 200 daPa/s. The equipment gives SAA values in 0.1 scale. In curves with a low discernible peak but no SAA value given, a value of 0.05cm^3 was assigned. TPP and TW receive values divisible by 5.

Three curves in a row were taken for both ears. The first technically successful curve was selected to be interpreted. The classification, modified after the classification introduced by Orchik et al. (1978), was applied in the interpretation of the tympanograms (Table 5, Figure 5). Because of the pediatric use, shallow counterparts for A and C (As and Cs) were included. Only type B tympanograms were interpreted as being pathological (Table 5). After the tympanometry, pneumatic otoscopy, and myringotomy when indicated, were performed.

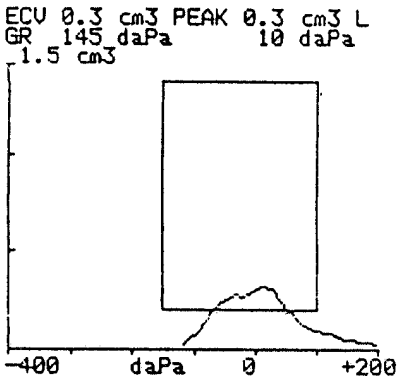
Figure 4. Grason-Stadler GSI38 Autotymp.

Table 5. Definitions of the tympanogram classification in the FinOM studies.

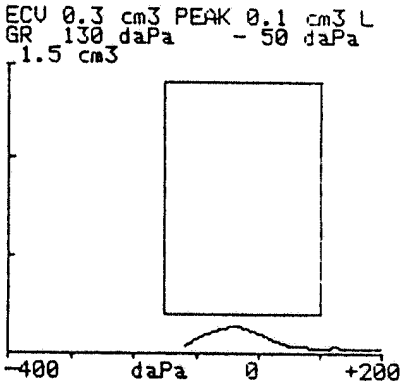
Tympano-gram type	Definition	Description	Probability of MEF
A	SAA≥0.2 cm^3*, TPP≥-100 daPa	High admittance, Normal middle ear pressure	Low
B	Flat curve, SAA=0 cm^3, no values for TPP	Low admittance	High
C	SAA≥0.2 cm^3, TPP<-100 daPa	High admittance, Decreased middle ear pressure	Low
As	SAA≤0.2 cm^3, TPP≥-100 daPa	Decreased admittance, Normal middle ear pressure	Intermediate
Cs	SAA≤0.2 cm^3, TPP<-100 daPa	Decreased admittance, Decreased middle ear pressure	Intermediate
P	ECV≥1.0 cm^3, or ECV increase ≥0.4 cm^3	Perforation of the tympanic membrane	Low, if no otorrhea
F	Erroneous peaks, no curve	Poor co-operation, occluding wax, probe against ear canal or wax	Not assessable

*The distinction between A and As (and C and Cs) when SAA was exactly 0.2 cm^3 was made by graphic display of the curve: curves exceeding the lower boundary of the graphic normal box were defined as A (or C, depending on the TPP).

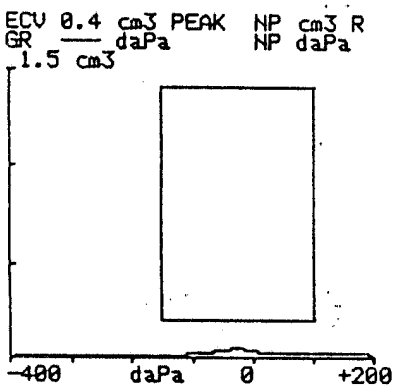
Figure 5. Tympanogram types according to the classification used in the study. Curves produced by the Grason Stadler GSI38 Autotymp.



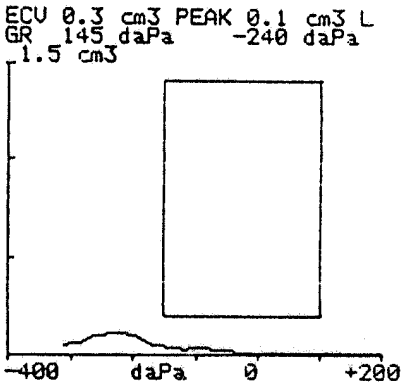
A



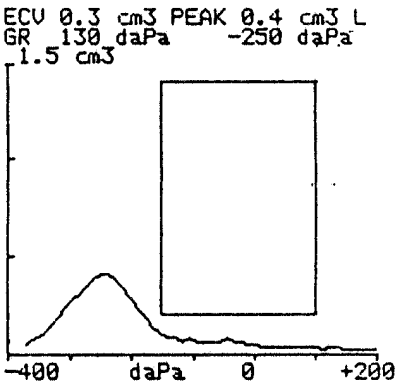
As



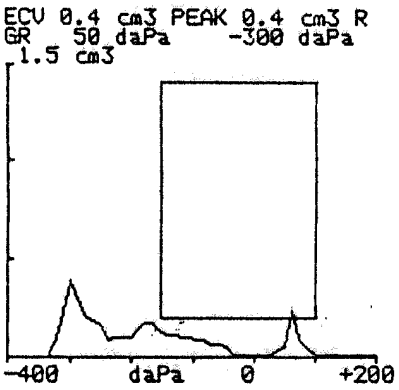
B



Cs



C



F

9.5 Bacteriological methods

MEF was aspirated after myringotomy into a sterile suction tip. MEF aspirates were immediately flushed from the suction tip into a 1 ml tube of phosphate-buffered saline. A disposable loop was used to immediately inoculate 10 µl of the sample for culture on an enriched chocolate agar plate and a sheep blood agar plate containing gentamicin (5 µg/ml). The plates were incubated overnight in the study clinics and sent to the laboratory of the bacteriological department of KTL in Oulu, Finland for further analysis. Bacterial colonies were identified using generally accepted methods. The main pathogens, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* were isolated and identified as described below. Other bacteria were rare findings or were considered as non-pathogens or contaminants.

To identify *S. pneumoniae,* four separate α-hemolytic colonies were picked up and cultured as four sectors onto a blood agar plate with optochin discs. The bacterial growth with optochin positive (diameter ≥14 mm) sectors was considered to be due to *S. pneumoniae*. If the colony morphology resembled *S. pneumoniae* but the optochin test was negative, a bile solubility test was used as an additional method. The colonies suggestive of *H. influenzae* on enriched chocolate agar plates were screened using the satellite test; positive strains were further identified by their requirement for X and V growth factors. The colonies suggestive of *M. catarrhalis* on enriched chocolate or selective blood agar plates were identified by Gram staining and tests for oxidase, nitrate reduction and the production of acid from dextrose and maltose.

9.6 Data processing and statistical methods

The data during the follow-up were collected on case report forms. Tympanograms were printed, dated and signed and finally copied for documentation. In the Cohort Study, the data on case report forms was manually double-recorded to an electronic form. In the Vaccine Trial optical transformation of CRF data to an electronic form was used. SPSS for Windows 8.0.1 was used for the data analysis. For all statistical analyses, the statistical significance was set at an α-level of 0.05.

Specific statistical methods

I Kappa statistics (Fleiss 1981) was used for the analysis of the concordance of interpretation of tympanometry. The kappa statistics measures concordance of rating by taking into account the concordance explained by chance. The kappa value receives a value from -1 to 1. High values denote a more concordant rating, zero means rating achieved by chance, and negative values mean a rating success less than chance. Values above 0.75 are considered excellent.

II From 2x2 tables, the following parameters for diagnostic value were calculated: sensitivity, specificity, positive and negative predictive value. Bayes' theorem (DeGroot 1986) was applied for the calculation of the predictive values.

III Only data on one ear per subject at scheduled 7- and 24-month visits were selected to prevent a dependence of data in the statistical analysis. A paired t-test was used for the analysis of the tympanometric variables between the two age points. A t-test for independent samples or one-way analysis of variance was employed for the analysis of factors influencing the normal values. Modeling using covariance analysis was performed for the simultaneous testing of associated factors.

IV Descriptive analysis was performed utilizing all available data of the longitudinal follow-up with two consecutive visits. Confirmatory statistical analysis was performed with the data of one randomly-selected ear. Odds ratios (OR) with 95% confidence intervals (CI) were calculated from 2x2 tables. A Chi-square test was used for the categorical data in other than 2x2 tables. A t-test or ANOVA for normally-distributed and Mann-Whitney U test for non-normal continuous data was used.

V Descriptive analysis was performed utilizing all available tympanometry data of the longitudinal follow-up. Confirmatory statistical analysis was performed with a nested matched (for visit type and month of visit) case-control design for bacteriological etiology of otitis media. Otitis media with negative TPP was selected as a case. Controls were selected from the same study (otitis media with other than negative TPP).

9.7 Ethical consideration

An informed consent was asked before entry in to the studies. The protocols of the studies were approved by the Ethical Review Board of KTL. Local approval was obtained from the Ethical Review Board of the city of Tampere and the administrative boards of Nokia and Kangasala (the two latter for the FinOM Vaccine Trial only). The principles of good clinical practice were followed in the trials.

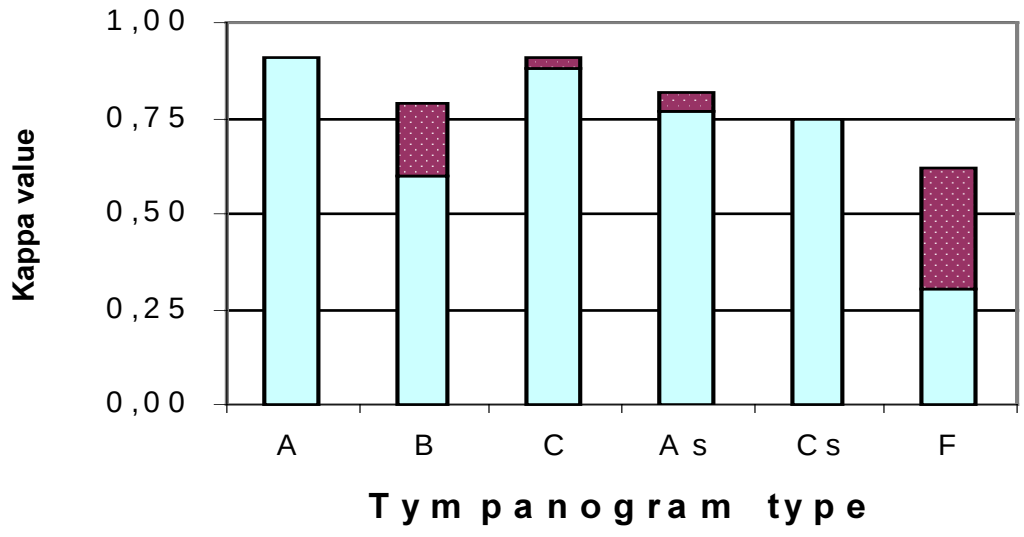
10 RESULTS

10.1 Interpretation (I)

The kappa value for the concordance of interpretation of the tympanograms by the ten study doctors was 0.80 (95% confidence interval 0.79 to 0.81), presenting an excellent concordance of the interpretation. In further subanalysis, the concordance of interpretation was slightly better for tympanograms taken at healthy visits and follow-up visits (Kappa 0.87) compared to tympanograms taken at sick visits (Kappa 0.76). In addition, if the middle ear status and co-operation of the infant was revealed to the interpreters, the kappa value was higher (0.84) than if no such data was given (0.75). There was no difference in the interpretation of tympanograms obtained from children less than seven months of age compared to children aged more than seven months of age.

There was substantial variation in the concordance of interpretation according to the type of tympanogram (as interpreted originally), especially when the middle ear status was not revealed. For type B curves (Kappa 0.60) and type F curves (Kappa 0.30) the concordance was substantially lower. However, the knowledge of ear status and co-operation of the infant markedly improved the concordance of these curve types (Figure 6).

Figure 6. Concordance of the interpretation of different tympanogram types. A high kappa value (>0.75) denotes excellent concordance. The inferior part of the columns represent the concordance achieved with no knowledge of the ear status or co-operation of the infant; the dark area represents the increased concordance achieved when this data was given.



10.2 Diagnostic value (II)

Tympanometry was performed successfully for 228/242 ears (94%) of infants aged 2 to 11 months. In the material from the Cohort Study 92% of the tests were successful. The probability of presence of MEF according to the tympanometric type is given in Table 6.

The sensitivity of tympanometry in the diagnosis of AOM of infants was 70% when type B tympanograms were considered indicative of MEF. The corresponding figure for specificity was 98%. Positive and negative predictive values (PPV and NPV), more suitable for clinical purposes, were 93% and 91%, respectively. The sensitivity was lower (61%) for children aged less than seven months compared to children aged 7 to 11 months of age (79%). Additionally, the sensitivity was lower also at sick visits (67%) compared to sensitivity at non-acute visits (82%). However, specificity was excellent in all subgroups. Inclusion of type As and Cs tympanograms as indicative of MEF increased the sensitivity up to 90% but decreased the specificity to 74%. The corresponding figures for PPV and NPV were 53% and 96%.

In the larger material of the Cohort Study, the sensitivity of a type B tympanogram to detect ears with MEF was 66% and specificity 97%. The positive and negative predictive values were 90% and 89%, respectively. Thus, in this material the diagnostic accuracy was slightly lower. To further assess the capability of tympanometry, the value of different tympanometric variables for the detection of MEF was studied. Only the equivocal As and Cs curves were selected for analysis. The distribution of ears with MEF according to the values of tympanometric variables is shown in Figure 7. None of the variables are clearly indicative of MEF, although an increased proportion of ears with MEF is seen with low SAA and TPP values and high TW values. The applicability of TPP and SAA are further decreased by missing data in 14% and 18% of ears, respectively.

Table 6. Probability of presence of middle ear fluid in different tympanogram curves in infants and children up to two years of age.

	Vaccine Trial	Cohort Study
	N=242 ears	N=3911 ears
Tympanogram type	**Probability of middle ear fluid, %**	
A	4	5
B	93	90
C	5	11
As	23	15
Cs	15	24
F	21	NA
Total	25	26

NA, not available

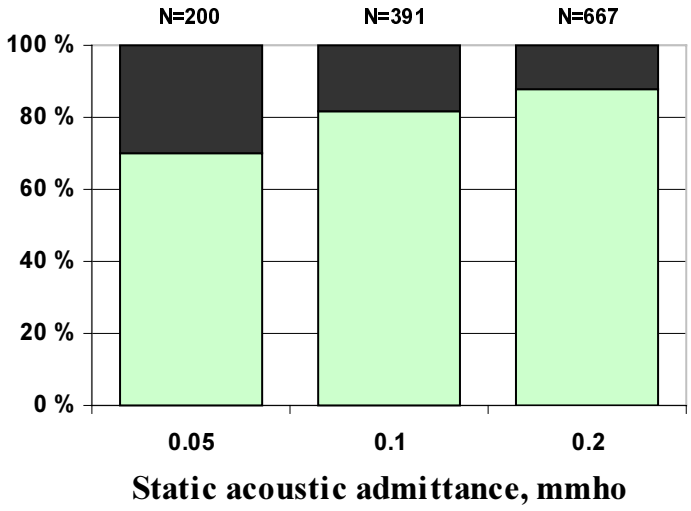
10.3 Normative values (III)

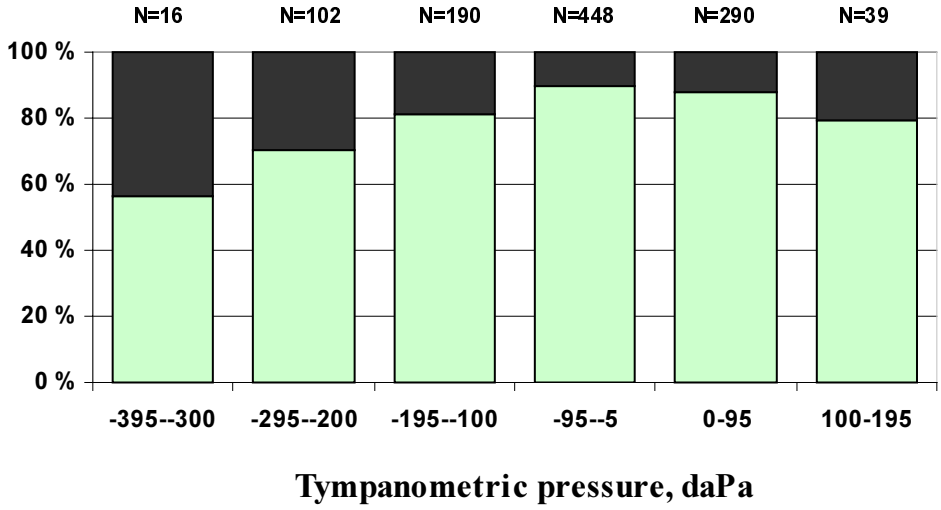
The mean SAA increased significantly from 0.25 cm^3 at seven months of age to 0.33 cm^3 at 24 months of age ($p<0.001$ by paired t-test, Table 7). Conversely, the mean TW decreased significantly from 140 daPa at seven months of age to 113 daPa at 24 months of age ($p<0.001$ by paired t-test). There was no change in TPP with increasing age (mean TPP -41 at both age points).

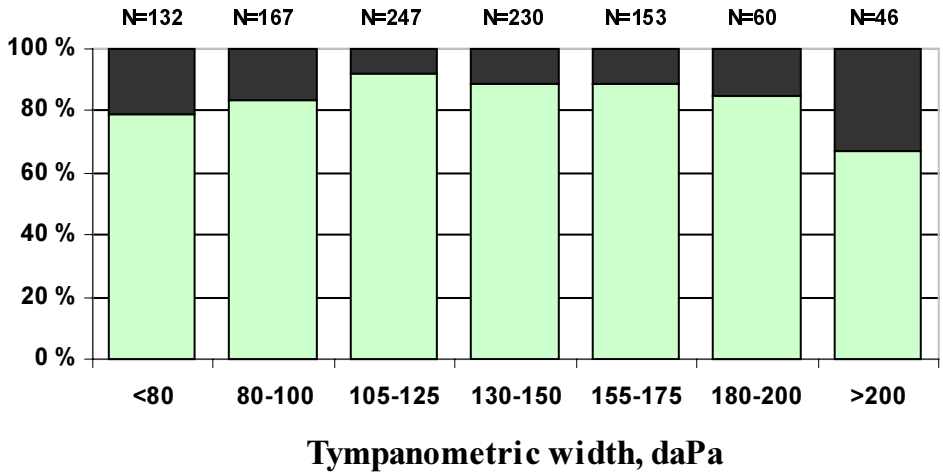
The 90% range for SAA was 0.1 to 0.4 cm^3 at 7 months of age and 0.1 to 0.6 cm^3 at 24 months of age (Table 7). However, only 5.5% of SAA values were lower than 0.2 cm^3, thus a more suitable lower limit for 90% range at 24 months of age would be 0.2 cm^3. For TW, the 90% range was 95 to 200 daPa at 7 months of age and 70 to 155 daPa at 24 months of age. For TPP, the 90% range was -155 to +30 daPa at seven months and -165 to +45 at 24 months of age.

Various factors were found to influence the normative values. Higher SAA values were associated with male sex and high birth weight at both age points. The high number of AOM events ($\geq$ 3) during the follow-up and history of previous grommets was associated with higher SAA values and lower TW values at 24 months of age.

Figure 7. Proportion of ears with middle ear fluid in type As and Cs curves according to the values of different tympanometric variables. The area with shading represents ears with middle ear fluid. Numbers above the columns are numbers of ears with the corresponding value.







Decreased TPP was associated with male sex and a high number of AOM events during the follow-up at seven months of age. The presence of nasal discharge (present in 9 and 14% of visits) was associated with decreased TPP, while poor co-operation increased TPP. There was also variation of TPP according to the season at both age points.

In covariance analysis, the effect of the associated factors on the tympanometric variables was low. The coefficient of determination (R^2) remained low in all models predicting the tympanometric variables.

Table 7. Normative values for tympanometric variables in healthy 7- and 24-month-old children.

	Static Acoustic Admittance, cm^3		**Tympanometric Peak Pressure, daPa**		**Tympanometric Width, daPa**	
Age, months	**7**	**24**	**7**	**24**	**7**	**24**
Number of ears	1618	1222	1616	1223	1582	1208
Mean	0.25	0.33	-41	-41	140	113
Median	0.20	0.30	-25	-25	140	115
Standard deviation	0.11	0.14	57	65	32	25
5^{th} Percentile	0.10	0.10	-155	-165	95	70
95^{th} Percentile	0.40	0.60	30	45	200	155

10.4 Prognostic implications (IV)

Negative pressure finding in tympanometry compared to other tympanogram types was associated with a higher probability of developing otitis media within three weeks when detected in healthy ears during a visit associated with respiratory infections. Totally, 40% of ears with negative middle ear pressure (TPP<-100 daPa, curve types C and Cs) developed MEF compared to 20% of ears with normal or positive pressure or a flat tympanogram (Table 8). The mean TPP was -86 daPa in ears developing MEF compared to -47 daPa in ears not developing MEF. SAA and TW were similar in both groups.

The finding was confirmed in the statistical analysis, when one measurement per subject was randomly selected for analysis. The presence of negative tympanometric pressure was associated with the development of MEF with an odds ratio of 4.8 (95% CI 2.4 to 9.6).

For the prediction of resolution of AOM, the association of the initial tympanometry result in AOM with the prognosis of the disease after three to five weeks was assessed. Negative pressure finding in tympanometry again showed special features. Negative TPP (curve types C and Cs combined) was associated with better prognosis (9% with poor outcome) compared with a normal TPP or flat tympanogram (24% with poor outcome, Table 8). In the confirmatory statistical analysis, however, the finding was not statistically significant (OR 0.6, 95% CI 0.2-2.0).

Table 8. Prognostic value of tympanometry in the development and resolution of otitis media.

	Development of otitis media within three weeks in a healthy ear		**Resolution of otitis media within three to five weeks after AOM**	
Curve type	Number of curves N	Ears with MEF at the subsequent visit %	Number of curves N	Ears with MEF at the follow-up visit %
A	292	17	38	26
B	19	32	254	24
C	135	41	30	7
As	209	22	68	22
Cs	66	38	28	11
F	NA	NA	14	14
Total	721	25	432	22

AOM, acute otitis media; MEF, middle ear fluid; NA, not available.

10.5 Negative pressure in tympanometry (V)

A negative pressure tympanogram (TPP < -100 daPa) was a common finding in visits of the study; 23% of all successful curves showed decreased middle ear pressure. The majority of ears with negative TPP were considered healthy; only 15% of ears (N=135) had signs suggestive of MEF. In 78% (N=105) of ears the presence of MEF was confirmed by myringotomy. The proportion of MEF increased in ears with decreasing pressure, yet not more than 29% of ears with a TPP of less than -300 daPa were diagnosed with MEF. Furthermore, in the statistical analysis the difference was not significant. However, the low-admittance tympanograms had significantly more commonly MEF compared to high-admittance tympanograms (22% in Cs compared to 11% in C, p<0.006).

The majority of bacterial cultures in AOM with negative pressure yielded no growth; especially rare were findings of *S. pneumoniae* and *H. influenzae* (Table 9). The association of negative TPP in otitis media and negative middle ear fluid culture for the main pathogens was confirmed in the statistical analysis (OR 3.6, 95% CI 1.7 to 7.4).

Table 9. Pathogen distribution of otitis media with negative tympanometric peak pressure in a longitudinal follow-up of 329 children from 2 to 24 months of age.

	ALL*	**C1†**	**C2†**	**Total, C1 and C2**
	N=1135	**N=53**	**N=52**	**N=105**
***Streptococcus pneumoniae*, %**	21	6	4	5
***Haemophilus influenzae*, %**	18	11	0	6
***Moraxella catarrhalis*, %**	15	19	17	18
Combinations, %	6	2	2	2
Negative/Other	40	62	77	70
All	100	100	100	100

* All MEF samples during the follow-up in the FinOM Cohort Study
† C1: TPP -105 to -195 daPa, C2: TPP -200 to -395 daPa

11 DISCUSSION

11.1 Study populations and methods

In both materials used for this thesis, the FinOM Cohort Study and the FinOM Vaccine Trial, healthy unselected children at two months of age were enrolled. For both studies, the enrollment was over 50% of the target population living in the study areas. The following inclusion criteria, in addition to parental consent, were used in the enrollment of the studies: at least one parent able to communicate fluently in Finnish, the child was in good health and able to be followed in the study, and no pneumococcal vaccination given. Additionally, in the Vaccine Trial no previous hepatitis B vaccination and no hypersensitivity to vaccines included in the protocol was allowed. However, the number of children excluded due to any of these reasons was low. Thus, the study populations are highly representative of normal children in primary care practice.

In both materials the prospective follow-up of the study children up to 24 months of age was scheduled in special study clinics established for the purpose. In the Cohort Study 85% of children finished the follow-up at 24 months of age; in the Vaccine Trial the respective figure was as high as 96%. During the follow-up a vast majority of AOM was diagnosed in the study clinics. In the Cohort Study, 86% of all events of AOM during the follow-up period (from 2 to 24 months of age) were diagnosed at the study clinic. Furthermore, in 89% of AOM events diagnosed at the study clinic at least one MEF sample was obtained for bacterial culture.

Tympanometry was performed every time when ears were examined except for the case of discharging perforation, as discharge may contaminate the instrument. In the analyses, the tympanometry data on ears with a perforation were excluded since patent perforations give flat curves with an increased ECV value and no values for the other tympanometric variables are obtained. Additionally, in the Cohort Study a different tympanometer was used at 133 visits (4.5% of all visits) during the weekend hours (years 1994 to 1995); these data are not included in the analyses (papers IV and V). The remaining cases were included in the analysis. Failure to obtain a reliable curve for interpretation occurred in 6 to 8% of ears. Thus, the available tympanometry data is highly representative of the study population and the visits in the study clinics.

Studies on AOM in children exclusively less than two years of age are rare even if the occurrence of otitis media is highest in this age group. Commonly children up to 16 years of age have been included in study populations. This may affect the results, since many factors associated with otitis media are age-dependent, like anatomy and immunologic defence mechanisms. Furthermore, previous preventive measures, i.e. tympanostomy surgery and/or adenotomy procedures, may affect the results, especially in studies in which only otitis-prone children are recruited. Thus, in the interpretation of otitis media studies the reference population has to be considered; generalization of the data may not be appropriate. Probably more consistent results are obtained in studies with a narrower age range of subjects.

The longitudinal study design produces multiple events per subject, since recurrence is very characteristic of otitis media. This introduces the problem of dependent events for statistical models. The statistical tests are based on a distribution of random events. The use of inter-dependent data produces bias that may produce erroneous results in statistical models.

The problem was circumvented in this series by describing the results of all data of the longitudinal follow-up. However, the statistical analyses were based on data with only one event per independent subject in the study. The selection was most commonly based on random selection of one of the many events potentially available, which decreased the number of events valid for analysis. The statistical analyses were considered as confirmatory for the results obtained in the descriptive analysis of the longitudinal data.

11.2 Definitions and procedures

A strict definition for AOM was utilized in the studies. For a diagnosis of AOM, there had to be acute symptoms (ear ache, ear pulling, irritability, poor sleeping, fever, cough, rhinorrhea, gastrointestinal symptoms or other respiratory symptoms) together with tympanic membrane signs suggestive of middle ear fluid (in regard to color, mobility and/or position of the tympanic membrane). Additionally, an acute purulent otorrhea not caused by external otitis was considered as AOM.

In children under two years of age, the symptoms are usually expressed by the parents. Consequently, there may be variation in the way the parents interpret the symptoms and how

they react to their child's behavior and symptoms. Additionally, it is difficult to assess the origin of the symptoms, i.e. if the symptoms are associated with a potential ear related problem or if the symptoms are purely due to a viral respiratory tract infection. However, this problem is universal and not specific for this study. The otitis media research community unanimously includes acute symptoms to the definition of AOM.

The phase of the disease in the continuum of otitis media is sometimes difficult to assess. Usually an asymptomatic middle ear disease is diagnosed as OME. However, when this is interrupted by a symptomatic viral respiratory infection, when is the diagnosis of AOM valid? This is partly solved by longitudinal follow-up with the same experienced physician caring for the children, thus enabling continuity in the follow-up. Additionally, a residual disease under healing may be interrupted by a new event of AOM, again making the interpretation of symptoms and signs difficult. Discrimination between AOM and OME using otoscopical criteria is difficult. Signs of inflammation on the tympanic membrane are commonly required for a diagnosis of AOM. However, redness of the tympanic membrane is not a specific finding, cloudiness is common as well in OME as in AOM (Karma et al. 1989). Bulging of the tympanic membrane is quite specific, yet sensitivity may be poor. Unambiguous universal definitions are hardly feasible.

All the procedures in the FinOM studies were defined in standard operating procedures, making the diagnostics and treatment consistent by all physicians and study clinics. Additionally, full-time personnel were employed specifically for the study to take care of the clinical follow-up. These features decrease the probability of differences between physicians and increase the validity of the follow-up data. On the other hand, the external validity may be questioned since the personnel were specifically educated for the purpose. However, generally-approved definitions were employed. The experience achieved during this study makes it easier to apply the procedures in general practice outside study organizations.

Tympanometry testing is easy to learn, the instruments usually proceed automatically when a hermetic seal has been obtained. In simple cases, the interpretation is uncomplicated. However, routine use of tympanometry is recommended even in simple cases since the interpretation of complex cases may be difficult without adequate experience. In this study, no differences were noticed between experienced and less experienced study physicians in tympanometry interpretation (I).

11.3 Instrument differences

In this study, only one type of tympanometer was used (Grason-Stadler GSI38 Autotymp). There are many instruments commercially available which may produce minor differences in healthy adults (De Chicchis and Nozza 1996). The majority of instruments share the same measurement specifications, i.e. probe tone frequency, range, speed and direction of the pressure sweep and ECV estimation procedure (De Chicchis and Nozza 1996). The tympanometric variables measured are usually the same, although some instruments do not give values for TW (De Chicchis and Nozza 1996). However, more significant differences affecting the interpretation of results are probably found when older instruments are compared with modern ones (see Section 7.2.11). Gaihede and Marker (1998) compared two instruments by the same manufacturer; they found good agreement with a modern instrument compared to an older one after adjustment for a comparable sweep rate. Nevertheless, to be on the safe side, the values determined for a specific instrument should be carefully evaluated when applied to a different instrument. This is especially important if different specifications are used. However, most commonly different phenomena (for example in this thesis interpretation of tympanograms, prediction of outcome of AOM by tympanometry, and association of tympanometry results with bacterial etiology of OM) are described which are not specific for given instruments. On the other hand, normative values and specific cut-off levels for abnormal tympanograms are more instrument-specific. However, the instrument studied shares the same technical specifications with other common instruments.

To my knowledge only two different instruments are distributed in Finland, the one used in the FinOM studies and the Welch-Allyn Microtymp. These tympanometers share the same probe tone, same tympanometric variables and the same direction of pressure sweep. In addition, the new version of the Welch-Allyn instrument, Microtymp2, has the same pressure range (+200 to -400 daPa) and the speed of the pressure sweep is comparable (around 400 daPa/s). Thus, only slight differences exist in the technical specifications. Compared to the Grason-Stadler GSI38 Autotymp the Microtymp2 gives a lower measurement range for admittance, has a less-refined graphic display, and produces no numerical value for low-admittance tympanograms (SAA below 0.3 mmho). The two latter may impede proper interpretation in young children and unco-operative children.

11.4 Interpretation of tympanometry

Interpretation of test results is important in any diagnostic test or procedure. In tests with a graphical curve or figure as the primary result, the physician has to compare the individual test result to the existing previous patterns and interpret it as a normal or abnormal finding. This is prone to individual variation, which may impair the validity of the test. The majority of reports on the validity of tympanometry have been designed to assess the value in detecting the presence of middle ear fluid. Only few studies have evaluated the interpretation of tympanogram curves in children (van Balen et al. 1999, Green et al. 2000) and adults (Nondahl et al. 1996). The objective of this study was to assess the reliability of interpretation of tympanograms obtained from infants, since poor co-operation of children is commonly a factor that makes the testing and interpretation more difficult.

Kappa statistics was selected since it is suitable for studies where no golden standard is available (Fleiss 1981). The Kappa statistics measures agreement, which is corrected for the agreement that occurs due to chance alone.

A high level of concordance was confirmed in this study. High-peaked tympanograms (type A and type C) were almost always interpreted concordantly, even without any knowledge of child co-operation, presence of ear wax or middle ear findings. Low-peaked tympanograms are more prone to variation. Increase of the tympanogram peak in successive tests may increase the SAA (Wilson et al. 1984, Karzon 1991, Gaihede and Ovesen 1997) and thus alter the tympanogram type from type As to type A or from type Cs to type C. However, this probably has little effect on the treatment decisions, as in young children all these curve types are most often indicative of a healthy ear. However, the shift of flat type B curve to a shallow type As or Cs would have more clinical relevance. However, the most common discordance was between type B and failed tympanograms. The majority of the discordance disappeared when the ear status and data on co-operation of the infant was revealed.

The lower concordance of interpretation at sick visits is probably due to the higher prevalence of MEF and the consequent higher proportion of type B tympanograms. However, the co-operation of the infant may be more difficult to achieve during a sick visit when the child is brought for consultation due to acute symptoms. A similar observation was reported by Green et al. (2000).

The present results are similar to those of van Balen et al. (1999) and Green et al. (2000), though our agreement was slightly higher. However, in these studies a different tympanometer (a microtymp) and classification system was used, and ordinary general practitioners, although engaged in research projects, were included. In the study of van Balen et al. (1999) the interpretation of different curve types was assessed. Contrary to our findings, the interpretation of type B curves was concordant and type C less concordant.

Specific education and training on the interpretation of tympanograms was performed prior to the start of the trial. Furthermore, in the beginning of the trial problematic curves were interpreted together and discussed to achieve concordant interpretation. During the trial, a written standard operating procedure was utilized which described in detail how to calibrate the equipment, and obtain interpret the curves. It was not studied which of the measures was the most important for high concordance, but written instructions for the interpretation are considered essential.

Concordant interpretation is mandatory for a diagnostic test. This can be achieved for tympanometry even when testing infants. Written instructions, a review of the problematic cases with a tutor, and routine daily use of the instrument are all considered important. When an abnormal test result is obtained, assessment of the co-operation during testing and the findings in pneumatic otoscopy are needed for reliable interpretation. In high-peaked tympanograms, no additional data is needed for interpretation.

11.5 Diagnostic value of tympanometry

The diagnosis of otitis media is far from easy, especially in infants and young children (Froom et al. 1990). Furthermore, the incidence of otitis media is highest in this age group. Thus, the need of reliable methods for otitis media diagnostics is obvious. The majority of diagnostic reports on tympanometry have been performed on older children submitted for otorhinolaryngologic surgery because of recurrent or persistent otitis media. The purpose of this study was to assess the diagnostic validity of tympanometry in non-selected children at open care level during routine consultations for respiratory symptoms.

Detection of middle ear fluid is considered a prerequisite for the diagnosis of otitis media. Accuracy of the diagnosis of otitis media is required for correct treatment decisions. Low sensitivity of the diagnosis would delay the treatment and result in additional consultations and possibly prolong the duration of the illness; low specificity would increase the use of unnecessary treatment. In acute pharyngitis it has been observed that the prescription of antimicrobial treatment, either useful or not, increases the belief of treatment in patients and also affects their future consultation rate (Little et al. 1997a, Little et al. 1997b). This is probably similarly true for AOM (Majeed and Harris 1997). Furthermore, as AOM has a favorable natural course in a large proportion of cases, it would be even more detrimental to prescribe antimicrobial treatment based on erroneous diagnosis. It would be easy to anticipate that the highest risk of "undue stigmatization" as otitis-prone would occur in parents with their first infant coming to consultation.

Pneumatic otoscopy is a subjective method which is dependent on the skills of the otoscopist, but also on other factors such as co-operation of the patient and the caregiver, availability of assistance by nurses, the presence of earwax, quality of the otoscope, time used for examination, etc. Tympanometry affords an objective tool for the diagnosis of otitis media. Some co-operation of the patient is required, but the testing procedure is quick and painless. Consequently, infants usually can be reliably tested. Additionally, a small amount of earwax does not impede testing. On the contrary, normal tympanometry results are reliable even in cases where no visibility can be achieved in otoscopy.

The high specificity and positive predictive value reported in this study are useful for verification of the presence of MEF in otitis media. However, the sensitivity was rather low. However, in the interpretation of type As and Cs curves as pathological, the sensitivity increases substantially, but a concomitant decrease in specificity is noticed. Thus, different classifications and diagnostic schemes may be appropriate, depending on the population being tested and the purpose of the testing (i.e. whether screening for otitis media, hearing impairment, or confirmation of a clinical diagnosis).

Tympanometry results have been found to correlate with the amount of fluid in the middle ear (Fiellau-Nikolajsen 1983, Ovesen et al. 1993, Koivunen et al. 1997). Thus, in otitis media with a small amount of fluid, peaked tympanograms can be obtained. This decreases the sensitivity of tympanometry in diagnostics. However, it has also been shown that the height of

the tympanogram peak is conversely associated with hearing impairment due to otitis media (Ben-David et al. 1981, Dempster and MacKenzie 1991, Kazanas and Maw 1994, MRC Multi-Centre Otitis Media Study Group 1999). Consequently, a wrong negative diagnosis would be more probable for a disease with little effect on hearing. Additionally, it has to be remembered that otitis media is a dynamic disease with continuous development or resolution, affected by the treatment provided or by spontaneous course of the disease. Thus, the diagnostics of otitis media, both tympanometry and pneumatic otoscopy, are dependent on the phase of the disease: more advanced and more severe cases are easier to diagnose, while incipient disease may be difficult to diagnose.

In this study, the patient population was highly different from the previous studies on the diagnostic value of tympanometry in otitis media. We tested non-selected outpatient children with respiratory illness seen at the study clinic when requested by the parents. The previous studies have dealt with older children sent for scheduled otologic surgery because of chronic OME or recurrent AOM (Table 4). In highly selected otitis-prone children the prevalence of MEF could be substantially higher compared to that in normal unselected children. With a sensitivity and specificity of 85%, the positive predictive value would be 85% with a disease prevalence of 50%. However, the same accuracy of test would give a PPV of 39% in a population with MEF prevalence of 10%.

The golden standard used in this study was pneumatic otoscopy and also myringotomy if indicated (myringotomy performed in 74% of ears with MEF). In ears with normal status of the tympanic membrane, no myringotomy was performed. However, normal tympanic membrane findings are reliable in excluding otitis media. Furthermore, use of myringotomy for verification of the diagnosis in cases of suspected AOM enhances the diagnostic skills in pneumatic otoscopy by providing immediate feedback.

The major weakness in this study was the unblinded nature of the study: tympanometry and diagnostic assessment were performed by the same physician. However, the definition of otitis media in the FinOM studies was based entirely on pneumatic otoscopy, and in the majority of ears myringotomy was performed to confirm the presence of MEF. Additionally, it is highly unlikely that the number of false negative diagnoses would be significant: 62% of children enrolled in this one specific clinic of the Vaccine Trial were diagnosed with AOM before their first birthday. This is a larger proportion than in any of the numerous published

Finnish reports on AOM epidemiology (Paavolainen 1966, Pukander et al. 1982, Sipilä et al. 1987, Alho et al. 1991, Kilpi et al. 2001).

Despite the high positive predictive value, tympanometry cannot be used alone for the diagnosis of otitis media. Otoscopy is needed for the confirmation of the diagnosis and assessment of inflammatory signs on the tympanic membrane; knowledge of the symptoms and previous history of otitis media is also important in the treatment decision. Additionally, false negative results are relatively common; otitis media with a sectorial accumulation of MEF should be easily detected using pneumatic otoscopy.

11.6 Normative values of tympanometry

Reports of normative values of tympanometric variables are scarce, especially in children aged two years and less. Data on normal values are needed for application of the test in routine practice and for development of new diagnostic algorithms. Additionally, the different instruments may produce varying results; instrument-specific data are needed. The objective of this study was to determine the normal values of tympanometry using a large group of 7 and 24-month-aged children.

A substantial increase in acoustic admittance and decrease in tympanometric width was found with increasing age. This is in agreement with previous findings (Page et al. 1995, Roush et al. 1995, De Chicchis et al. 2000).

The normative values obtained in our study were considerably lower for SAA and TW compared to previous studies in the same age groups (Roush et al. 1995, De Chicchis et al. 2000). Some of this difference might be due to the equipment used, though the same probe tone and same measurement scale were utilized. It has been reported that lower values for TW are obtained with the instrument we used (Grason-Stadler GSI38, De Chicchis and Nozza 1996). Additionally, in our study special attention was paid on increasing SAA at repetitive testing: the first technically successful curve was chosen for interpretation even if later recordings were technically more perfect.

The results of this study are based on a large cohort of children. The ears representing normalcy were selected by otoscopical examination and showed normal findings in all respects. The study physicians performing the otoscopy were all employed full-time for the study. Although formal validation had not been performed, the study physicians were experienced otoscopists and had used routine myringotomy for verification of AOM according to the protocol of the study. To further increase the reliability of the study, tympanograms obtained with any of the interfering factors during testing (poor co-operation, excessive earwax or crust on the tympanic membrane) were excluded from the analyses.

Various factors were found to affect the tympanometric variables even in children with normal otoscopical status. Probably middle ear and tympanic membrane size was reflected in the association of higher SAA values in children with high birth weight and in males. The effect of birth weight was surprisingly still evident at 24-month age. In children with previous grommets, the SAA was significantly higher at 24 months of age, probably reflecting local tympanic membrane atrophy after closure of the perforation.

When multiple statistical tests are performed the probability of finding a significant result increases due to chance alone, especially in large materials. Despite statistically significant differences in the variables, clinical significance is obscure and different norms for children with these factors are hardly feasible. However, a tympanic membrane with marked atrophy may show normal admittance even in the case of otitis media with a considerable amount of MEF (Margolis and Shanks 1985).

Age-adjusted normal values are needed in the interpretation of tympanometry results. It is also important to be aware of the fact that various factors influence the normal values, and these may also affect the interpretation of the test result.

11.7 Prediction by tympanometry

Development of OM is the most common complication of a viral respiratory infection. A knowledge of the factors associated with the prognosis of the respiratory infection would help in focusing further follow-up measures in children with a high risk of acquiring otitis media.

Children with a negative TPP had an increased risk of development of otitis media to a healthy ear within 3 weeks of a visit due to respiratory illness. The result is concordant with earlier studies (Moody et al. 1998). However, not all children were re-examined within this period; re-examinations occurred according to the parents' wishes for a new consultation because of prolonged or new episode of symptoms. Consequently, also children who did not come back for a new visit might have developed middle ear fluid. Thus, a systematic follow-up in short time intervals would be needed to assess the progress of the events more thoroughly.

On the other hand, the identification of factors associated with good prognosis in AOM would potentially enable a more expectant approach to the treatment of AOM. This might decrease the antibiotic consumption for otitis media and thus be one measure to combat antimicrobial resistance. Additionally, a decrease in other side effects of antimicrobial use, a decrease in treatment costs and possibly also a decrease in parental concern and extra caring could be achieved. One step towards the goal would be to identify factors which are associated with good prognosis in AOM with adequate treatment.

The resolution of AOM was slightly better, again, in children with a negative TPP in connection with AOM compared to children with flat or normal pressure tympanograms. However, due to the low number of AOM with negative TPP, the result could not be confirmed in the statistical analysis. The better resolution might be due to identification of non-severe forms of otitis media. Additionally, the phase of the disease might have initially been different.

Poorer prognosis in association with a type B tympanogram has been reported earlier (Lampe et al. 1981, Iino et al. 1993, Sakaguchi et al. 1994). However, the children were older in these studies, 4 to 5 years on average. In the study of younger children aged 5 months to 5 years by Green et al. (1994) no association between initial tympanometry and prognosis of AOM was found.

The routine use of myringotomy might have affected the resolution of AOM in this study. It is possible that myringotomy had more effect on ears with type B tympanograms with a higher quantity of MEF (Fiellau-Nikolajsen 1983). Furthermore, as the proportion of ears with other than type B tympanograms is considerably low in otitis media, the sample size should be

much bigger to have enough power for statistically significant results for minor clinical differences (type II error).

Careful follow-up after AOM is suggested for all children. Tympanometry has little value in the prognostic assessment in this respect. However, negative pressure in tympanometry in a healthy ear is associated with an increased risk of development of MEF. If the symptoms persist or new symptoms emerge, the parents should be advised to bring the child for a re-consultation. It thus seems that a negative pressure finding in tympanometry is associated with a change in the state of the middle ear (either the middle ear is developing disease or the middle ear is resolving disease) more commonly than with other tympanogram types. This suits well to the pathogenesis of otitis media.

11.8 Negative pressure in tympanometry

The reports on the value of negative tympanometric peak pressure in the diagnosis of otitis media are controversial. Some researchers consider pronounced negative TPP (TPP<-200 daPa) indicative of MEF (Ovesen et al. 1993, Sassen et al. 1994, van Balen and de Melker 1994), while other researchers consider it pathological only if connected with another finding suggesting MEF (Paradise et al. 1976, Fiellau-Nikolajsen 1983). Yet most researchers consider it indicative of a healthy ear with decreased middle ear pressure (Jerger 1970, Toner and Mains 1990, Babonis et al. 1991, Finitzo et al. 1992, Koivunen et al. 1997, Watters et al. 1997). The purpose of this study was to clarify the role of negative TPP as an indicator of MEF. Additionally, we were also able to investigate if any specific bacteria were associated with otitis media with a decreased middle ear pressure.

Middle ear fluid was detected in only a minor proportion of ears with low middle ear pressure in this material. Even in profoundly negative middle ear pressure, the proportion of ears with MEF remained low. Our results may be explained by the different study population (see above), but also by different testing circumstances. We mainly tested children during acute viral respiratory infections, which commonly produces negative middle ear pressure due to Eustachian tube blockage. Probably the time factor is important; if the Eustachian tube dysfunction resolves promptly otitis media does not develop.

When compared to children with otitis media without negative middle ear pressure, the children with negative middle ear pressure were similar in respect to the duration of the symptoms prior to the diagnosis and history of previous AOM within one month. The number of children with current antimicrobial treatment was low in both groups.

In otitis media with decreased middle ear pressure, the result of the bacterial culture rarely yielded positive cultures, especially those of *S. pneumoniae* or *H. influenzae*. The most plausible explanation for the different culture results is the progression of the middle ear disease when viable bacterial pathogens enter the middle ear cleft and initiate the inflammatory process, with an accumulation of fluid and TM changes. Consequently, the type of tympanogram changes accordingly; a flat type B tympanogram is obtained instead of a peaked negative pressure curve. On the contrary, there was no difference in isolations of *M. catarrhalis* between otitis media with negative TPP and otitis media without negative TPP. This is in accordance with the fact that *M. catarrhalis* is not as aggressive a pathogen as *S. pneumoniae* or *H. influenzae* (Coffey et al. 1967, Van Hare and Shurin 1987, Heikkinen et al. 1998, Rodriguez and Schwartz 1999).

The implication of negative pressure finding in otitis media should be reassessed. A recently reported study (van Balen et al. 1996) on otitis media still used type C2 curves as being indicative of MEF; furthermore the definition of OME was based on C2 curves in tympanometry. In the light of the results of the present study, the erroneous definition may lead to overdiagnosis and thus to misleading results which are not compatible with the results from studies with more elaborate means of diagnosing OME.

The application of the finding of association of negative pressure tympanogram result with negative middle ear bacterial culture in clinical practice could mean a more conservative treatment of AOM and avoidance of routine antimicrobial treatment. However, the current data do not answer the question of what would happen if these cases were left untreated, although the negative pressure tympanograms showed a better prognosis in treated AOM. Nevertheless, an appropriate study protocol would be needed to address the specific issue of studying factors implicating good prognosis in expectant follow-up.

12 CONCLUSIONS

1. A high concordance of interpretation of tympanometry curves can be achieved. Written instructions, routine daily use and consultations regarding controversial or difficult-to-interpret curves especially during the initiation of routine use of the methodology are considered important steps to achieve concordance.
2. The interpretation of a tympanogram as abnormal requires assessment of the co-operation of the child and otoscopical examination of the external ear canal to exclude occlusion.
3. The diagnostic value of tympanometry is good in infants and children less than two years of age. The importance of high validity is augmented by the weaknesses of conventional diagnostic methods, i.e. interview for symptoms and otoscopy, in this age group.
4. The purpose of tympanometric testing determines the definition of abnormal result; the trade-off between high sensitivity and high specificity can be adjusted by appropriate definitions.
5. Otitis media coincides in ears with normal high-peaked tympanograms only rarely. Together with highly concordant interpretation, the finding of a high-peaked tympanogram does not necessitate ascertainment by otoscopical examination.
6. Normal values for static acoustic admittance and tympanometric width are age-related.
7. Various factors like gender, history of grommets and child co-operation during testing affect the tympanometry variables. However, their clinical implication is minor, although in individual cases these may be relevant in the interpretation of the results.
8. The risk of developing middle ear disease is increased in children with profoundly negative middle ear pressure during respiratory infection without otitis media. On the other hand, the risk of persistent otitis media may be lower in children with profoundly negative middle ear pressure during respiratory infection with acute otitis media. Thus, negative middle ear pressure may be an indicator of a dynamic change in the middle ear.
9. The value of profoundly negative middle ear pressure as an indicator of middle ear disease has been overestimated; only a low proportion of children with profoundly negative middle ear pressure reveals otitis media.
10. Negative bacterial culture is a common finding in middle ear fluid samples obtained from ears with negative middle ear pressure and otitis media. Especially the more aggressive pathogens *Streptococcus pneumoniae* and *Haemophilus influenzae* are uncommon findings.

13 FUTURE CONSIDERATIONS

These studies contribute to the knowledge base for further studies which evaluate the large-scale application of tympanometry in general practice. Further considerations are e.g. the assessment of tympanometry in everyday work in open care. The impact of a routine application of tympanometry in increasing diagnostic accuracy, and potentially in improving treatment results; in the potentially greater satisfaction among patients and physicians, as well as the resulting economic implications, would all be essential to document. Furthermore, new diagnostic schemes and practices utilizing tympanometry should be evaluated.

The diagnostic value of tympanometry might be improved by the application of subject-specific norms. This would reduce the effect of individual differences. This could be accomplished by routine testing at healthy visits without any signs of otitis media. Due to age-related changes, the testing should be repeated at suitable intervals. The routine check-up visits at well-baby clinics in Finland could be an example of visits during which this might be studied.

Part of the cohort of study children presented in paper III has been re-examined at a follow-up visit at the age of 4 to 5 years. The determination of normative data based on this closely followed child cohort would further increase the knowledge of age-dependent changes in tympanometry.

The implications of the findings associated with negative pressure tympanograms need further assessment. Especially if the association of negative pressure tympanogram and negative findings in the bacterial culture of middle ear fluid is confirmed, this finding might be important in decreasing antimicrobial consumption in general. The present results suggest a possibility for more restrictive use of antimicrobial treatment in these cases, but expectant follow-up of these children is still necessary to observe the natural course of this kind of otitis media. A well-planned prospective follow-up study would be needed to address the issue.

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16 APPENDIX: The specifications of the Grason-Stadler GSI38 tympanometer

Tympanometry

Probe tone:	226 Hz, +/- 3%
Sound pressure level:	85.5 dB SPL, +/- 2.0 dB, measured in a 2.0 cm^3 coupler
Harmonic distortion:	<5%
Admittance range:	0 to 1.5 cm^3 or 0 to 3.0 cm^3, selected automatically
Admittance accuracy:	+/- 0.1 cm^3 or +/- 5%, whichever is greater
Cavity limits for initiation of pressure sweep:	0.2 to 6.0 cm^3
Pressure range:	+200 to -400 daPa
Pressure accuracy:	+/- 10 daPa or +/- 15%, whichever is greater
Rate of sweep:	600 daPa/s except near tympanogram peak, where sweep rate slows to 200 daPa/sec
Direction of sweep:	Positive to negative
Test time:	1 to 2 seconds

LED indicators in the probe for guiding in the testing procedure

Yellow	Occlusion of the probe
Orange	Leak of air
Blinking green	Ready to test
Steady green	Test in progress
Lights off	Test ready

17 ORIGINAL REPORTS (I-V)