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TYMPANOMETRY AND SPECTRAL GRADIENT ACOUSTIC REFLECTOMETRY IN THE DIAGNOSIS OF OTITIS MEDIA IN YOUNG CHILDREN

Miia Laine

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To my dear family Timo, Emilia, and Eemil,
and to the grandparents Kristiina and Matti, Marita and Kaarlo
for all their support

ABSTRACT

Miia Laine

Tympanometry and Spectral Gradient Acoustic Reflectometry in the Diagnosis of Otitis Media in Young Children

University of Turku, Faculty of Medicine, Institute of Clinical Medicine, Department of Paediatrics, Doctoral Programme of Clinical Investigation - CLIDP; and Turku University Hospital, Turku, Finland.

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Acute otitis media (AOM) is the most prevalent bacterial infection among children. Tympanometry and spectral gradient acoustic reflectometry (SG-AR) are adjunctive diagnostic tools to pneumatic otoscopy. The aim was to investigate the diagnostic accuracy and success rates of tympanometry and SG-AR performed by physicians and nurses.

The study populations comprised 515 (I-II), 281 (III), and 156 (IV) outpatients (6-35 months). Physicians performed 4246 tympanometric (I) and SG-AR (II) examinations. Nurses performed 1782 (III) and 753 (IV) examinations at symptomatic and asymptomatic visits, respectively. Pneumatic otoscopy by the physician was the diagnostic standard. The accuracy of test results by physicians or nurses (I-IV) and the proportion of visits with accurate exclusive test results from both ears (III-IV) were analyzed.

Type B tympanogram and SG-AR level 5 (<49˚) predicted middle ear effusion (MEE). At asymptomatic visits, type A and C1 tympanograms (peak pressure > -200 daPa) and SG-AR level 1 (>95˚) indicated healthy middle ear. Negative predictive values of type A and C1 tympanograms by nurses in excluding AOM at symptomatic and MEE at asymptomatic visits were 94% and 95%, respectively. Nurses obtained type A or C1 tympanogram from both ears at 94/459 (20%) and 81/196 (41%) of symptomatic and asymptomatic visits, respectively. SG-AR level 1 was rarely obtained from both ears.

Type A and C1 tympanograms were accurate in excluding AOM at symptomatic and MEE at asymptomatic visits. However, nurses obtained these tympanograms from both ears only at one fifth of symptomatic visits and less than half of asymptomatic visits.

Keywords: acute otitis media; otitis media with effusion; middle ear effusion; tympanometry; spectral gradient acoustic reflectometry; pneumatic otoscopy; diagnosis; children; nurse

TIIVISTELMÄ

Miia Laine

Tympanometri ja akustinen reflektometri välikorvatulehduksen diagnostiikassa pienillä lapsilla

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Lastentautioppi, Turun yliopiston kliininen tohtoriohjelma (TKT); Turun yliopistollinen keskussairaala, Turku

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Äkillinen välikorvatulehdus on lasten yleisin bakteeri-infektio perusterveydenhuollossa. Tympanometri ja akustinen reflektometri ovat pneumaattisen otoskopian diagnostisia apuvälineitä. Väitöskirjan tavoitteena oli selvittää lääkärien ja hoitajien suorittamien tympanometri- ja reflektometrimittausten diagnostista luotettavuutta sekä onnistumisprosenttia pienillä lapsilla.

Tutkimuksiin osallistui 515 (I-II), 281 (III) ja 156 (IV) 6-35 kuukauden ikäistä lasta perusterveydenhuollon tasolla. Lääkärit suorittivat 4246 mittausta tympanometrilla (I) ja akustisella reflektometrilla (II). Hoitajat suorittivat 1782 mittausta oireisilla (III) ja 753 mittausta oireettomilla (IV) käynneillä. Lääkärin suorittama pneumaattinen otoskopia toimi diagnostisena standardina. Lääkärien ja hoitajien mittaustulosten diagnostinen luotettavuus määritettiin (I-IV); samoin niiden käyntien osuus, joissa hoitajat saivat äkillisen välikorvatulehduksen (III) tai välikorvaeritteen (IV) luotettavasti poissulkevan testituloksen lapsen molemmista korvista.

Lääkäreiden mittaamat tyypin B tympanogrammi ja reflektometriluokka 5 (<49˚) ennustivat luotettavasti välikorvaeritettä. Oireettomilla käynneillä tyypin A ja C1 tympanogrammit (huippupaine > -200 daPa) ja reflektometriluokka 1 (>95˚) osoittivat terveen välikorvan. Hoitajien mittaamien tyypin A ja C1 tympanogrammien negatiivinen ennustearvo oli 94 % äkillisen välikorvatulehduksen poissulussa oireisilla käynneillä ja 95 % välikorvaeritteen poissulussa oireettomilla käynneillä. Niiden oireisten käyntien osuus, joissa hoitajat saivat tyypin A tai C1 tympanogrammin lapsen molemmista korvista, oli 94/459 (20 %). Vastaavasti oireettomien käyntien osuus, joissa tyypin A tai C1 tympanogrammi saatiin molemmista korvista, oli 81/196 (41 %).

Tyypin A ja C1 tympanogrammit ovat luotettavia äkillisen välikorvatulehduksen poissulussa oireisilla käynneillä ja välikorvaeritteen poissulussa oireettomilla käynneillä. Hoitajat saivat kyseiset tympanogrammitulokset pienen lapsen molemmista korvista kuitenkin vain yhdellä viidestä oireisesta käynnistä ja alle puolessa oireettomista käynneistä.

Avainsanat: äkillinen välikorvatulehdus, välikorvaerite, tympanometri, akustinen reflektometri, pneumaattinen otoskopia, diagnoosi, lapset, hoitaja

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ABBREVIATIONS

AOM	acute otitis media
a-AOM	air-interface AOM (AOM with air-fluid interface)
c-AOM	complete AOM (middle ear completely filled with effusion)
CI	confidence interval
daPa	deca-Pascal
ET	Eustachian tube
MEE	middle ear effusion
OME	otitis media with effusion
a-OME	air-interface OME (OME with air-fluid interface)
c-OME	complete OME (middle ear completely filled with effusion)
ROC	receiver operating characteristic curve
RTI	respiratory tract infection
RSV	Respiratory syncytial virus
SAA	static acoustic admittance
SG-AR	spectral gradient acoustic reflectometry
TPP	tympanometric peak pressure

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I–IV, and on some supplementary unpublished data.

I. Helenius KK, Laine MK, Tähtinen PA, Lahti E, Ruohola A. Tympanometry in discrimination of otoscopic diagnoses in young ambulatory children. Pediatr Infect Dis J. 2012;31:1003-6.

II. Laine MK, Tähtinen PA, Helenius KK, Luoto R, Ruohola A. Acoustic reflectometry in discrimination of otoscopic diagnoses in young ambulatory children. Pediatr Infect Dis J. 2012;31:1007-11.

III. Laine MK, Tähtinen PA, Ruuskanen O, Löyttyniemi E, Ruohola A. Can nurses exclude acute otitis media without otoscopy in symptomatic children in primary care? Submitted.

IV. Laine MK, Tähtinen PA, Ruuskanen O, Löyttyniemi E, Ruohola A. Can nurses exclude middle-ear effusion without otoscopy in young asymptomatic children in primary care? Scand J Prim Health Care. 2015;Early online:1-6.

1. INTRODUCTION

The accurate diagnosis of acute otitis media (AOM) is important because AOM is the most prevalent bacterial infection and the most common reason for antimicrobial treatment among young children in primary health care (Vergison et al. 2010). Viral respiratory tract infection (RTI) causes obstruction of the Eustachian tube (ET), negative middle ear pressure, and accumulation of middle ear effusion (MEE) (Bluestone and Klein 2007). Viral and bacterial pathogens may invade the middle ear and cause an episode of AOM. Symptoms of AOM are nonspecific in young children and cannot be used to diagnose AOM (Niemelä et al. 1994, Heikkinen and Ruuskanen 1995, Kontiokari et al. 1998a, Laine et al. 2010).

AOM and otitis media with effusion (OME) are diagnosed with pneumatic otoscopy in primary health care. However, performing pneumatic otoscopy is complicated due to the young age of the children, acute symptoms and signs of AOM and concomitant viral RTI, cerumen occluding the external auditory canal, and often poor equipment, such as old pneumatic otoscopes with low light output (Pichichero 2000a, Pichichero 2002, Steinbach et al. 2002). Thus, overdiagnosis of AOM may result (Pichichero 2000a), which predisposes children to unnecessary antimicrobial treatment, follow-up, and may even lead to unnecessary referral for tympanostomy tube placement (Casey and Pichichero 2014).

Tympanometry and spectral gradient acoustic reflectometry (SG-AR) are adjunctive diagnostic tools to pneumatic otoscopy. Tympanometry is slightly more accurate than SG-AR (Chianese et al. 2007). However, tympanometry requires an air-tight seal to the external auditory canal and the cooperation of the young, often acutely ill, child. Flat (type B) tympanograms have been found to predict the presence of MEE (Fiellau-Nikolajsen 1983, Palmu et al. 1999). On the other hand, peaked tympanograms with normal or slightly negative (>-200 deca-Pascals [daPa]) tympanometric peak pressure (TPP) seem to associate with a healthy middle ear (Fiellau-Nikolajsen 1983, Palmu et al. 1999). In addition, wide tympanograms (width >300 daPa) and low peaked tympanograms (static acoustic admittance [SAA] <0.2 mmho) have been associated with increased likelihood of MEE (Nozza et al. 1994, Smith et al. 2006). Furthermore, SG-AR level 1 seems to be associated with a healthy middle ear and levels 4-5 with MEE (Barnett et al. 1998).

If nurses could reliably exclude part of AOM or perform part of routine ear control visits after an AOM episode, physicians' time might be saved to perform other duties in primary health care. In fact, children's access to reliable ear evaluation might be enhanced in primary health care settings with a lack of physicians. Even though the

success rate of tympanometry from both ears of the child at asymptomatic visits has not been studied, the Finnish Current Care Guideline on the diagnosis and management of AOM (Heikkinen et al. 2010) states that routine ear controls can be performed with tympanometry by physicians or nurses. The proportion of visits where nurses can obtain accurate test results from both ears of the child is unknown.

2. REVIEW OF THE LITERATURE

"Accurate diagnosis of acute otitis media is essential for appropriate management and high quality research."

Siddiq et al. 2014

2.1 Definitions of otitis media

Current American guidelines on the diagnosis and management of AOM (Lieberthal et al. 2013) and tympanostomy tube placement (Rosenfeld et al. 2013) have adopted the terms defined by Bluestone and Klein (2007) (Table 1).

Table 1. Terms, abbreviations, and definitions of otitis media. Modified with permission from the thesis "Treatment of acute otitis media" by Paula Tähtinen, MD, PhD (2012).

Term	Definition
Otitis media	Inflammation of the middle ear, without reference to etiology or pathogenesis; middle ear effusion is present.
Acute otitis media (AOM)	Rapid onset of signs and symptoms of acute infection in the middle ear; middle ear effusion is present.
Otitis media with effusion (OME)	Presence of effusion in the middle ear without acute inflammatory signs on the tympanic membrane or middle ear.
Chronic otitis media with effusion (Chronic OME)	Otitis media with effusion persisting for three months or longer.
Middle ear effusion (MEE)	Any effusion in the middle ear without reference to etiology, pathogenesis, or duration.
Otorrhea	Discharge from the ear.

In the 2000s, before the recent guideline on AOM (Lieberthal et al. 2013), the three diagnostic criteria for AOM were: 1) acute onset of symptoms; 2) presence of MEE; and 3) signs of acute middle ear inflammation. These diagnostic criteria are still used in the Finnish Current Care Guideline on AOM (Heikkinen et al. 2010).

OME is defined as middle ear effusion without any signs of acute infection (i.e. bulging, distinct erythematous patches, or markedly increased vascularity) on the tympanic membrane (Rosenfeld et al. 2013). In contrast, MEE is a general term for any effusion

present in the middle ear regardless of etiology, pathogenesis, or duration. Thus, the term MEE comprises both AOM and OME.

The recent American guideline on AOM (Lieberthal et al. 2013) aimed to further clarify the diagnostic differences between AOM and OME in order to reduce unnecessary antimicrobial treatment. Thus, the guideline emphasized that AOM should be diagnosed only if the tympanic membrane is in bulging position as that is the most accurate indicator of acute infection (Lieberthal et al. 2013).

2.2 Pathogenesis

2.2.1 Anatomy

The nose, nasopharynx, ET, middle ear, and mastoid gas cells form an anatomical and functional entity which is covered by continuous respiratory mucosa (Bluestone and Klein 2007). The anatomy is depicted in Figure 1.

The middle ear is a gas-filled cavity located in the temporal bone between the external auditory canal and the inner ear. The middle ear includes the three ossicles: malleus, incus, and stapes. The tympanic membrane separates the middle ear from the external auditory canal. Posterior to the middle ear, is the mastoid cavity consisting of multiple gas cells of variable size. The growth and pneumatization of the mastoid is not complete until the age of 5 to 10 years. The immature anatomy predisposes young children to the development of AOM (Bluestone and Klein 2007).

Concerning the pathogenesis of otitis media, the ET is an essential part of anatomy, which is positioned between the nasopharynx and the middle ear. The nasopharyngeal orifice of the ET is located in the posterior wall of the nasopharynx next to the adenoid, i.e., the pharyngeal tonsil. The four paratubal muscles associated with the ET are: the tensor veli palatini, levator veli palatini, salpingopharyngeus, and tensor tympani. In children, the inclination of the ET is only 10˚ upwards whereas in adults, the angle is 45˚ in relation to the horizontal plane (Bluestone and Klein 2007). The width of the ET is 1-2 mm, and its length is approximately 2 cm in children and 4 cm in adults (Ishijima et al. 2000). The shortness and horizontal position of the ET in young children predispose to the development of AOM. The isthmus is the narrowest portion of the ET, and it is located near the end of the cartilaginous ET (i.e. the anterior two thirds of the ET) before the posterior osseus ET. The isthmus is the portion of the ET which obstructs most easily as the result of mucosal congestion during viral RTI (Bluestone and Klein 2007).

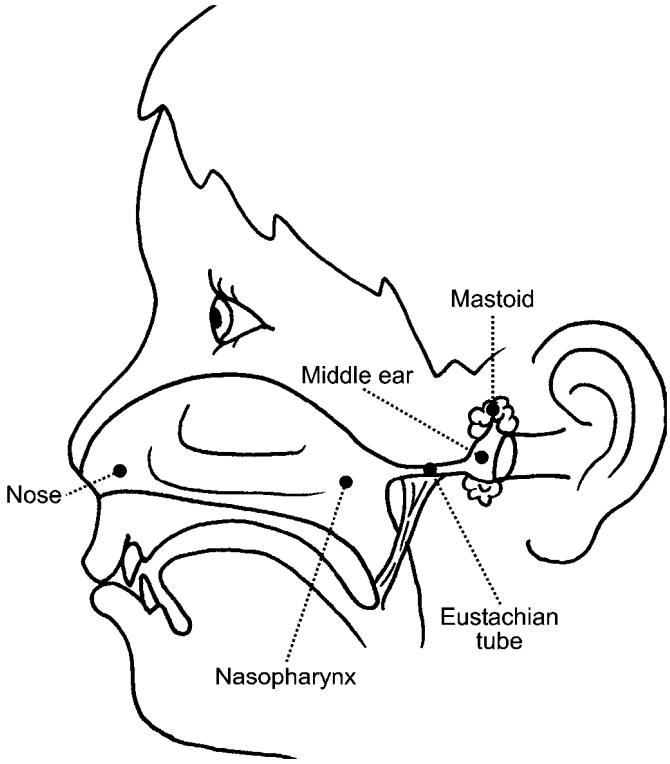


Figure 1. Anatomy of the nasopharynx, Eustachian tube, and middle ear. The figure represents a child approximately 1 year of age: the Eustachian tube is short and positioned almost horizontally. Modified from the thesis "Treatment of acute otitis media" by Paula Tähtinen, MD, PhD (2012). Published with the permission of the person who drew the figure, Jenni Jalkanen, MD, PhD.

2.2.2 Function of the Eustachian tube

The function of the ET is crucial in the development and resolution of otitis media. The three physiological functions of the ET include ventilation, clearance, and protection of the middle ear (Bluestone 1996).

The first main function of the ET is to equilibrate the middle ear pressure with atmospheric pressure. Physiological middle ear pressure is slightly negative, as summarized in Table 2. The ventilatory function of the ET is of great importance, because hearing is optimal when the pressure is similar on both sides of the tympanic membrane, i.e. in the middle ear and external auditory canal (Bluestone 1996). The cartilaginous portion of the ET is physiologically collapsed and opens during swallowing, sneezing, and yawning. However, in children, this active muscular opening of the ET is less efficient due to immature cartilage support of the ET and less efficient function of the tensor veli palatini muscle (Bluestone and Klein 2007). Bylander et al. (1980) studied the ventilatory function of the ET in children and adults who had healthy middle ears. They found that 36% of

the children were not able to equilibrate applied negative pressure in the middle ear by swallowing. In contrast, only 5% of adults could not equilibrate the negative pressure. Furthermore, children between 3-6 years of age had poorer results than children between 7-12 years of age. Thus, young healthy children seem to have more negative middle ear pressure than older children and adults. Negative middle ear pressure reflects the less efficient active opening of the ET (Bylander 1980, Bylander et al. 1983). With age, the physiological function of the ET gradually improves.

Table 2. Middle ear pressure in healthy children and adults, as measured with mean tympanometric peak pressure (TPP). 90% range for the mean TPP is presented because it was reported in all the studies.

Study	Number of ears	Age	Mean TPP (90% range)
Margolis and Heller 1987	Children: 92 ears; Adults: 87 ears	Children: 2 to 5 y; Adults: 19 to 61 y	Children: -30 daPa (-139 to +11 daPa) Adults: -19 daPa (-83 to 0 daPa)
Palmu et al. 2001a	1616 ears	7 mo	-41 daPa (-155 to +30 daPa)
Palmu et al. 2001a	1223 ears	24 mo	-41 daPa (-165 to +45 daPa)
Palmu and Rahko 2003	590 ears	4 to 5 y	-48 daPa (-155 to +30 daPa)

Abbreviations: TPP, tympanometric peak pressure; mo, months; y, years

Abnormal pressure conditions either in the middle ear or nasopharynx predispose the child to a flow of nasopharyngeal secretions into the middle ear through the ET. High positive pressure in the nasopharynx causes insufflation of secretions into the middle ear. This can result from nose blowing, crying, closed-nose swallowing (Toynbee phenomenon), diving, or ascent in an airplane. On the other hand, high negative pressure in the middle ear causes aspiration of secretions into the middle ear. This can result from the obstruction of the ET due to mucosal congestion during RTI or descent in an airplane. Furthermore, perforation of the tympanic membrane, patent tympanostomy tube, and radical mastoidectomy lead to loss of the physiological air cushion formed by the middle ear and the mastoid, which enables reflux of secretions into the middle ear (Bluestone and Klein 2007).

The ventilatory function of the ET is impaired in several conditions. Unrepaired palatal cleft causes functional obstruction of the ET and thus, predisposes to AOM and OME (Paradise and Bluestone 1974). Functional obstruction of the ET is also common in craniofacial abnormalities and Down syndrome. On the other hand, pathological obstruction of the ET can arise either inside the ET due to mucosal congestion during

RTI, or externally due to tumor or adenoid mass surrounding the ET (Bluestone 1996). Highlighting the importance of the ET, poor ventilatory function has been associated with children being otitis-prone (Stenström et al. 1991) or having persistent MEE (van Heerbeek et al. 2001).

The second main function of the ET is the clearance of secretions from the middle ear. The paratubal muscles pump secretions towards the nasopharynx during the closing of the ET (Honjo et al. 1985). Furthermore, the mucociliary system of the ET actively removes secretions from the middle ear. Thus, ciliary dysfunctions, such as Kartagener's syndrome, often cause chronic OME (Mygind et al. 1983).

The third main function of the ET is the protection of the middle ear. The cartilaginous part of the ET is normally collapsed, thus protecting the middle ear from nasopharyngeal secretions. Consequently, abnormally patent ET has been found to predispose the child to MEE (Beery et al. 1980). Furthermore, the shorter ET of children is less efficient in protecting the middle ear and allows more reflux of secretions into the middle ear. Additionally, in a horizontal position, the function of the ET is less efficient than in an upright position (Ingelstedt et al. 1967). On the other hand, nonspecific factors, such as oxidative and hydrolytic enzymes, have bacteriolytic activity and are part of the protection of the middle ear (Bluestone and Klein 2007).

2.2.3 Viral respiratory tract infection

Viral RTI is an initiating event in the cascade that leads to the development of AOM (Bluestone and Klein 2007). The intranasal challenge of influenza A virus (Doyle et al. 1994) or rhinovirus (McBride et al. 1989, Buchman et al. 1994) has been shown to cause obstruction of the ET, negative middle ear pressure, and accumulation of MEE.

In addition to causing viral RTI episodes, viruses are pathogens which cause AOM even without bacteria (Pitkäranta et al. 1998, Heikkinen et al. 1999, Ruohola et al. 2006). Different viruses have been found to differ in their ability to cause AOM. Henderson et al. (1982) were the first to show the increased incidence of AOM with concomitant viral RTI. They found that respiratory syncytial virus (RSV), influenza viruses A and B, and adenovirus were most often associated with AOM. Correspondingly, Ruuskanen et al. (1989) showed significant correlation between AOM and seasonal peaks of RTI episodes. In their study, AOM was found in over 50% of RSV episodes.

Since then, studies have consistently shown that RSV is strongly associated with AOM when analyzed either from nasopharyngeal samples (Arola et al. 1990, Uhari et al. 1995a, Pettigrew et al. 2011) or directly from MEE (Heikkinen et al. 1999). Since the introduction of PCR techniques for enhanced detection of viruses, RSV has still been found a major viral risk factor for AOM. On the other hand, PCR techniques have

enabled the accurate detection of rhinoviruses. Since rhinoviruses are the most frequent pathogens in viral RTI, they are the most frequently found viruses in nasopharyngeal samples (Vesa et al. 2001, Chonmaitree et al. 2008, Ruohola et al. 2013, Chonmaitree et al. 2015) and MEE (Pitkäranta et al. 1998, Ruohola et al. 2006) of children with AOM.

Viral RTI causes mucosal congestion in the ET leading to impairment of the ventilatory function. The resulting negative middle ear pressure can cause aspiration of nasopharyngeal contents into the middle ear (Bluestone et al. 1977, Winther et al. 2002). Elkhatieb et al. (1993) showed that in adults, over 50% of uncomplicated RTI episodes caused by rhinoviruses were associated with negative middle ear pressure (<-100 mmH_2O; 1 daPa = 1.02 mmH_2O). In their study, negative middle ear pressure resolved within 2 weeks. Correspondingly, Winther et al. (2002) studied the effect of viral RTI on middle ear pressure in previously healthy school-aged children and found that transient negative middle ear pressure occurred in two thirds of uncomplicated RTI episodes. Moody et al. (1998) reported that during a viral RTI episode, children 2-6 years of age had abnormal middle ear pressure (<-150 mmH_2O) approximately 50% of the time. Interestingly, the middle ear pressure began to decrease 2 days before the parents identified the onset of RTI symptoms. In addition, Moody et al. (1998) showed that the children who developed MEE during RTI had lower middle ear pressure compared to children who did not develop MEE (Table 3). Similarly, Doyle et al. (2008) showed that in children 1-8 years of age, middle ear pressure was significantly more negative during RTI episodes compared to days when the children were healthy. However, they did not report the TPPs; only the average pressure difference (of approximately 35 mmH_2O) between the days with and without RTI. Demonstrating the effect of age to the function of the ET during RTI, Revai et al. (2008a) showed that children 6-11 months of age had abnormal tympanograms (type B) significantly more frequently than children 12-35 months of age.

In summary, transient, abnormally negative, middle ear pressure seems to be a common phenomenon during viral RTI. Furthermore, notable negative middle ear pressure can be a transitional stage in the development of MEE (Orchik et al. 1978, Palmu et al. 2002). Additionally, even though abnormal tympanograms have been found in two thirds of children, most of these tympanograms have been type C1 (TPP from -100 to -199 daPa) showing only mild abnormality (Winther et al. 2002). Thus, it seems that in the majority of RTI episodes, abnormal negative middle ear pressure is only mild.

In addition to causing dysfunction of the ET, viral RTI weakens the defensive mechanisms against bacteria. Viruses may promote the production of inflammatory mediators leading to destruction of the mucosa; depress ciliary clearance function; or alter bacterial adherence (Moody et al. 1998, Bluestone and Klein 2007, McCullers 2014).

Table 3. Middle ear pressure, as defined by tympanometric peak pressure, in 20 children from 2 to 6 years of age with viral respiratory tract infection, as reported by Moody et al. (1998).

	Children with MEE (Mean TPP, mmH_2O)	Children without MEE (Mean TPP, mmH_2O)
Day -2	-104	-83
Day 0[1]	-155	-101
Day 2	-183	-118

[1]Day 0: the day when MEE was diagnosed.
Abbreviations: MEE, middle ear infection; TPP, tympanometric peak pressure

2.2.4 Bacterial pathogens

The most important bacterial pathogens of AOM include *Streptococcus pneumoniae,* nontypable *Haemophilus influenzae,* and *Moraxella catarrhalis* (Bluestone and Klein 2007). The nasopharynx becomes colonized with bacteria soon after birth, and by the age of 6 months, 70% of infants are colonized with one or more pathogenic bacteria (Faden et al. 1997). The carriage rates of these common pathogens differ according to the child's age, day care, siblings, dietary factors, breastfeeding, and viral RTI. In addition, the number and strain of colonizing bacteria alter the child's risk of developing AOM (Faden et al. 1997, Revai et al. 2008b, Tapiainen et al. 2014a).

Consequently, *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* are the bacteria which are most often found in nasopharyngeal samples (Arola et al. 1990, Pettigrew et al. 2011, Ruohola et al. 2013) and MEE (Ruuskanen et al. 1989, Palmu et al. 2004, Ruohola et al. 2006) from children with AOM. As much as 70% of AOM episodes are most probably coinfections caused by both bacteria and viruses (Pitkäranta et al. 1998, Ruohola et al. 2006). Bacteria can produce surrounding biofilm which protects them from the immune system. Consequently, biofilm formation in the middle ear mucosa can prolong MEE into a chronic stage (Ehrlich et al. 2002).

2.2.5 Immunology

The immune system protects against viral and bacterial pathogens with several mechanisms. First, the lymphoid tissue in the pharynx protects the middle ear from microbial and environmental antigens ("the gatekeeper function") (Bluestone and Klein 2007). The lymphoid tissue includes the palatine tonsils and adenoids; lingual tonsil at the base of the tongue; pharyngeal tonsil on the posterior wall of the pharynx; and a circular ring of lymphoid tissue called Waldeyer's ring (Bluestone and Klein 2007).

The epithelial, dendritic, and mast cells located in the respiratory mucosa of the middle ear produce immune response for microbial antigens. Various substances of immunological

cascades have been identified from MEE of children with AOM or OME, including all major classes of immunoglobulins, humoral and cellular factors (i.e. complement, prostaglandins, chemotactic substances, macrophage inhibitory factor, lactoferrin, histamine, and collagenase); cytokines (tumor necrosis factor, interleukins 1, 2, and 6, and interferon gamma); and oxidative and hydrolytic enzymes (Bluestone and Klein 2007). Neutrophils, macrophages, and lymphocytes are the main cell types found in MEE (Sipilä and Karma 1982).

In addition, inflammation may also worsen the damage of the middle ear mucosa and thus, enhance the invasion of pathogens and the development of AOM. Patel et al. (2006) and Revai et al. (2009) have shown that tumor necrosis factor α^{-308} and interleukin 6^{-174} cytokine gene polymorphisms increase the risk of developing AOM in children 6 to 35 months of age. Since these polymorphisms enhance the production of respective cytokines, the underlying mechanism behind the increased risk of AOM might be worsened mucosal damage caused by excessive cytokine production. Furthermore, in persisting MEE, excessive stimulation of cytokines enhances the production of inflammatory mediators. In addition, cytokines increase the amount of submucosal receptors, i.e. selectins and integrins, which bind lymphocytes which in turn, produce more cytokines leading to enhanced inflammation (Bluestone 1996).

2.3 Epidemiology and risk factors

AOM is the most prevalent bacterial infection in young children (Vergison et al. 2010). In Finland, the estimated annual incidence of AOM is 500 000 episodes with the total annual cost of 138 million US dollars (Niemelä et al. 1999). Furthermore, AOM is the most frequent reason for antimicrobial treatment in children in primary health care and thus, has a marked effect on antibiotic resistance (Rautakorpi et al. 2001, Rautakorpi et al. 2006).

AOM affects approximately 70% of children by the age of 2 years and 80% of children by the age of 3 years (Teele et al. 1989, Alho et al. 1991). The incidence of AOM is highest at the age of 6-18 months and peaks at the age of 10-12 months (Pukander et al. 1982, Sipilä et al. 1987, Alho et al. 1991, Vesa et al. 2001). The proportion of children having recurrent AOM ($\geq$3 episodes in 6 months or $\geq$4 in 12 months) has been estimated to be 20-30% (Sipilä et al. 1987, Teele et al. 1989, Pichichero 2000b). Casey and Pichichero (2014) followed children from 6 months of age until 30 months of age and found that with strict diagnostic criteria (i.e. bulging of the tympanic membrane) and effective antimicrobial treatment (i.e. amoxicillin-clavulanate), the proportion of children suffering at least four AOM episodes was only 8%. In comparison, when AOM was diagnosed without bulging, and AOM was treated with amoxicillin, the proportion of children suffering at least four AOM episodes was 20%.

Mandel et al. (2008) have reported the basal prevalence of MEE as 20% in children 1-8 years of age followed from November until the end of April, with the peak prevalence of 30-35% in December and early March. In addition, Paradise et al. (1997) followed 2253 children up to the age of 2 years. MEE was estimated to be present on average 20% of the time during the first year of their life and 17% of the time during the second year. Similarly, Fiellau-Nikolajsen (1983) estimated the point prevalence of MEE as 18-21% in children 3 years of age, with bilateral point prevalence of 8-10%. Correspondingly, in the American guideline on OME, Rosenfeld et al. (2004) have summarized the point prevalence of MEE as 15-40%.

Persistent MEE lasting for 3 months or longer after an AOM episode has been reported to occur in 10-26% of episodes (Teele et al. 1980, Mandel et al. 1995, Rosenfeld and Kay 2003). In the guideline on tympanostomy tube placement, Rosenfeld et al. (2013) presented that by the age of 3 years, approximately 7% of children will undergo tympanostomy tube placement. Day care attendance was reported to double the need for tympanostomy tubes. Casey and Pichichero (2014) reported that with strict diagnostic criteria for AOM, tympanostomy tube placement was performed in 6% of children compared to 15% of children in whom bulging of the tympanic membrane was not required for the diagnosis.

Of viral RTI episodes in young children, approximately one third (18-43%) are complicated by AOM (Arola et al. 1990, Heikkinen and Ruuskanen 1995, Vesa et al. 2001, Chonmaitree et al. 2008, Chonmaitree et al. 2015). Furthermore, Chonmaitree et al. (2008) studied 294 children between 6-35 months of age and reported that the overall incidence of MEE complicating RTI was 61%, of which 37% was AOM and 24% OME. Thus, it seems that the majority of young children develop MEE during RTI.

AOM is most frequently diagnosed 2-6 days after the onset of viral RTI. Heikkinen and Ruuskanen (1994) and Koivunen et al. (1999) reported the highest incidence of AOM on days 3-4 and Chonmaitree et al. (2008) on days 3-5 after the onset of RTI. Arola et al. (1990) and Chonmaitree et al. (2008) have found a median of 4 days between the onset of RTI and diagnosis of AOM.

In addition to young age and viral RTI episodes, day care attendance is a major risk factor for AOM (Pukander et al. 1985, Paradise et al. 1997, Joki-Erkkilä et al. 1998). The risk for AOM is specifically associated with the number of children in day care and the number of siblings. Other risk factors include a positive family history of AOM (genetic predisposition), parental smoking, male gender, and use of a pacifier (Teele et al. 1980, Uhari et al. 1996). In contrast, breastfeeding has a protective effect against AOM. Furthermore, the incidence of AOM varies according to the season of the year (Ruuskanen et al. 1989, Joki-Erkkilä et al. 1998, Vesa et al. 2001, Mandel et al. 2008). Episodes of viral RTI predisposing children to AOM have a seasonal variation and peak

during the late fall and winter. Thus, the incidence of AOM is lowest during the summer months and highest in the winter. Between the 1970s and the 1990s, the incidence of AOM increased, which may have been caused by increased day care attendance (Joki-Erkkilä et al. 1998) and by the implementation of the health centre system enabling easy access to a physician. In the 2000s and the 2010s, physician visits made due to AOM have declined, which coincidences with the introduction of conjugate vaccines (PCV-7, PCV-10, and PCV-13) against *Streptococcus pneumoniae* (Marom et al. 2014). However, physician visits made due to AOM started to decrease even before the implementation of pneumococcal vaccinations. In fact, increased acceptance of the initial observation of AOM before antimicrobial treatment (i.e. "watchful waiting"), stricter diagnostic criteria, and decreased exposure to tobacco smoke may have decreased AOM-related physician visits (Taylor et al. 2012).

2.4 Diagnostics

Accurate diagnosis of AOM is crucial for the optimal management and high quality research, as the guidelines on the diagnosis and management of AOM (Heikkinen et al. 2010, Lieberthal et al. 2013) state. However, the diagnoses of AOM and OME are complicated because they are not definitive diagnoses but form a spectrum of varying otoscopic findings.

2.4.1 Symptoms of acute otitis media

Acute symptoms and signs are used for several purposes in clinical practice and research settings concerning AOM. In clinical practice, symptoms are part of the parental suspicion of AOM, the diagnostic criteria of AOM, choosing the optimal management option for AOM, and following its resolution (Lieberthal et al. 2013). In research settings, symptoms and signs are used in different severity scores to separate children into different treatment groups (Kaleida et al. 1991), to study a particular severity grade of AOM (McCormick et al. 2005), and as one outcome to evaluate the effect of antimicrobial treatment of AOM (Kaleida et al. 1991).

Despite the wide use of acute symptoms and signs for clinical and research purposes, most acute symptoms and signs have consistently been found nonspecific for AOM in children less than 3 years of age (Niemelä et al. 1994, Heikkinen and Ruuskanen 1995, Kontiokari et al. 1998a, Laine et al. 2010). Since AOM and the concomitant viral RTI cause similar symptoms, few symptoms can be used to predict AOM. Arola et al. (1990) and Laine et al. (2010) showed that more than 90% of children with AOM have respiratory symptoms, namely rhinitis, cough, and/or nasal stuffiness, and nonspecific symptoms, such as irritability, night restlessness, or poor appetite. Approximately 50% of children with AOM suffer from fever (≥38˚C) (Arola et al. 1990, Niemelä et al. 1994,

Kontiokari et al. 1998a, Palmu et al. 2004, Laine et al. 2010). In outpatients between 6-35 months of age with RTI and parental suspicion of AOM, the occurrences of fever, ear pain, ear pulling, respiratory symptoms, nonspecific symptoms, or gastrointestinal symptoms did not differentiate children with and without AOM (Laine et al. 2010). Moreover, the duration and severity of symptoms did not differ in children with and without AOM. *Haemophilus influenzae* has been shown to cause AOM associated with conjunctivitis (otitis-conjunctivitis syndrome) (Bodor 1982, Palmu et al. 2004). On the other hand, AOM caused by *Streptococcus pneumoniae* has been associated with higher occurrence of ear pain and fever compared to AOM caused by *Haemophilus influenzae* or *Moraxella catarrhalis* (Palmu et al. 2004).

Ear pain is the only symptom which has consistently been shown to predict AOM (Niemelä et al. 1994, Heikkinen and Ruuskanen 1995, Uhari et al. 1995b, Kontiokari et al. 1998a). However, only half of children with AOM suffer from ear pain (Arola et al. 1990, Niemelä et al. 1994, Heikkinen and Ruuskanen 1995). Furthermore, most of the children less than 3 years of age are at a preverbal age and cannot describe ear pain or other symptoms. As stated by Shaikh et al. (2009, 2010), parental evaluation of ear pain in young children is subjective and difficult. Demonstrating the difficulties of parental assessment of ear pain in young children, Arola et al. (1990) reported that ear pain was significantly less frequent in children less than 2 years of age (27%) compared to older children (69%) who could describe their pain. On the other hand, negative middle ear pressure during RTI or throat pain may also cause a feeling of ear pain. Thus, children can describe ear pain even without AOM (Laine et al. 2010).

To summarize, symptoms cannot be considered useful in predicting AOM in children less than 3 years of age. Therefore, careful pneumatic otoscopy is required to differentiate children with and without AOM (Laine et al. 2010).

2.4.2 Pneumatic otoscopy and otomicroscopy

As the guidelines on AOM (Heikkinen et al. 2010, Lieberthal et al. 2013) and OME (Rosenfeld et al. 2004) state, careful pneumatic otoscopy is recommended as the primary diagnostic method to differentiate AOM from OME. Otomicroscopy offers the best visualization of the tympanic membrane. However, the use of otomicroscopy in primary health care is limited by the cost of the device and the training required. On the other hand, high magnification of the tympanic membrane can also be obtained with certain models of otoscope, such as the Macroview otoscope model 23810 (Welch Allyn, Skaneateles Falls, NY, USA).

The meta-analysis by Takata et al. (2003) reported a pooled sensitivity of 94% and a specificity of 80% for trained otoscopists diagnosing OME with pneumatic otoscopy compared to myringotomy. The specificity of pneumatic otoscopy is decreased by false

positive diagnoses of MEE, which indicate that physicians have difficulties in diagnosing healthy middle ears (Rosenfeld 2002). The diagnostic accuracy of pneumatic otoscopy is summarized in Table 4.

In the hands of experienced otoscopists, pneumatic otoscopy is accurate. In addition, pneumatic otoscopes are cost effective and readily available in primary health care. However, in clinical practice, the accuracy of less experienced otoscopists in diagnosing AOM is substantially lower than the performance of experienced otoscopists (Pichichero 2002, Steinbach et al. 2002). In fact, Blomgren et al. (2004) showed that the strict diagnosis of AOM made by an experienced otoscopist reduced the number of AOM diagnoses by 56%, and nearly 80% of children had fewer AOM episodes during the 6 months' follow-up period. Furthermore, even among experienced otoscopists, the proportions of reported otoscopic findings differ (Paradise et al. 1976, Karma et al. 1989, Shaikh et al. 2011). Performing pneumatic otoscopy is often complicated due to lack of cooperation, which can be caused by young age and/or acute symptoms, such as fever or pain. Further challenges for pneumatic otoscopy are caused by cerumen occluding the external auditory canal and poor diagnostic equipment, such as old otoscopes with low light output (Pichichero 2000a, Rothman et al. 2003). In fact, a high quality, well-illuminated pneumatic otoscope is crucial in making an accurate diagnosis.

Table 4. The diagnostic accuracy of pneumatic otoscopy by a trained otoscopist versus myringotomy in detecting middle ear effusion (MEE).

	Age	Definition for MEE in pneumatic otoscopy	Sensitivity	Specificity
Paradise et al. 1976[1]	0 mo to 5 y	Impaired mobility of the tympanic membrane or air-fluid level	91%	83%
Cantekin et al. 1980[2]	7 mo to 15 y	Not reported	Otoscopist A: 94% B: 81%	Otoscopist A: 78% B:74%
Toner and Mains 1990	18 mo to 12 y	Immobility of the tympanic membrane	87%	89%
Finitzo et al. 1992	6 mo to 9 y	Opaqueness and immobility of the tympanic membrane	93%	58%
Nozza et al. 1994	1 to 12 y	Not reported	85%	71%

[1]Uncertain otoscopic diagnoses were included in ears without effusion.
[2]The study reported the sensitivity and specificity separately for Otoscopists A and B.
Abbreviations: MEE, middle ear effusion; mo, months; y, years

2.4.3 Otoscopic findings

Otoscopic assessment should always include the position, translucency, color, light reflex, vascularity, and mobility of the tympanic membrane. Previously, criteria for the

diagnosis of AOM varied greatly between studies on AOM (Pichichero and Casey 2008a). Pichichero and Casey (2008a) analyzed the diagnostic criteria for AOM from studies in which AOM was initially followed without antimicrobial treatment. Demonstrating the confusion around optimal diagnostic criteria, they found that only 7/25 (28%) of studies required the presence of MEE for the diagnosis of AOM. In contrast, redness of the tympanic membrane was required for the diagnosis of AOM in 17/25 (68%) studies. Redness is a poor predictor of AOM, because redness may be caused by the crying or struggling of the young child, or even cerumen removal (Karma et al. 1989). In addition, redness may easily be overdiagnosed to justify antimicrobial treatment when the diagnosis is uncertain (Pichichero 2000a). Risk for overdiagnosis of otoscopic findings was also demonstrated by Finitzo et al. (1992), who reported a sensitivity of 93% but specificity of only 58% for pneumatic otoscopy versus myringotomy in diagnosing OME. Thus, in their study, false positive diagnoses of OME reduced the specificity. Interestingly, Blomgren and Pitkäranta (2003) have shown that inexperienced otoscopists make the AOM diagnosis based on children's symptoms and the color of the tympanic membrane, while experienced otoscopists base the AOM diagnosis on the position and mobility of the tympanic membrane.

Karma et al. (1989) compared the diagnostic accuracy of otoscopic findings to myringotomy in 2911 children 0.5-2.5 years of age. They concluded that distinctly impaired mobility of the tympanic membrane was the best predictor of AOM with a sensitivity of 95% and specificity of 85%. In addition, opaqueness ("cloudiness") and bulging position predicted the presence of MEE. For bulging position, the specificity was 97% but the sensitivity only 51%. On the other hand, redness of the tympanic membrane was detected in approximately 20% of the ears with AOM, and the proportion did not markedly differ in children with and without AOM. Reducing the diagnostic accuracy in the study, AOM was diagnosed by the presence of MEE and acute symptoms (such as fever, ear pain, irritability, respiratory tract symptoms, or vomiting), and acute inflammatory signs on the tympanic membrane were not required. Furthermore, Arola et al. (1990) found a full or bulging position of the tympanic membrane in 89% of AOM cases and redness in 46%. Moreover, the bulging position of the tympanic membrane has been reported to associate with the presence of bacterial pathogen (Schwartz et al. 1981, McCormick et al. 2000, Palmu et al. 2004).

Thus, the bulging position of the tympanic membrane has been proven as the most specific sign of AOM (Karma et al. 1989, Arola et al. 1990, Shaikh et al. 2011). Consequently, the recent AOM guideline (Lieberthal et al. 2013) aiming for a strict definition of AOM adopted the bulging position of the tympanic membrane as the primary diagnostic criterion. Otoscopic findings of AOM are summarized in Table 5.

In contrast, with OME, the position of the tympanic membrane is usually retracted or convex, the color of the tympanic membrane is grey and opaque, and acute inflammatory signs on the tympanic membrane are absent (Bluestone and Klein 2007). The mobility of the tympanic membrane is reduced or absent. On the other hand, for the diagnosis of a healthy middle ear, normal mobility of the tympanic membrane has to be detected with pneumatic otoscopy to exclude the presence of MEE.

Complicating the diagnostics, AOM and OME are the ends of the spectrum of effusions. Between these certain diagnoses is a wide range of effusions which are either developing into AOM, at a resolution stage from AOM to OME, or effusions without an association to AOM (Lieberthal et al. 2013). Kalu et al. (2011) studied the characteristics of AOM complicating URI in 294 children. They concluded that AOM is a spectrum of acute middle ear infections which may present at different stages, even in the right and left ears of the same child. The spectrum of otoscopic findings from a healthy middle ear to a perforated AOM is presented in Figure 2.

Table 5. Otoscopic findings of acute otitis media. Only proportions are shown because the total numbers of children with otoscopic findings were not reported in all the studies.

	Bulging position (%)	**Opaqueness ("cloudiness") (%)**	**Yellow color (%)**	**Redness (%)**	**Reduced/ lack of mobility (%)**
Karma et al. 1989	Group 1: 61%; Group 2: 41%	Group 1: 81%; Group 2: 67%	Not reported	Group 1: 18%; Group 2: 27%	Group 1: 83%; Group 2: 84%
Arola et al. 1990	Full or bulging:89%	52%	24%	46%	Not reported
Shaikh et al. 2011	96%	100%	White or yellow: 90%	20%	99%
Laine et al. 2010	Full or bulging: 93%	100%	81%	Not reported	Not reported

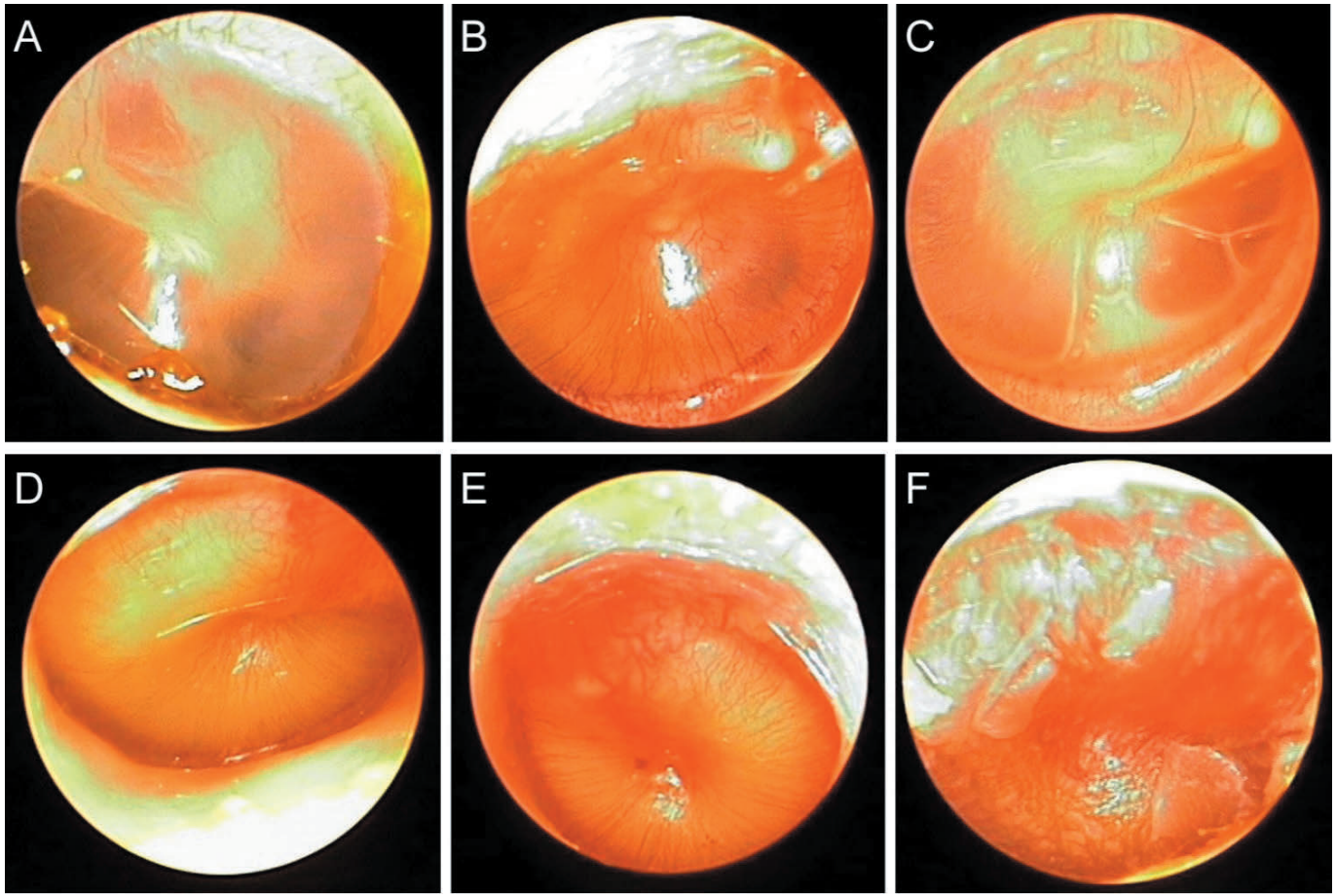


Figure 2. The spectrum of otoscopic findings from a healthy middle ear (A) to middle ear effusion (MEE) without acute otitis media (AOM) (B-C), bulging AOM (D-E), and perforated AOM (F). The photographs have been taken by Miia Laine, MD, Aino Ruohola, MD, PhD, and Paula Tähtinen, MD, PhD, and are published with their permission. The figure has been modified from the thesis "Treatment of acute otitis media" by Paula Tähtinen, MD, PhD (2012).

2.4.4 Tympanocentesis and myringotomy

Tympanocentesis is defined as aspiration of MEE through a needle placed into the inferior portion of the tympanic membrane (Rothman et al. 2003), while myringotomy is an incision of the tympanic membrane to allow drainage of MEE (Bluestone and Klein 2007). Previously, these procedures were diagnostic standards in research settings and also used for the treatment of AOM. However, tympanocentesis and myringotomy cause pain for the child, are less effective than antimicrobial treatment for AOM, and do not give any additional treatment effect compared to antimicrobial treatment alone (Engelhard et al. 1989, Kaleida et al. 1991). Thus, these procedures are currently performed only in complicated cases of AOM where bacterial pathogens have to be identified, such as suspected mastoiditis, seriously ill children, or children with immunodeficiency (Heikkinen et al. 2010).

2.4.5 Tympanometry

Tympanometry is an adjunctive diagnostic tool for pneumatic otoscopy used to detect the presence or absence of MEE (Jerger 1970). In addition, TPP provides an indirect measure of the pressure in the middle ear (Orchik et al. 1978). The advantages of tympanometry include the fact that it is both painless and relatively simple to perform. As a disadvantage, tympanometry requires an air-tight seal to the external auditory canal and at least some cooperation of the young child. The diagnostic accuracy of tympanometry has been confirmed when performed by physicians. However, few studies have reported results from children less than 3 years of age, or tympanometric examinations performed by nurses. To date, none of the studies have analyzed the proportion of visits where clinically useful test results are obtained from both ears of the child. Figure 3 presents a tympanometer (MicroTymp2, Welch Allyn, Skaneateles Falls, NY, USA), pneumatic otoscopes, and equipment for removal of cerumen. In Figure 4, the probe tip of a tympanometer is presented.

Figure 3. Tympanometer (MicroTymp2, Welch Allyn, Skaneateles Falls, NY, USA), pneumatic otoscopes, and equipment for removal of cerumen. The photograph is published with the permission of Aino Ruohola, MD, PhD.

Figure 4. The probe tip of a tympanometer.

2.4.5.1 Principles

Terkildsen and Nielsen (1960) developed the first commercially available tympanometric device (Madsen Electronics Model Z061). The device measured acoustic impedance, which refers to resistance to acoustic energy flow (Brookhouser 1998). These earliest devices gave results in arbitrary units and thus, the results of different studies could not be directly compared. Since the 1960s, the devices have been further developed. The current tympanometers measure acoustic admittance, which quantifies the ease with which acoustic energy is transmitted from one medium to another (Brookhouser 1998). The middle ear transfers sound energy from the air medium of the external auditory canal (high admittance) to the liquid medium of cochlea (low admittance). Transmission is optimal when the external auditory canal and middle ear are both normally filled with air (i.e. no MEE), and the pressure is similar on both sides of the tympanic membrane. Currently, tympanometers show acoustic admittance in absolute units which allow direct comparison of results from different studies.

When performing a tympanometric examination, the probe tip (shown in Figure 4) has to be pressed tightly against the meatus of the external auditory canal to achieve an air-tight seal. The sound stimulus generator of a tympanometer produces a constant probe tone of typically 226 Hz, and a microphone detects sound energy reflected back from the tympanic membrane (Brookhouser 1998). Simultaneously, the vacuum pump of the tympanometer changes the pressure in the external auditory canal and usually produces a pressure sweep from the positive pressure of +200 daPa to the negative pressure of -400 daPa with the speed of 400 daPa/s. At the beginning of the measurement, applied positive pressure stretches the tympanic membrane towards the middle ear (Palmu 2002). The tympanic membrane is stiffened, and transmission of sound energy to the middle ear is reduced. When the amount of applied positive pressure reduces, the ease of acoustic energy flow (admittance) increases. SAA (i.e. static acoustic admittance) is the point of maximum admittance, where the air pressure is equal on both sides of the tympanic membrane, and thus, the tympanic membrane vibrates normally (Brookhouser 1998). When negative pressure is applied to the external auditory canal, the tympanic membrane is stretched towards the external auditory canal. The tympanic membrane is again stiffened, and admittance decreases. The results are presented as a tympanogram (Figure 5), which graphically displays acoustic admittance (y-axis) as a function of air pressure (x-axis).

SAA is the point where the air pressure is equal on both sides of the tympanic membrane. It is an estimate of admittance at the lateral surface of the tympanic membrane (Brookhouser 1998). In the tympanogram, SAA is the maximum height of the tympanometric curve. The unit for acoustic admittance is millimho (mmho; reciprocal of milliohm). Ears with MEE usually have markedly decreased SAA, and the threshold for the presence of MEE is usually set as 0.2 mmhos.

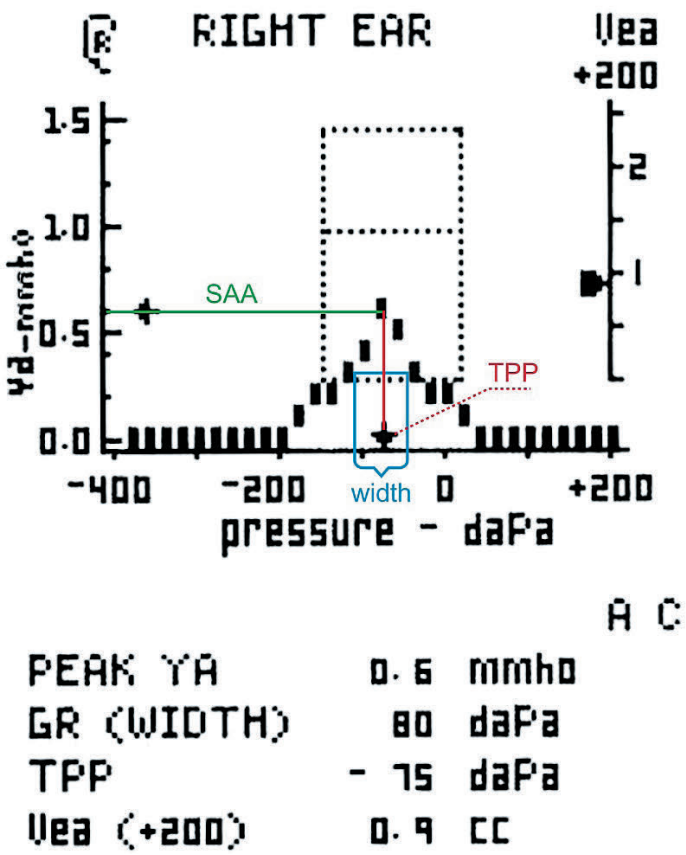


Figure 5. Tympanogram displays acoustic admittance as a function of air pressure. Abbreviations: SAA, static acoustic admittance; TPP, tympanometric peak pressure.

TPP is an indirect measure of middle ear pressure (Brookhouser 1998). TPP is calculated in deca-Pascals (daPa). Earlier studies reported TPP as millimetres of water (mmH_2O); 1 daPa equals 1.02 mmH_2O (Bluestone and Klein 2007). In the tympanometric curve, TPP is the pressure where the maximum height (SAA) of the tympanometric curve occurs. At that point of maximum admittance, the pressure is similar on both sides of the tympanic membrane and thus, TPP can serve as an indirect estimate of middle ear pressure. During the accumulation of MEE, TPP usually turns to being significantly negative. However, TPP may overestimate the negativity of middle ear pressure (Brookhouser 1998). Furthermore, negative TPP alone is a poor predictor for MEE (Palmu et al. 1999, Palmu et al. 2001b).

Tympanometric width (gradient) is a measure of the sharpness of the tympanometric peak (Brookhouser 1998). It is most commonly described as the pressure interval in the x-axis defined by the sides of the tympanometric curve at 50% of the maximum height (SAA) of the curve. In a tympanogram, it is thus the width of the curve at half of the peak height (Babonis et al. 1991). Wide tympanograms (>300 daPa) suggest the presence

of MEE (Nozza et al. 1994, Smith et al. 2006). Tympanometric width is automatically calculated by current tympanometers, such as Microtymp 2 (Welch Allyn, Skaneateles Falls, NY, USA) and GSI tympanometers (Grason-Stadler, Eden Prairie, MN, USA).

Equivalent ear canal volume (Veq) is an estimate of the volume in front of the tympanometric probe tip. High values may implicate perforation of the tympanic membrane. Low values may implicate cerumen occluding the external auditory canal or the probe tip pressed against the wall of the external auditory canal (Margolis and Heller 1987).

As shown in Table 6, Margolis and Heller (1987) have found that SAA, TPP, and tympanometric width have different normative values in children (2 to 5 years of age) compared to adults. With age, SAA increases and tympanometric width decreases (Palmu et al. 2001a, Palmu and Rahko 2003).

Table 6. Normative values for tympanometry by Margolis and Heller (1987) and Palmu et al. (2001a).

	Children, 7 months (Palmu et al. 2001a)	**Children, 24 months (Palmu et al. 2001a)**	**Children, 2 to 5 years (Margolis and Heller 1987)**	**Adults (Margolis and Heller 1987)**
Static acoustic admittance, mmho (mean, 90% range)	0.3 (0.1 to 0.4)	0.3 (0.1 to 0.6)	0.6 (0.2 to 0.9)	0.8 (0.3 to 1.5)
Tympanometric peak pressure, daPa (mean, 90% range)	-41 (-155 to +30)	-41 (-165 to +45)	-30 (-139 to + 11)	-19 (-83 to 0)
Width (gradient), daPa (mean, 90% range)	140 (95 to 200)	113 (70 to 155)	100 (59 to 151)	77 (51 to 114)
Equivalent ear canal volume, ml (mean, 90% range)	Not reported	Not reported	0.7 (0.4 to 1.0)	1.1 (0.6 to 1.5)

2.4.5.2 Classification of tympanograms

Jerger (1970) was the first to introduce the widely-used classification system of type A, B, and C tympanograms. Jerger defined type A tympanograms as peaked tympanograms with normal TPP and found that type A tympanograms were most commonly associated with a healthy middle ear. Type B was defined as a flat tympanogram, and these tympanograms were associated with MEE. On the other hand, type C tympanogram was defined as a peaked tympanogram with negative TPP of ≤-100 mmH_2O (1 daPa = 1.02 mmH_2O), and type C tympanograms were associated with a healthy middle ear with significantly negative middle ear pressure.

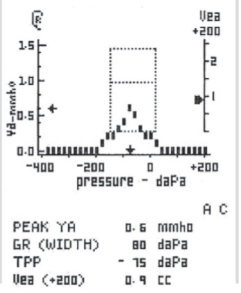
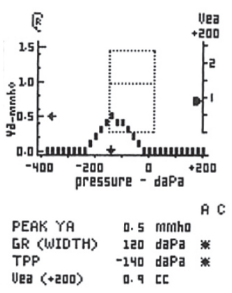
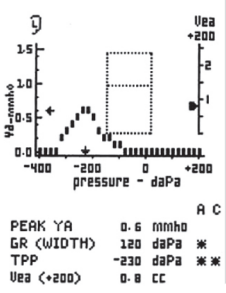
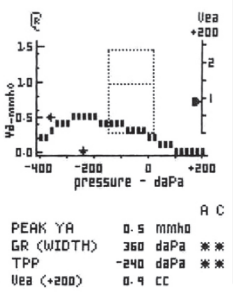
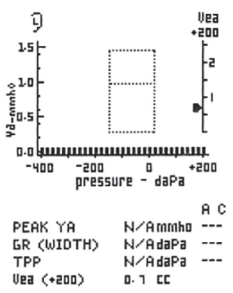
Paradise et al. (1976) modified the classification of Jerger by introducing their version of the curve gradient, i.e. steepness of the tympanometric curve. They calculated a ratio by drawing a horizontal line at the point where tympanometric width was 100 mmH_2O. Then they divided the height above the horizontal line by the total height of the curve. Paradise et al. concluded that low peaked tympanograms were associated with MEE. In addition, rounded curves with a shallow gradient were more likely to be associated with MEE than curves with sharp peaks (i.e. with steep gradient). Furthermore, negative middle ear pressure tended to increase the likelihood of MEE. It is of note that children less than 7 months of age had a high rate of false negative results because of the greater compliance of the external auditory canal wall.

Orchik et al. (1978) modified the classification of Jerger by introducing the definition of wide tympanograms, As and Cs. They defined As and Cs as shallow tympanograms using arbitrary units. As and Cs were found to be evenly associated with notable MEE and no or minimal MEE. Later, the research group of Paradise found that wide tympanograms (width >300 daPa) are associated with a greater likelihood of MEE when compared to tympanograms with normal width (Smith et al. 2006).

Fiellau-Nikolajsen and Lous (1979) differentiated type C tympanograms into type C1 tympanograms with a slightly negative TPP from -100 to -199 mmH_2O, and type C2 tympanograms with a markedly negative TPP of $\leq$-200 mmH_2O. They studied the spontaneous resolution of MEE and concluded that type C1 tympanograms almost always returned to type A tympanograms and thus, type C1 tympanograms did not significantly differ from type A when predicting the resolution of MEE (Fiellau-Nikolajsen and Lous 1979, Fiellau-Nikolajsen 1983).

Table 7 summarizes the classification of type A, C, and B tympanograms (Jerger 1970) and separates type C1 and C2 tympanograms (Fiellau-Nikolajsen and Lous 1979) and wide tympanograms (Orchik et al. 1978, Smith et al. 2006).

Table 7. Classification of tympanograms by Jerger (1970), Fiellau-Nikolajsen and Lous (1979), Orchik et al. (1978), and Smith et al. (2006).

	Type of tympanogram					
	A	**As**	**C1**	**C2**	**Cs**	**B**
Static admittance (mmho)	≥ 0.2	< 0.2; or ≥ 0.2 if width > 300 daPa	≥ 0.2	≥ 0.2	< 0.2; or ≥ 0.2 if width > 300 daPa	< 0.2
Tympanometric peak pressure (daPa)	> –100	> –100	–100 to –199	≤ –200	≤ –100	No peak
Width (daPa)	≤ 300	> 300	≤ 300	≤ 300	> 300	No peak
						

2.4.5.3 Diagnostic accuracy of tympanograms obtained by physicians and nurses

The diagnostic accuracy of tympanometry to detect MEE has been widely studied. Table 8 summarizes the diagnostic accuracy of tympanometry in detecting MEE, and Table 9 summarizes the accuracy of tympanometry in detecting AOM. The studies presented in Table 9 reported only the sensitivity because these studies included only ears with AOM.

Most of the studies in Tables 8 and 9 have included children older than 3 years of age and/or children undergoing tympanostomy tube placement, i.e. children having persistent or recurrent MEE. Since the majority of children with AOM and OME are outpatients less than 3 years of age, most of these results might not be widely generalizable. Furthermore, most of the studies have included only the ears with successful tympanometry, which excludes the option of counting the success rates of tympanometry.

For diagnosing the presence of MEE, type B tympanogram has been shown to be rather accurate as the sensitivities summarized in Table 8 are generally approximately 80%. Demonstrating the strong association of type B tympanogram with middle ear pathology, type B tympanogram has been reported as prognostic indicator for persistence of OME (Lampe et al. 1981, Fiellau-Nikolajsen 1983, Rosenfeld and Kay 2003).

Adding type C2 as a positive result for predicting MEE reduces the specificity, i.e. increases the proportion of false positive results. As shown in Table 8, the specificities of tympanometry with type B tympanogram as a positive result for MEE are generally between 80% and 90%. However, the specificity is reduced to the level of 50% when type B and C2 tympanograms are interpreted as positive results for MEE (Ovesen et al. 1993, van Balen and de Melker 1994). Fiellau-Nikolajsen (1983) compared the tympanometric results of 88 ears to myringotomy. He found that when only type B tympanogram was considered as a positive result for MEE, the sensitivity was 83% and specificity was 100%. On the other hand, with type B and C2 tympanograms as positive results for MEE, the sensitivity was 91%, and the specificity was reduced to 88%. Generally, in children undergoing tympanostomy tube placement, half of the ears with a type C2 tympanogram have been associated with MEE (Fiellau-Nikolajsen 1983, Sassen et al. 1994, van Balen and de Melker 1994). In an outpatient population less than 2 years of age, type C2 tympanograms have been associated with MEE in 20% (TPP between -200 and -295 daPa) to 29% (TPP between -300 and -395 daPa) of ears (Palmu et al. 2001b). Thus, peaked tympanograms with markedly negative middle ear pressure (≤-200 daPa) cannot be used in clinical practice in predicting MEE or in excluding MEE.

Tympanometric width and peak height (SAA) have been shown as the most accurate tympanometric variables for differentiating the ears with MEE from healthy middle ears (Nozza et al. 1994, Palmu and Syrjänen 2005, Smith et al. 2006). For the tympanometric width of greater than 275 daPa, an 81% sensitivity and an 82% specificity have been

reported for detecting MEE (Nozza et al. 1994). Smith et al. (2006) developed algorithms to predict the likelihood of MEE. In the algorithms, they included tympanometric width, SAA, and TPP. They concluded that the lower the height and the greater the width of a tympanometric curve, the greater is the likelihood of MEE.

For diagnosing a healthy middle ear, type A tympanogram seems to be accurate (Fiellau-Nikolajsen 1983). Type A tympanogram has been reported to associate with the diagnosis of MEE in only 3-4% of ears (Fiellau-Nikolajsen 1983, Palmu et al. 1999). Furthermore, according to studies performed in primary health care, type C1 tympanograms seem to correspond to the diagnostic accuracy of type A tympanograms (Palmu et al. 1999, Palmu et al. 2001b). In fact, several studies have included type C1 tympanograms as part of type A tympanograms (TPP for type A tympanogram >-200 daPa) (Koivunen et al. 1997, Renko et al. 2006, Tapiainen et al. 2014b). Type C1 tympanograms have been interpreted as slightly abnormal tympanograms often obtained during RTI, demonstrating mild dysfunction of the ET (Lous et al. 2012, Lous 2014).

The diagnostic accuracy of tympanometry may be affected by several factors: The experience of the examiner; the age of the child (Koivunen et al. 1997); the cooperation of the child (Koivunen et al. 1997); the tympanometric model used (Patricoski and Ferguson 2006); and the prevalence of MEE in the setting. On the other hand, diagnostic accuracy is not affected by moderate amounts of cerumen occluding less than half of the external auditory canal diameter (Block et al. 1998). Sassen et al. (1994) reported that tympanometric examinations failed more often in children of 5 months to 2 years of age when compared to children of 2 to 11 years of age. Koivunen et al. (1997) reported that children with failed tympanometric examinations were significantly younger than children with successful tympanometry (1.5 years versus 5.8 years). If the child cooperated, the sensitivity for MEE was 79% and specificity 93%. If the child did not cooperate, the sensitivity was 71% and specificity only 38%. Poor cooperation of the child has been reported to result in slightly higher TPP, but no effect on SAA or tympanometric width (Palmu et al. 2001a). Better success rates are obtained with young infants less than 7 months of age versus older children who tend to struggle more during the examination (Palmu et al. 1999). Conversely, tympanometry may be less reliable in children less than 7 months of age compared to older children, because lower sensitivities have been reported in these youngest children due to greater compliance of the external auditory canal wall (Paradise et al. 1976, Palmu et al. 1999).

Poor cooperation of children has been shown to cause especially false positive results (Koivunen et al. 1997). Since a type B tympanogram can be obtained when the probe tip is directed towards the wall of the external auditory canal, type B tympanograms

should be repeated 3 times whenever possible to prevent false positive results. False negative results can be obtained especially when air-fluid interface is present in the middle ear (Fiellau-Nikolajsen 1983). However, Koivunen et al. (1997) have shown that the ears with MEE and normal (i.e. type A or C) tympanogram usually include only small amounts of MEE.

The diagnostic accuracies of tympanometry and pneumatic otoscopy by experienced otoscopists have been reported to correspond (Toner and Mains 1990). Toner and Mains (1990) reported a sensitivity of 86% for tympanometry and 87% for pneumatic otoscopy compared to myringotomy. On the other hand, they reported a specificity of 93% for tympanometry and 89% for pneumatic otoscopy. In fact, several studies have reported somewhat higher specificities for tympanometry compared to pneumatic otoscopy by experienced otoscopists (Paradise et al. 1976, Cantekin et al. 1980, Finitzo et al. 1992). Thus, tympanometry may be better in avoiding false positive diagnoses of MEE compared to pneumatic otoscopy. In addition, interobserver agreement with tympanometry may be higher than with pneumatic otoscopy (Karma et al. 1989, Palmu et al. 2000, Shaikh et al. 2011).

Demonstrating the usefulness of tympanometry in primary health care, Blomgren and Pitkäranta (2003) have shown that the use of tympanometry as a supplementary tool for pneumatic otoscopy reduced the number of AOM diagnoses by 30% and thus reduced overdiagnosis of AOM. In summary, the advantages of tympanometry when compared to pneumatic otoscopy include the relatively simple use and objectivity, i.e. tympanometry can avoid false positive results and achieve slightly higher specificity compared to pneumatic otoscopy (Paradise et al. 1976, Cantekin et al. 1980, Toner and Mains 1990). Nevertheless, the disadvantages of tympanometry include the fact that tympanometric success rates may only be approximately 75% in young symptomatic children (Chianese et al. 2007).

The data concerning the diagnostic accuracy of tympanometric examinations performed by nurses is scarce. Only Blomgren et al. (2007) have reported results as regards training nurses to perform tympanometric examinations. Prior to the study, the nurses participated in one training session on the principles and use of tympanometry. After the session, 12 nurses performed tympanometric examinations on children 0.5 to 18 years of age before tympanostomy tube placement. The sensitivity of a type B tympanogram obtained by the nurses was only 54% and specificity 82%. MEE was detected in 23% of ears with type A tympanogram (≥-199 daPa) and 45% of ears with type C tympanograms (<-199 daPa). As the most conflicting result, the nurses reported that the teaching session for tympanometry had been sufficient and that tympanometry was easy and rapid to perform. Thus, Blomgren et al. (2007) concluded that one training session was inadequate to qualify nurses to perform reliable tympanometry.

Table 8. Diagnostic accuracy of tympanometry in detecting middle ear effusion (MEE).

	Patients, n	Examinations (ears), n	Age (range)	Manufacturer and model of the instrument	Performer of tympanometry	Success rate of tympanometry	Definition for abnormal (positive) tympanogram	Diagnosis of MEE	Sensitivity	Specificity
Paradise et al. 1976	280	531	0 mo to 5 y	Madsen type ZO-70 (electroacoustic impedance bridge)	Audiologist	95%	types EFF, HN-g, and TR-g[1]	Myringotomy in 107 children; otoscopy in 173 children	95% in the myringotomy group; 74% in the otoscopy group[2]	76% in the myringotomy group; 93% in the otoscopy group[2]
Orchik et al. 1978	75	142	Not reported	electroacoustic impedance bridge	Not reported	Not reported	type B	Myringotomy	43%	100%
Cantekin et al. 1980	333	599	7 mo to15 y	electroacoustic impedance bridge	Audiologist	Not reported	Tympanometric variants 8,12, 13, and 14[3] **with otoscopy** positive for OME	Myringotomy	97%	90%
Fiellau-Nikolajsen 1983	44	88	3 to 4 y	Madsen impedance meter	Physician	Not reported	Flat curve; (or flat curve or TPP ≤-200 mmH_2O)	Myringotomy	83% ; (or 91%)	100% ; (or 88%)
Toner and Mains 1990	121	222	18 mo to 12 y	Rexton, Tymp82	Physician	Not reported	Type B	Myringotomy	86%	93%
Babonis et al. 1991	120	220	6 mo to 10 y	Welch Allyn, MicroTymp,	Physician	95%	type B	Myringotomy	78%	82%
Finitzo et al. 1992	86	163	6 mo to 9 y	Maico, Screening Immittance Bridge (Model 610)	Audiologist	95%	type B	Myringotomy	90%	86%
Ovesen et al. 1993	220	440	10 mo to 14 y	Madsen, Tympan-O-scope ZS 330	Physician	Not reported	types B and C2	Myringotomy	94%	53%
Nozza et al. 1994	171	249	1 to 12 y	Grason-Stadler, GSI-33 Version 1	Audiologist	Not reported	width >275 daPa	Myringotomy	81%	82%
Sassen et al. 1994	266	515	5 mo to 11 y	Grason-Stadler, GSI-27A and TYMP-85TT	Not reported	Not reported	type B	Myringotomy	children less than 2 years of age: 90%; 2 to 11 years: 81%	children less than 2 years of age: 67%; 2 to 11 years: 63%

	Patients, n	Examinations (ears), n	Age (range)	Manufacturer and model of the instrument	Performer of tympanometry	Success rate of tympanometry	Definition for abnormal (positive) tympanogram	Diagnosis of MEE	Sensitivity	Specificity
van Balen and de Melker 1994	142	233	6 mo to 12 y	Welch Allyn, MicroTymp	Physician	92%	type B and C2	Myringotomy	94%	48%
Koivunen et al. 1997	162	314	7 mo to 8 y	Welch Allyn, MicroTymp	Trained nurse	87%	type B	Myringotomy	Cooperative children: 79%; uncooperative: 71%	Cooperative children: 93%; uncooperative: 38%
Watters et al. 1997	501	955	11 mo to 15 y	Grason-Stadler, GSI-33	Audiologist	Not reported	type B	Myringotomy	91%	79%
Barnett et al. 1998	155	299	6 mo to 14 y	American Electromedics, Race Car Model	Research assistant	Not reported	peak compliance ≤0.1; (or ≤0.2)	Myringotomy	54%; (or 63%)	84%; (or 75%)
Block et al. 1998	528	874	6 mo to 18 y	American Electromedics, Race Car Model	Trained study nurse	96%	see footnote 4	Pneumatic otoscopy	61%	91%
Palmu et al. 1999	58	242	2 to 11 mo	Grason-Stadler, GSI 38 Autotymp	Physician	94%	type B	Pneumatic otoscopy	70%	98%
Blomgren et al. 2007	199	392	6 mo to 18 y	Grason Stadler, GSI 38 Autotymp	Nurse	91%	type B	Myringotomy	54%	82%
Puhakka et al. 2014	600	2152	7 mo to14 y	Welch Allyn, MicroTymp2	Physician	Not reported	type B	Pneumatic otoscopy	56%	96%

[1]Tympanogram type EFF (effusion) corresponds to type B; HN-g (high negative with shallow gradient) corresponds to type Cs; and TR-g (transitional zone curve with shallow gradient) corresponds to type As.

[2] Uncertain otoscopic diagnoses were included in ears without effusion.

[3]The study included 15 different variants of tympanograms. OME was defined to be present when tympanometric variants 8 (HN-g; please see the previous footnote),12, 13, or 14 (EFF, please see the previous footnote) were obtained in combination with otoscopy positive for OME; or with tympanometric variant 12 in combination with otoscopy negative for OME and absent stapedius reflex.

[4]Definition for abnormal tympanogram: equivalent ear canal volume of 0.4-2.3 and ≥1 of the following: flat curve, width >180 daPa, or peak-compensated static acoustic admittance <0.22 mmho. Peak-compensated static acoustic admittance is the peak admittance minus admittance at +200 daPa.

Abbreviations: MEE, middle ear effusion; TPP, tympanometric peak pressure; mo, months; y, years

Table 9. Diagnostic accuracy of tympanometry in detecting acute otitis media (AOM).

	Patients, n	Examinations (ears), n	Age (range)	Manufacturer and model of the instrument	Performer of tympanometry	Success rate of tympanometry	Definition for abnormal (positive) tympanogram	Diagnosis of AOM	Sensitivity[1]
Schwartz and Schwartz 1980	103	161	4 mo to 17 y	Teledyne Model 1-D (electroacoustic impedance meter)	Not reported	Not reported	Flat and shallow/ rounded tympanograms	Pneumatic otoscopy	75%
Lampe et al. 1981	32	43	Not reported	acoustic impedance meter	Audiologist or physician	91%	type B	Pneumatic otoscopy	38%
Wheeler 1986	154	438	less than 12 y	Peters AP 61c (electroacoustic impedance meter)	Not reported	Not reported	type I (flat; defined as effusion present)	Pneumatic otoscopy	64%
Block et al. 1999	102	160	6 mo to 12 y	American Electromedics, Race Car Model	Physician or research personnel	79%	types B and C; (type B)	Tympanocentesis	83%; (type B: 78%)

[1]Only sensitivity was reported by these studies because the studies included only ears with acute otitis media.
Abbreviations: AOM, acute otitis media; mo, months; y, years

2.4.6 Spectral gradient acoustic reflectometry

In addition to tympanometry, SG-AR is an adjunctive diagnostic tool for pneumatic otoscopy used to detect the presence or absence of MEE (Kimball 1998). The diagnostic accuracy of SG-AR may be slightly lower than the accuracy of tympanometry (Chianese et al. 2007). However, SG-AR has advantages compared to tympanometry. The device is of affordable cost, easy to handle, and makes a pleasant chirping noise. SG-AR is convenient for the young child during the examination, which may enhance the success rate with the device. Most importantly, SG-AR does not require an air-tight seal or cooperation of the child. Thus, the success rates of SG-AR are generally higher than those of tympanometry. The proportion of visits where useful test results are obtained from both ears of the child is unknown.

2.4.6.1 Principles

Acoustic reflectometry was introduced in the early 1980s by Teele and Teele (1984). The technique was improved in the 1980s and 1990s to enhance the diagnostic accuracy and ease of use. The diagnostic accuracy of the first devices was highly dependent on the user because the technique required that the device was directed straight towards the tympanic membrane (Bluestone and Klein 2007). In the late 1990s, spectral gradient analysis improved acoustic reflectometry (Kimball 1998). SG-AR is less dependent on the technique of a user because it does not require a direct line to the tympanic membrane. Furthermore, an air-tight seal to the external auditory canal is not needed and thus, SG-AR can also be performed without the cooperation of the child. SG-AR is commercially available as EarCheck PRO Otitis Media Detector (Innovia Medical LLC, Omaha, NE, USA) for clinicians and as EarCheck Middle Ear Monitor for parental use. Comparable diagnostic accuracy has been reported for both of these devices (Barnett et al. 1998, Block et al. 1998, Teppo and Revonta 2007). The EarCheck Middle Ear Monitor is presented in Figure 6.

SG-AR is based on both sound waves emitted by the device and sound waves reflected back from the tympanic membrane. The acoustic speaker of the SG-AR device emits a frequency spectrum sweep of 44 closely spaced frequencies in the audible range of 1.8 to 4.4 kHz (Kimball 1998). The microphone of the device analyzes the sum of emitted and reflected sound waves. The spectral gradient angle is calculated from the slope of the sum curve of emitted and reflected sound waves at the point of maximum nullification of sound waves (Kimball 1998).

When the middle ear is normally filled with air, the mobility of the tympanic membrane is normal, and approximately half of the sound energy is reflected back from the tympanic membrane. The tympanic membrane vibrates normally and reflects back a number of wavelengths, resulting in a broad frequency spectrum and a wide (high) spectral gradient

angle value. On the other hand, if the middle ear contains MEE, the mobility of the tympanic membrane is reduced or restricted. In this case, the tympanic membrane reflects back only a narrow frequency spectrum, and a narrow (low) spectral gradient angle value is obtained (Combs and Combs 1996).

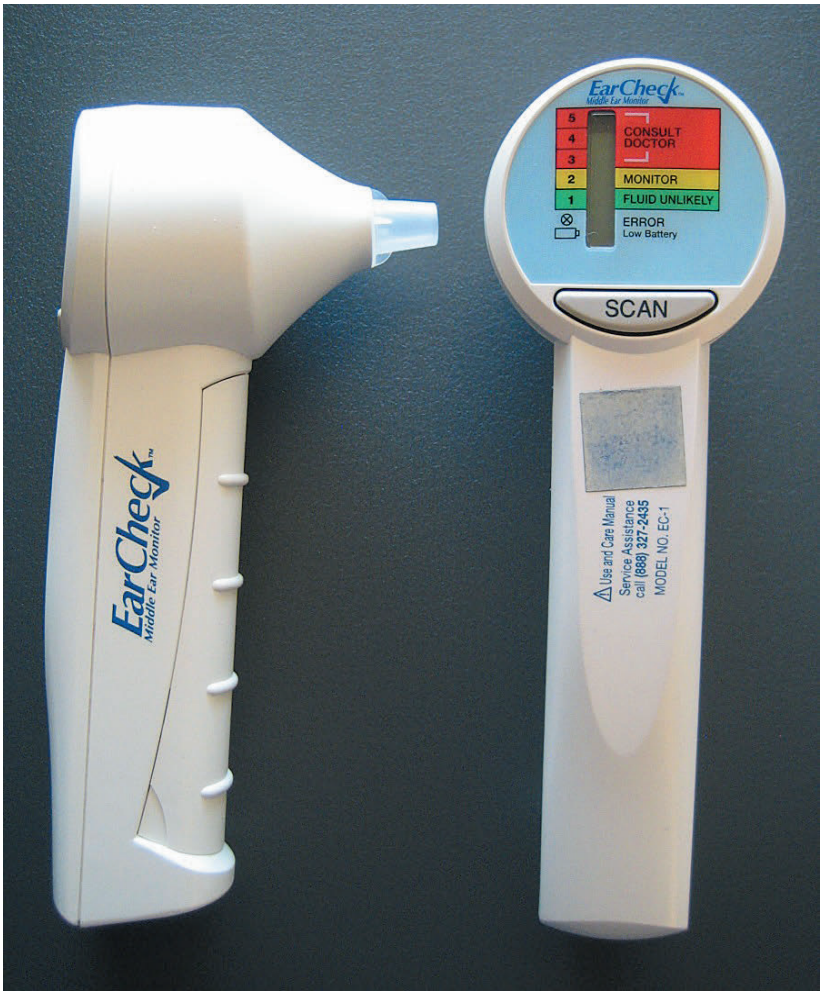


Figure 6. Spectral gradient acoustic reflectometry (SG-AR) device (EarCheck Middle Ear Monitor; Innovia Medical LLC, Omaha, NE, USA).

2.4.6.2 Classification of results

The result of SG-AR is given as an angle value, and the maximum angle value is 120˚. The manufacturer of SG-AR has classified the angle value range into five levels which are differently associated with MEE (Kimball 1998). Generally, high angle values are associated with a low likelihood of MEE, and low angle values are associated with a high likelihood of MEE. The classification is shown in Table 10.

Table 10. The five spectral gradient acoustic reflectometry (SG-AR) levels and their association with middle ear effusion (MEE) (Kimball 1998). The proportions of ears (N=870) with MEE diagnosed with pneumatic otoscopy have been reported by Block et al. (1998).

SG-AR level	SG-AR angle value range	Likelihood of MEE (Kimball et al. 1998)	Proportion of ears with diagnosed MEE (Block et al. 1998)
Level 1	>95˚	Low	3%
Level 2	70-95˚	Low to moderate	16%
Level 3	60-69˚	Moderate	34%
Level 4	49-59˚	Moderate to high	58%
Level 5	<49˚	High	92%

Abbreviations: SG-AR, spectral gradient acoustic reflectometry; MEE, middle ear effusion

2.4.6.3 Diagnostic accuracy of results obtained by physicians and nurses

The diagnostic accuracy of SG-AR to detect MEE has been studied. However, similar to the literature concerning tympanometry, several studies include children undergoing tympanostomy tube placement and/or children older than 3 years of age. Thus, these results may not be generalizable to young outpatient populations. Table 11 summarizes the diagnostic accuracy of SG-AR. As with tympanometric studies, success rates with the device have been scarcely reported, and the proportion of visits with successful results has not been analyzed. In Table 11, only the sensitivities and specificities are reported. Positive and negative predictive values are not presented in Table 11, because they have been reported only in a few studies. In addition, positive and negative predictive values are highly dependent on the prevalence of MEE, which greatly varies between these studies.

As shown by Table 11, low SG-AR angle values (<49˚) reliably predict the presence of MEE. In contrast, high SG-AR angle values (>95˚) reliably predict a healthy middle ear. However, between these extremities of the SG-AR angle value range is a “diagnostic grey area”. The middle portion of the SG-AR angle value range (levels 2-3) cannot be used to predict either MEE or healthy middle ear. Thus, several studies separately report diagnostic test results predictive for MEE and results predictive for healthy middle ear.

Since an air-tight seal to the external auditory canal is not needed for SG-AR, the success rates of SG-AR are approximately 95%. Thus, the cooperation of the child does not have corresponding importance during the examination compared to tympanometry. Furthermore, Teele and Teele (1984) have reported that acoustic reflectometry succeeds even with cerumen present in the external auditory canal. Only cerumen totally occluding the canal was reported to affect the results of reflectometry. Correspondingly, Block et al. (1998) reported that moderate amounts of cerumen

(i.e. less than half of the diameter of the external auditory canal) did not affect the diagnostic accuracy of SG-AR. Teppo and Revonta (2007) have shown that SG-AR is not accurate during general anesthesia (in tympanostomy tube placement) or when the child is in a horizontal position (lying down). Thus, SG-AR and tympanometry have to be performed in an upright position.

Compared to tympanometry, the diagnostic accuracy of SG-AR seems to be corresponding (Barnett et al. 1998, Block et al. 1998) or slightly lower (Chianese et al. 2007, Puhakka et al. 2014). The comparison between the sensitivities and specificities of tympanometry and SG-AR is difficult since the study settings and cut-off points used vary between the studies. Chianese et al. (2007) reported that the area under the curve (receiver operating characteristic curve [ROC]) analysis gave significantly greater results (0.83) for tympanometry compared to SG-AR (0.77) for differentiating MEE from healthy middle ears. Moreover, tympanometric results are often divided as type B tympanograms versus other types, whereas SG-AR results are difficult to be separated into two classes. The diagnostic difficulty with SG-AR is the wide middle portion of the SG-AR angle value range which does not predict MEE or healthy middle ear.

Only Teppo et al. (2006) have reported results of teaching nurses performing SG-AR examinations. The nurses participated in one teaching session of two hours on the principles and use of SG-AR. After that, 7 nurses performed SG-AR examinations on children aged 1.5 to 2 years. The success rate was 79%, and the authors hypothesized that myringotomies performed in the study may have decreased the success rate. The nurses obtained accurate SG-AR results when compared to pneumatic otoscopy by trained physicians. Because of the "diagnostic gray area", Teppo et al. (2006) recommended separate cut-off points for detecting MEE at acute sick visits and excluding MEE at non-acute visits. SG-AR angle values $\leq 59^{\circ}$ (levels 4-5) were recommended as positive results for MEE at acute visits and angle values $\geq 100^{\circ}$ as results showing healthy middle ear at non-acute visits. At acute visits with a high prevalence of MEE, even these highest SG-AR values of $\geq 100^{\circ}$ were not accurate in predicting a healthy middle ear (negative predictive value 75%).

Table 11. The diagnostic accuracy of spectral gradient acoustic reflectometry (SG-AR) in diagnosing middle ear effusion (MEE).

	Patients, n	Examinations (ears), n	Age (range)	Model	Performer of SG-AR	Success rate of SG-AR	Definition for abnormal (positive) SG-AR result	Diagnosis of MEE	Sensitivity	Specificity
Teele and Teele 1984	160	290	0 mo to 13 y	Prototype device of acoustic reflectometry	Physician	Not reported	Result of ≥4.0 dB (preceded the development of SG-AR)	Pneumatic otoscopy and tympanometry; myringotomy in some cases	94%	79%
Barnett et al. 1998	155	299	6 mo to 14 y	EarCheck PRO	Research assistant	Not reported	Levels 2-5 (≤95˚); or Level 5 (<49˚)	Myringotomy	Levels 2-5: 95%; or Level 5: 38%	Levels 2-5: 31%; or Level 5: 93%
Block et al. 1998	528	874	6 mo to 18 y	EarCheck PRO	Trained study nurse	99%	Levels 3-5 (≤69˚)	Pneumatic otoscopy	67%	87%
Block et al. 1999	102	160	6 mo to 12 y	EarCheck PRO	Physician or research personnel	79%	Levels 3-5 (≤69˚)	Tympanocentesis for diagnosing AOM	86% for AOM	Not applicable (only ears with AOM)
Babb et al. 2004	33 children; 44 adults	66 ears + 94 ears	1 to 12 y; or 15 to 88 y	EarCheck PRO	Not reported	Children 92%; Adults 96%	Levels 3-5 (≤69˚)	Pneumatic otoscopy or tympanometry (type B)	Children 77%; Adults 78%	Children 96%; Adults 94%
Teppo et al. 2006	271	739	1.5 to 2 y	EarCheck PRO	Nurse	79%	Acute sick visits: Levels 4-5 (≤59˚); Non-acute visits: <100˚	Pneumatic otoscopy; myringotomy in some cases	Acute visits: 42%; Non-acute visits: 87%	Acute visits: 95%; Non-acute visits: 51%
Chianese et al. 2007	647	3096	6 mo to 2 y	EarCheck PRO	Physician, pediatric nurse practitioner, or research nurse	Not reported	Levels 3-5 (≤69˚)	Pneumatic otoscopy	47%	90%
Linden et al. 2007	199	398	7 mo to 15 y	EarCheck PRO	Physician	94%	Levels 4-5 (≤59˚); or <100˚	Myringotomy	Levels 4-5: 46%; or <100˚: 89%	Levels 4-5: 90%; or <100˚: 44%
Teppo and Revonta 2007	50	100	10 mo to 6 y	EarCheck PRO and Ear Check Middle Ear Monitor (consumer model)	Physician	83%	Levels 3-5 (≤69˚)	Myringotomy	Ear Check PRO: 83%; Ear Check Middle Ear Monitor 77%	Ear Check PRO: 84%; Ear Check Middle Ear Monitor 85%
Puhakka et al. 2014	600	2152	7 mo to 14 y	Ear Check Middle Ear Monitor (consumer model)	Physician	Not reported	Levels 3-5 (≤69˚)	Pneumatic otoscopy	53%	93%

Abbreviations: SG-AR, spectral gradient acoustic reflectometry; MEE, middle ear effusion; AOM, acute otitis media; mo, months; y, years

2.4.7 Hearing measurements

MEE reduces the mobility of the tympanic membrane and ossicles, and hearing impairment may result (Rosenfeld et al. 2013). Children with AOM or OME usually suffer from mild and short-termed conductive hearing loss (Bluestone and Klein 2007). When MEE is present, the hearing loss is typically less than 40 dB (i.e. mild). An average hearing loss of 27 dB has been reported, but the loss can be as high as 60 dB (Fria et al. 1985). Interestingly, the amount of MEE seems to correspond to the severity of hearing impairment (Fiellau-Nikolajsen 1983, Koivunen et al. 2000). Fiellau-Nikolajsen (1983) reported that the mean hearing thresholds in audiometric testing varied according to the amount of MEE: healthy middle ears, 17 dB; minimal MEE, 23 dB; moderate MEE, 29 dB; and the middle ears full of MEE, 34 dB. Thus, the child's hearing during an AOM episode seems to correlate with the amount of effusion in the middle ear.

When the middle ear is full of MEE, tympanometry usually shows type B tympanogram (Fiellau-Nikolajsen 1983, Koivunen et al. 1997). In addition, type B tympanogram has been shown to predict the persistence of MEE (Lampe et al. 1981). Dempster and MacKenzie (1991) studied children 3 to 12 years of age (with the mean age of 6 years) and found that type B tympanograms were sensitive (93%) in detecting a hearing impairment of ≥25 dB caused by OME. However, the positive predictive value of type B tympanograms was only 49%, and thus, only half of children with a type B tympanogram had hearing impairment. On the other hand, peaked tympanograms were associated with normal hearing. Therefore, Dempster and MacKenzie (1991) suggested that in the presence of OME, peaked tympanograms would indicate normal hearing, and type B tympanograms would necessitate hearing measurements.

Hearing usually returns to normal when MEE has resolved. However, recurrent acute or chronic inflammation in adhesive otitis media may rarely cause permanent conductive hearing impairment (Bluestone 2000). The guideline on tympanostomy tube placement by Rosenfeld et al. (2013) recommends an age-appropriate hearing test if OME persists for 3 months or longer, and when considering tympanostomy tube placement. The guideline emphasizes the importance of distinguishing children with recurrent AOM or OME of any duration who are at increased risk for speech and language delays. Factors predisposing to speech and language delays include craniofacial disorders, such as cleft palate; syndromes, such as Down's syndrome; permanent hearing or visual impairment; suspected or confirmed speech, language, or developmental delay; and autism-spectrum disorders (Rosenfeld et al. 2013). The preferred method to measure hearing is pure tone audiometry. Audiometry can be performed in primary health care for children at least 4 years of age. The fail criterion has been defined as hearing impairment of >20 dB at ≥1 frequency in one or both ears

(Rosenfeld et al. 2013). However, conventional audiometry is unreliable in children less than 4 years of age, who have to be evaluated by an audiologist by special methods such as visual response audiometry or play audiometry.

2.5 Management

2.5.1 Symptomatic treatment

Most children with AOM have a concomitant viral RTI and suffer from acute symptoms which may include rhinitis, cough, irritability, restless sleep, fever, or loss of appetite (Niemelä et al. 1994, Heikkinen and Ruuskanen 1995, Kontiokari et al. 1998a, Laine et al. 2010). Thus, most of these acutely ill children need analgesic treatment whether or not the diagnosis of AOM is made. Even if AOM is diagnosed and antimicrobial treatment started, analgesic medication, such as paracetamol (acetaminophen) or ibuprofen, is needed at least during the first 24 hours until the effect of antimicrobial treatment initiates (Heikkinen et al. 2010, Lieberthal et al. 2013).

2.5.2 Antimicrobial treatment

Acute symptoms and otoscopic signs of AOM generally resolve during the first week after the diagnosis even without antimicrobial treatment (Venekamp et al. 2013). Hoberman et al. (2011) and Tähtinen et al. (2011) studied children less than 2 years and 3 years of age, respectively. Both studies found that in two thirds of the AOM episodes, resolution also occurred with placebo treatment. However, resolution of both acute symptoms and otoscopic signs was significantly accelerated by amoxicillin-clavulanate treatment of 7 days. Rescue treatment (i.e. amoxicillin-clavulanate prescription of 7 days) was required by 7% of children in the amoxicillin-clavulanate group compared to 34% of children in the placebo group (Tähtinen et al. 2011). Individual symptoms resolved an average of 1 to 2 days faster with antimicrobial treatment (Tähtinen et al. 2011).

Since antimicrobial treatment has been shown more effective than placebo in the treatment of AOM in young children, the Finnish and American guidelines on the diagnosis of management of AOM (Heikkinen et al. 2010, Lieberthal et al. 2013) emphasize the importance of an accurate diagnosis. In the Finnish Current Care Guideline on AOM (Heikkinen et al. 2010), if the diagnosis of AOM is certain, antimicrobial treatment is recommended in most cases. If antimicrobial treatment is not prescribed, a follow-up visit has to take place in 2-3 days to ensure the resolution of acute symptoms. The first-line antimicrobial is amoxicillin (40 mg/kg/day), and amoxicillin-clavulanate is recommended when treatment with amoxicillin fails, or if betalactamase producing bacteria are cultured from MEE (Heikkinen et al. 2010). In the American guideline

on AOM (Lieberthal et al. 2013), all children with AOM and severe symptoms (i.e. moderate to severe otalgia, mild otalgia longer than 48 hours, or a temperature ≥39˚C in the previous 48 hours) are recommended to be treated with an antimicrobial. An observation option is limited to unilateral AOM of children 6-24 months of age (without severe symptoms), and unilateral or bilateral AOM in children at least 2 years of age (without severe symptoms). When AOM is treated without an antimicrobial, a follow-up visit is recommended, corresponding to the Finnish guideline. In the American guideline, high-dose amoxicillin (80-90 mg/kg/day) is the recommended first-line antimicrobial. Amoxicillin-clavulanate is recommended for children who suffer from concurrent conjunctivitis or have used amoxicillin during the previous month. Antimicrobial treatment seems to be most beneficial in children less than two years of age with bilateral AOM, and in children having AOM with perforated tympanic membrane (Venekamp et al. 2013).

2.5.3 Resolution of middle ear effusion

The resolution of MEE after an AOM episode has been complicated to study because relapses and reinfections of AOM often interfere with the resolution of MEE (Bluestone 2000). Somewhat contradictory to the current Cochrane Systematic Reviews (van Zon et al. 2012, Venekamp et al. 2013), Tapiainen et al. (2014b) showed that the total duration of MEE was shorter when AOM was treated with an antimicrobial compared to a placebo. Tapiainen et al. (2014b) studied the resolution of MEE after AOM with daily tympanometry (and weekly pneumatic otoscopy) in 84 children (0.5 to 15 years of age) and showed that the mean duration of MEE was 2.7 weeks with a 7-day amoxicillin-clavulanate treatment and 4.7 weeks with placebo treatment. Two weeks after the diagnosis of AOM, 69% of children who had received antimicrobial treatment had normal tympanometry (type A or C1) compared to only 38% of children in the placebo group (Figure 7). Two months after the diagnosis, 5% of children in the antimicrobial group and 24% in the placebo group had MEE. Thus, they concluded that antimicrobial treatment significantly reduced the duration of MEE and the risk for persistent MEE. The discrepancy between the results of Tapiainen et al. (2014b) and the Cochrane Systematic Reviews (van Zon et al. 2012, Venekamp et al. 2013) might be caused by the inclusion of children with an uncertain diagnosis of AOM in some of the previous randomized controlled trials (Pichichero and Casey 2008a, Pichichero and Casey 2008b, Pichichero 2015). Thus, children with an uncertain diagnosis of AOM may dilute the true effect of antimicrobial treatment on the resolution of MEE (Pichichero 2015).

Correspondingly, Ruohola et al. (2003) showed that the duration of acute tympanostomy tube otorrhea was significantly shorter with amoxicillin-clavulanate treatment compared to a placebo (median duration 3 and 8 days, respectively).

Renko et al. (2006) studied the resolution of MEE in 90 children after an episode of AOM treated with amoxicillin or cefuroxime-axetil for 10 days. The median time of effusion was reported as 8 days, as shown with normalization of a type B tympanogram into a type A or C tympanogram. In 69% of children, MEE resolved in 2 weeks. In addition, unilateral AOM resolved faster than bilateral AOM.

Teele et al. (1980) enrolled 2565 children before the age of 3 months and followed these children at a primary health care level until the age of 3 years. They reported that after an AOM episode treated with an antimicrobial, 40% of children had persistent MEE 4 weeks after the diagnosis of AOM, and 10% of children had MEE after 3 months (Figure 7). As a limitation of this study, Teele et al. (1980) did not report the interval between the follow-up visits.

Shurin et al. (1979) studied the persistence of MEE after AOM treated with an antimicrobial in children 2 months to 12 years of age. They found that in 45/107 (42%) children, MEE persisted for at least 13 weeks. The major risk factor for persistence of MEE was an age of less than 2 years. However, their study was biased by the long interval between the follow-up visits. These children were examined only on study days 3, 10, and 42, and additional visits were arranged when needed by the child. Of note, the children were examined only a median of two times. Thus, persistent and recurrent MEE could not be differentiated in their study.

Mandel et al. (2008) have shown that long interval (28 days vs. 7 days) between study visits causes significant biases by prolonging estimates for the duration of MEE and reducing estimates for incidence of MEE. They showed a mean duration of OME (without preceding AOM diagnosis) as 17 days and duration of MEE after AOM (with antimicrobial treatment) as 21-24 days. When analyzed with a 28-day interval between the study visits, the mean duration of MEE increased significantly with 10-28 days (Mandel et al. 2008). Thus, frequent follow-up visits are crucial when studying the duration of MEE after AOM.

For different visit types of young children in primary health care, a different prevalence of MEE has been reported. Teppo et al. (2006) studied the diagnostic accuracy of SG-AR performed by nurses in children less than 2 years of age. They reported the prevalence of MEE as 50% at acute sick visits, 20% at scheduled ear control visits 3 to 5 weeks after the first visit (after AOM or OME), and 5% at scheduled healthy follow-up visits at 2 years of age. Correspondingly, Teele et al. (1983) detected MEE at approximately 5% of well-child visits. In a study carried out by Kontiokari et al. (1998b), trained nurses screened with tympanometry children 0.6-6.9 years of age and had a success rate of 92%. The point prevalence of AOM in these children was 3% and OME 4%. Thus, the point prevalence of MEE was 7% (bilateral MEE in 3%). The prevalence of MEE varies according to whether children or ears (i.e. examinations)

are analyzed. The prevalence of MEE at visits (in children) is higher compared to ears because at visits, both unilateral and bilateral cases of MEE are counted positive for MEE. In summary, the prevalence of MEE seems to be approximately 50% at acute sick visits with RTI, 20-40% at routine ear control visits 4 weeks after the diagnosis of AOM, and 5% at well-child visits.

Fiellau-Nikolajsen has studied the resolution of MEE as defined by different tympanogram types (Fiellau-Nikolajsen and Lous 1979, Fiellau-Nikolajsen 1983). Fiellau-Nikolajsen and Lous (1979) screened with tympanometry 1005 ears in 504 children who were 3 years of age. A total of 372 tympanograms were type B or C, and the normalization of these tympanograms was followed for 6 months (i.e. from January to June). Type B tympanograms were found to persist, while virtually all type C1 tympanograms and most of type C2 tympanograms converted to normal type A tympanograms. Of type B tympanograms, 58% were still type B after one month, 34% after 3 months, and 18% after 6 months. Marked spontaneous resolution of MEE was seen during the first 2 to 3 months but after that, the normalization rate of tympanograms declined.

MEE shows good spontaneous resolution after an AOM episode during the first 3 months, during which the resolution of MEE occurs in approximately 75-90% of episodes (Fiellau-Nikolajsen 1983, Rosenfeld et al. 2013). In contrast, chronic MEE, which has persisted longer than 3 months, has a poor recovery rate of 19% after additional 3 months and 25% after additional 6 months (Rosenfeld and Kay 2003). To summarize, after the diagnosis of AOM, MEE rapidly resolves during the first 2 to 3 months. However, with persistent MEE, resolution rarely occurs.

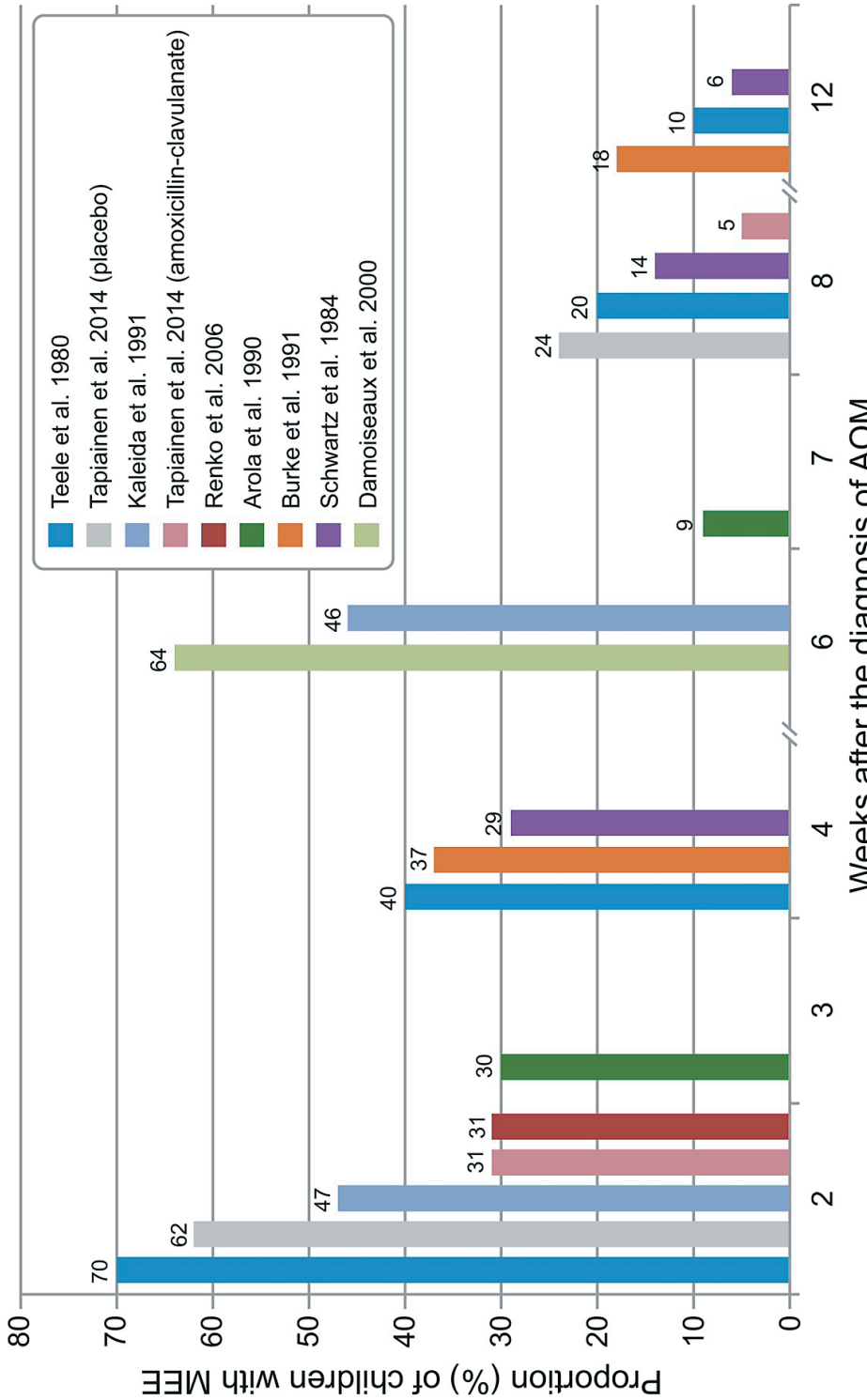


Figure 7. Proportion of children with middle ear effusion (MEE) after the diagnosis of acute otitis media (AOM). All presented children received antimicrobial treatment except the placebo group of Tapiainen et al. (2014b).

2.5.4 Routine ear controls after an episode of acute otitis media

In Finland and Norway, routine ear controls are performed after an AOM episode to exclude the persistence of MEE, which might affect hearing and the development of speech in young children (Lindbaek and Kvaerner 2004, Heikkinen et al. 2010). In Sweden, routine ear controls are performed in selected cases: perforation of the tympanic membrane, bilateral findings (AOM/AOM, or AOM/OME) in children less than 4 years of age, or in case of persisting symptoms (Läkemedelsverket 2010). In Finland, a routine ear control is recommended 3-4 weeks after the onset of AOM (Heikkinen et al. 2010). At this time point, the prevalence of MEE has been reported as 20-40% (Teele et al. 1980, Arola et al. 1990, Teppo et al. 2006). If MEE is detected, a new ear control is recommended after 3-4 weeks. If MEE persists for 3 months or longer, children are recommended to be referred to an otolaryngologist for the consideration of tympanostomy tube placement.

Notably, the current Finnish and Swedish guidelines on AOM state that no data exists concerning the effectiveness of routine ear controls or optimal timing of these visits (Heikkinen et al. 2010, Läkemedelsverket 2010). In Sweden, a routine ear control is recommended 3 months after the diagnosis of AOM (in selected cases) (Läkemedelsverket 2010). In Norway, the recommended timing of a routine ear control is 6 to 12 weeks after the diagnosis of AOM, and the importance of ear control visits is emphasized for cases in which antimicrobial treatment is not prescribed (Lindbaek and Kvaerner 2004, Norsk Forening for Otorhinolaryngologi, Hode- og Halskirurgi 2012). To summarize, optimal timing of routine ear control visits is complicated because after an AOM episode, MEE is usually detected for several weeks. In addition, new episodes of AOM and OME can occur at any time during the resolution of MEE. Thus, timing of routine ear controls has to balance these sides.

In contrast, the American clinical practice guideline on OME (Rosenfeld et al. 2004) does not recommend population-based screening programs in healthy, asymptomatic children. Screening is not recommended because of the high point prevalence of MEE in young children, lack of demonstrable benefits (Zielhuis et al. 1989), potential false positive diagnoses of AOM, and risk of overtreating a self-limited condition (Rosenfeld et al. 2004). However, the guideline emphasizes the importance of distinguishing children at risk for speech, language, or learning difficulties. Paradise et al. (2001, 2003, 2005, 2007) followed 429 otherwise healthy children who had tympanostomy tube placement due to persistent MEE at less than 3 years of age either promptly or up to 9 months later if MEE persisted. They found no significant differences in the language skills of these children at the age of 3, 4, 6, and 9 years. Some studies show minor speech, language, or learning delays in children with persistent MEE while other studies report no delay and, thus, the literature concerning possible long-term consequences of persistent MEE remains controversial (Rosenfeld et al. 2004, Rosenfeld et al. 2013). In summary, the critical

aspects seem to be differentiating children who have a baseline condition predisposing to speech, language, or learning difficulties, and following their recovery from AOM.

2.5.5 Tympanocentesis and tympanostomy tubes

Tympanocentesis is less effective than antimicrobial treatment for AOM (Engelhard et al. 1989) and causes pain to the child. Thus, tympanocentesis is no longer performed in primary health care. Tympanocentesis is performed only when the identification of pathogens is needed, i.e. in complicated cases of AOM or in children with conditions predisposing to severe infections, such as immunodeficiencies (Heikkinen et al. 2010). Tympanostomy tubes seem to be effective in managing persistent MEE (Rosenfeld et al. 2013) and in preventing recurrences of AOM (Kujala et al. 2012). In the clinical practice guideline on tympanostomy tube placement, Rosenfeld et al. (2013) summarized that tympanostomy tubes reduce the prevalence of MEE by 32% during the first year after placement. Moreover, average hearing levels are improved by 5 to 12 dB (Browning et al. 2010). Furthermore, AOM episodes are easier to diagnose and treat with topical antimicrobial drops (Rosenfeld et al. 2013).

Tympanostomy tubes may improve the quality of life. Interestingly, Kujala et al. (2014) followed children less than 2 years of age who had been admitted for tympanostomy tube placement due to recurrent AOM episodes. They compared the quality of life in children for whom tympanostomy tube placement was performed to children with only frequent follow-up visits. Although the children without the surgical intervention suffered more AOM episodes, the quality of life did not differ between the groups. Thus, frequent follow-up visits seem to be the major factor improving the quality of life in children with recurrent AOM.

3. AIMS OF THE STUDY

The aims of the thesis were to study the diagnostic accuracy and success rates of tympanometry and SG-AR performed by physicians and nurses in outpatients less than 3 years of age.

The specific aims of the original publications were:

I To study the usefulness of tympanometry performed by physicians in discriminating otoscopic diagnoses in young outpatients.

II To study the usefulness of SG-AR performed by physicians in discriminating otoscopic diagnoses in young outpatients.

III To study whether nurses can reliably exclude AOM with tympanometry or SG-AR in young symptomatic outpatients.

IV To study whether nurses can reliably exclude MEE with tympanometry or SG-AR in young asymptomatic outpatients.

4. MATERIALS AND METHODS

The thesis consisted of four original publications which include the detailed methods of Studies I-IV.

4.1 Study population and visits in the study clinic

This study was conducted between the years 2006 and 2009, and it was part of a project examining the optimal diagnostics and management of AOM at primary health care level in Turku, Finland (Tähtinen et al. 2011). Written informed consent was obtained from the parents of each child. The study protocol was approved by the Ethical Committee of the Hospital District of Southwest Finland.

Children eligible for the diagnostic screening of AOM were 6-35 months of age and suffered from RTI. The families in the region of Turku (in Turku, Kaarina, Lieto, Naantali, and Raisio) were informed about the study through health centres, well-child clinics, day care centres, other study projects in the Department of Paediatrics and Adolescent Medicine at Turku University Hospital, and by sending information to families in Turku who had children less than 3 years of age. The parents were informed that they could contact the study clinic when they suspected AOM in their child. The exclusion criteria of the project were: ongoing antimicrobial treatment, spontaneous perforation of the tympanic membrane; systemic or nasal steroid therapy within the 3 preceding days; antihistamine therapy within the 3 preceding days; oseltamivir therapy within the 3 preceding days; allergy to penicillin or amoxicillin; tympanostomy tube present in tympanic membrane; clinical evidence of infection requiring systemic antimicrobial treatment (e.g. pneumonia, meningitis, septicemia, or urinary tract infection); documented Epstein-Barr virus infection within the 7 preceding days; Down's syndrome or other condition affecting middle ear infections; known immunodeficiency; vomiting or other symptom preventing per oral dosage; poor parental cooperation due to language or other reasons; and use of any investigational drugs during the 4 preceding weeks.

At the first study visit, children were divided into two cohorts on the basis of a pneumatic otoscopic diagnosis by the study physician. In the first cohort, children with AOM participated in the AOM treatment trial, and were examined on study days 1, 3, 8, 15, 30, and 60. In the second cohort, the signs and symptoms of children who did not have AOM were followed, and the children were re-examined approximately 12 days later. In addition, sick visits were arranged for both cohorts whenever needed.

To minimize the inclusion of similar diagnostic test results in Studies I-IV, visits by a child that were less than 3 days apart were excluded from the analyses. If the child had

more than 6 visits, only the first 6 visits were included. Furthermore, only the visits where the study physician succeeded in performing SG-AR, tympanometry, and pneumatic otoscopy were included.

Since the aim of Study III was to investigate the exclusion of AOM in symptomatic outpatients, only the symptomatic visits were included in the analyses, i.e. the children suffered from acute symptoms and signs of RTI (such as rhinitis, cough, or conjunctivitis) or nonspecific symptoms causing the parental suspicion of AOM (i.e. irritability, excessive crying, restless sleep, less playful or active, or poor appetite). The symptomatic visits included visits with and without the parental suspicion of AOM. Since most of the children were at preverbal age and could not describe their symptoms, parental evaluation was used to assess the symptoms of the child. Accordingly, since the aim of Study IV was to investigate the exclusion of MEE in asymptomatic outpatients, only the asymptomatic visits were included in the analyses. According to the parents, these children did not have any symptoms or signs during the preceding 48 hours before the visit. Of these symptomatic (III) or asymptomatic (IV) visits, all the tympanometric and SG-AR examinations performed by the nurses were included in the analyses.

4.2 Diagnostic procedures

Children were always examined in an upright position. The order of diagnostic procedures was chosen to optimize the cooperation of children during tympanometry and SG-AR because cerumen removal and otoscopic examination often cause fussiness and struggling, leading to possible failure of tympanometry and SG-AR.

For Studies III-IV, three nurses were taught the principles of tympanometry and SG-AR and how to perform examinations with these devices. The nurses had no experience with pneumatic otoscopy, tympanometry or SG-AR. In one training session lasting approximately two hours, the nurses were taught the principles of tympanometry and SG-AR and how to perform examinations with these devices. During teaching, the nurses' technique to use the devices was checked. During the study visits, one of the three nurses performed the examinations whenever she was available (i.e. was not handling other tasks in the project). On rare occassions, the nurse performed an examination in only one ear of the child due to the device being unavailable or if the device had temporarily stopped working. The nurses' examinations were independently performed without any guidance of the study physician.

At the study visit, the nurse first performed SG-AR (EarCheck PRO Otitis Media Detector, Innovia Medical LLC, Omaha, NE, USA) and then tympanometry (MicroTymp2, Welch Allyn, Skaneateles Falls, NY, USA). After the nurse, the study physician first performed SG-AR, then tympanometry, and finally, pneumatic otoscopy (Macroview Otoscope

Model 23810, Welch Allyn, Skaneateles Falls, NY, USA). Cerumen was carefully removed before pneumatic otoscopy. Digital pneumatic video otoscopy was used to document the findings (Jedmed, St. Louis, MO, USA). All the study physicians were trained to assess otoscopic findings. Of the five study physicians, three (Miia Laine, Paula Tähtinen, and Aino Ruohola) made more than 90% of the otoscopic diagnoses and had an excellent interobserver agreement (kappa values ranging from 0.80 to 0.92).

Pneumatic otoscopy by the study physician served as the diagnostic standard. The diagnosis of AOM required the following three criteria. First, MEE had to be detected with a pneumatic otoscopic examination that showed at least two of the following tympanic membrane findings: bulging position, decreased or absent mobility, abnormal color or opacity not due to scarring, or air-fluid interface. Second, at least one of the following acute inflammatory signs on the tympanic membrane had to be present: distinct erythematous patches or streaks or increased vascularity over full, bulging or yellow tympanic membrane. Third, signs and symptoms of acute infection had to be present.

The diagnosis of OME was based on the presence of effusion in the middle ear shown by reduced mobility of the tympanic membrane or by visible air-fluid interface; retracted or normal (i.e. slightly concave) position of the tympanic membrane; and the absence of acute inflammatory signs on the tympanic membrane (i.e. distinct erythematous patches or streaks).

For Studies I-II, the otoscopic findings were divided into 5 otoscopic diagnoses. OME was categorized as air-interface OME (a-OME) when visible air-fluid interface and/or air bubble(s) were seen or as complete OME (c-OME) when the otoscopic examination showed that the middle ear was completely filled with effusion. Correspondingly, AOM was categorized as air-interface AOM (a-AOM) with visible air-fluid interface and/or air bubble(s) or complete AOM (c-AOM) when the middle ear was completely filled with effusion. Finally, if no pathologic otoscopic findings were detected, the middle ear was categorized as healthy.

In Study IV investigating the exclusion of effusion by nurses, the definition MEE was used to describe effusion in the middle ear instead of OME. The definition MEE was used since the previous duration of effusion before a control visit in the study ranged from 1 week to 4 weeks, and the term OME has traditionally been associated with effusion of long duration. Study IV included no cases of AOM, and thus, all the cases of effusion were non-acute.

4.3 Classification of diagnostic test results

Tympanometry was performed with a MicroTymp 2 tympanometer with a printer. The device uses a probe tone of 266 Hz and a sweep range of +200 to −400 daPa, from positive to negative pressure with a speed of 400 ± 40 daPa/s.

Tympanograms were classified according to the original classification of Jerger (1970), with modifications of Fiellau-Nikolajsen and Lous (1979) defining type C1 and C2 tympanograms; and Orchik et al. (1978) and Smith et al. (2006) defining wide As and Cs tympanograms. The detailed classification of tympanograms is shown in Table 7 (Section 2.4.5.2). In brief, type A tympanograms were peaked tympanograms (SAA ≥0.2 mmho) with TPP greater than -100 daPa; type C1 peaked tympanograms with TPP between -100 and -199 daPa; type C2 peaked tympanograms with TPP -200 daPa or less; type Cs low peaked (SAA <0.2 mmho) or wide (width >300 daPa) with TPP ≤-100 daPa; and type B tympanograms were flat. Since type As tympanograms were few, they were included in type A tympanograms. Flat tympanograms were repeated three times whenever possible.

All the tympanograms were evaluated by two study physicians (Miia Laine and Aino Ruohola) who were blinded to the results of the otoscopic examination. When disagreeing, Aino Ruohola made the final decision. Only clearly interpretable tympanograms without artifacts were classified. The nurses did not interpret any tympanograms.

The SG-AR angle value was classified according to the manufacturer's recommendations into five levels corresponding to the risk of MEE: <49˚, high risk of middle ear effusion (level 5); 49–59˚, moderate to high risk (level 4); 60–69˚, moderate risk (level 3); 70–95˚, low to moderate risk (level 2) and >95˚, low risk (level 1) (Table 10; Section 2.4.6.2). SG-AR was performed only once if a successful angle value was immediately obtained. Otherwise, SG-AR was repeated according to the cooperation of a child. The examination was considered failed if the SG-AR instrument displayed an error symbol or if the angle value was seen only for a moment.

4.4 Statistical analyses

Studies I-II

The proportions of different tympanogram types (A, C1, C2, Cs, and B) in relation to otoscopic diagnoses (healthy middle ear, a-OME, c-OME, a-AOM, and c-AOM) were calculated for both symptomatic and asymptomatic visits.

Correspondingly, the proportions of the five SG-AR levels in relation to the five otoscopic diagnoses were calculated for both symptomatic and asymptomatic visits. The ROC curves consisting of sensitivity and 1-specificity values were constructed with their respective 95% CI. The area under the ROC curve can receive a value between 0.5 and 1. If a diagnostic test cannot categorize the diagnostic findings at all, the value is 0.5; if a test is perfect, the value is 1. Diagnostic accuracy can be interpreted as follows: the area under the curve 0.60–0.70, poor; 0.71–0.80, fair; 0.81–0.90, good; and >0.90, excellent.

Studies III-IV

In Study III, test characteristics for the diagnostic test results of the nurses were calculated by comparing the pneumatic otoscopic diagnosis of AOM by the study physician (the positive reference standard) to the non-AOM situation, i.e. the middle ear was healthy or OME was detected (the negative reference standard). Correspondingly, in Study IV, test characteristics were calculated by comparing the pneumatic otoscopic diagnosis of MEE (the positive reference standard) by the study physician to the healthy middle ear (the negative reference standard).

In Studies III-IV, the tympanometric diagnostic test result for AOM (Study III) or MEE (Study IV) was the grouped result of type C2, Cs, and B tympanograms (the positive test result) which was contrasted with type A and C1 tympanograms (the negative test result). Correspondingly, test characteristics for SG-AR were calculated for levels 2-5 ($\leq$95˚; the positive test result) vs. level 1 (>95˚; the negative test result).

Test characteristics, i.e. sensitivity, specificity, positive predictive value, and negative predictive value were calculated with their respective 95% CI for the diagnostic test results. Since the aim was to study the exclusion of AOM (Study III) or MEE (Study IV), the focus was on the negative predictive values. For the accurate exclusion, the negative predictive value for the diagnostic test result was considered to be at least 95%.

Finally, the proportion of visits where the nurses obtained the exclusive diagnostic test result for AOM (Study III) or MEE (Study IV) from both ears of the child with tympanometry or SG-AR was calculated. In Studies I-II, the statistical analyses were performed with the SPSS software (version 16.0 for Windows, SPSS Inc, Chicago, IL, USA) and in Studies III-IV, with the SAS software (version 9.3 for Windows, SAS Institute Inc., Cary, NC, USA).

5. RESULTS

5.1 Characteristics of the study populations

The characteristics of the study populations in Studies I-IV are summarized in Table 12.

Table 12. Characteristics of the study populations.

	Studies I-II	Study III	Study IV
Included children, n	515	281	156
Included visits, n	2123	459	196
Included examinations, n	4246	tympanometry: 890 SG-AR: 892	tympanometry: 373 SG-AR: 380
Median age, months (range)	14 (6-35)	14 (6-35)	13 (6-35)
Median number of previous AOM episodes, n (range)	1 (0-12)	1 (0-11)	1 (0-10)
Median age at first AOM episode, months (range)	9 (0-29)	9 (0-27)	9 (0-27)

Abbreviations: SG-AR, spectral gradient acoustic reflectometry; AOM, acute otitis media

5.2 Tympanometry performed by physicians (I)

Studies I-IV were part of a project studying the optimal diagnostics and management of AOM (Tähtinen et al. 2011), and a total of 2856 visits took place in the study clinic. To minimize the repetition of the same diagnostic test result, 733 visits were excluded according to the previously explained criteria (Methods, Section 4.1). Thus, Studies I-II included 2123 visits leading to 4246 performed tympanometric, SG-AR, and pneumatic otoscopic examinations by the study physicians (Table 12).

Of the 4246 tympanometric examinations performed by physicians, 3212 (76%) were successful and 1034 (24%) failed, i.e. the tympanogram was not obtained or could not be interpreted due to the lack of cooperation of the young child. The success rate was not affected by the otoscopic diagnosis, i.e. whether a healthy middle ear, OME, or AOM was diagnosed.

At symptomatic visits, 2206/2932 (75%) of tympanometric examinations were successful. With type A, C1, and C2 tympanograms, healthy middle ear was diagnosed in 559/717 (78%), 259/416 (62%), and 112/209 (54%) examinations, respectively (Figure 8A). When any peaked tympanogram (type A, C1, C2, or Cs) was obtained, the otoscopic diagnosis was a healthy middle ear in 942/1407 (67%) examinations. On the other hand,

type B tympanogram was associated with any OME or any AOM in 337/799 (42%) or 423/799 (53%) examinations, respectively.

At asymptomatic visits, 1006/1314 (77%) of tympanometric examinations were successful. With type A, C1 and C2 tympanograms, healthy middle ear was diagnosed in 526/570 (92%), 157/192 (82%), and 21/45 (47%) examinations, respectively (Figure 8B). When any peaked tympanogram was obtained, the otoscopic diagnosis was a healthy middle ear in 713/824 (87%) examinations. On the other hand, type B tympanogram was associated with any OME at 159/182 (87%) examinations.

5.3 Spectral gradient acoustic reflectometry performed by physicians (II)

Of the total of 4246 SG-AR examinations by physicians, 4042 (95%) were successful. The amount of effusion in the middle ear affected SG-AR results. With the otoscopic diagnoses of a-OME and a-AOM, higher proportions of SG-AR levels 1-2 (≥70˚) vs. levels 3-5 (<70˚) were obtained compared to c-OME and c-AOM, respectively.

At symptomatic visits, when an SG-AR level 1 result (>95˚) was obtained, the otoscopic diagnosis was a healthy middle ear or a-OME in 540/708 (76%) or 94/708 (13%) examinations, respectively (Figure 9A). Levels 2 (70–95˚) and 3 (60–69˚) did not associate with any particular otoscopic diagnosis. Level 4 (49-59˚) and level 5 (<49˚) results associated with any effusion (a-OME, c-OME, a-AOM, or c-AOM) in 368/441 (83%) and 433/452 (96%) examinations, respectively. Levels 4 and 5 were related to any AOM in 221/441 (50%) or 290/452 (64%) examinations, respectively. The area under the curve value of the ROC analysis was 0.81 (95% CI 0.79-0.83) which corresponds to good diagnostic accuracy in detecting any effusion.

At asymptomatic visits, SG-AR levels 1, 2 and 3 were associated with a healthy middle ear in 461/527 (87%), 303/428 (71%) and 67/124 (54%) examinations, respectively (Figure 9B). When a level 4 or level 5 result was obtained, any effusion was diagnosed in 56/89 (63%) or 60/72 (83%) examinations. The area under the curve value of the ROC analysis was 0.76 (96% CI 0.73-0.79) which corresponds to fair diagnostic accuracy in detecting any effusion.

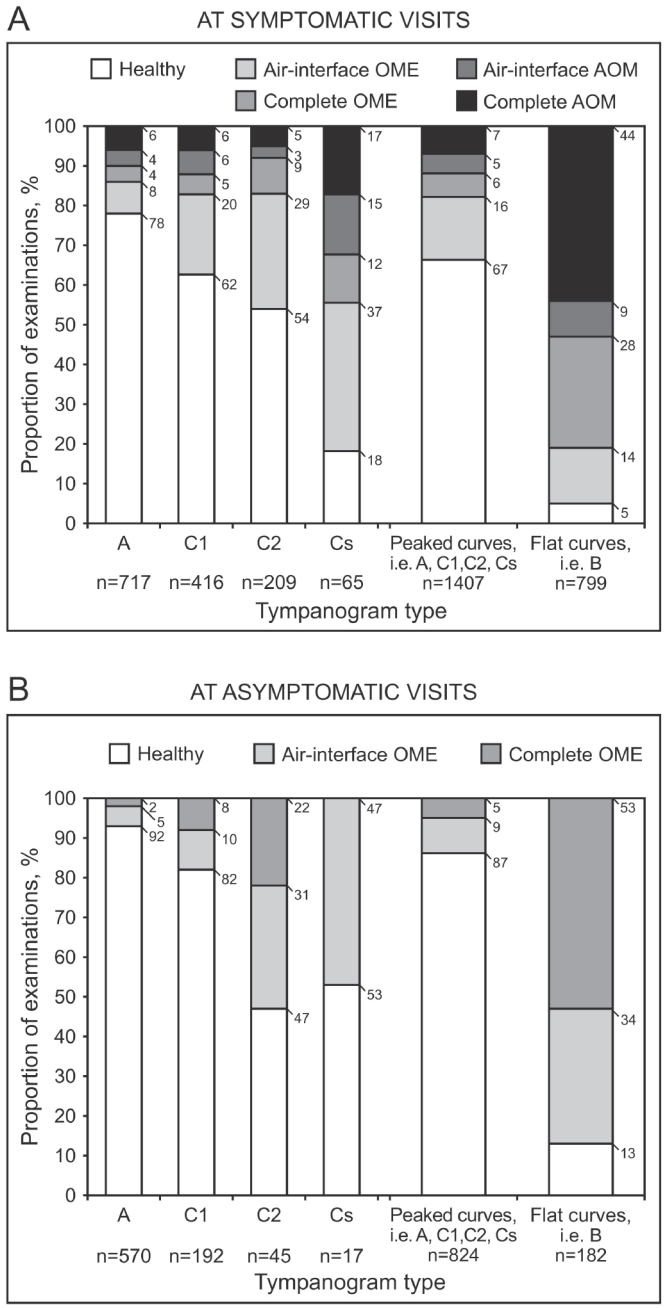


Figure 8. The proportions of otoscopic diagnoses in relation to successful tympanograms obtained by physicians A) at symptomatic visits and B) at asymptomatic visits. From Original publication I (Pediatr Infect Dis J. 2012;31:1003-6). Published with the permission of the copyright holder.

Classification of tympanogram types. A: tympanometric peak pressure >-100 daPa; C1: -100 to -199 daPa; C2: ≤-200 daPa; Cs: ≤-100 daPa and static acoustic admittance <0.2 mmho or width >300 daPa; B: flat tympanogram.

Abbreviations: OME, otitis media with effusion; AOM, acute otitis media.

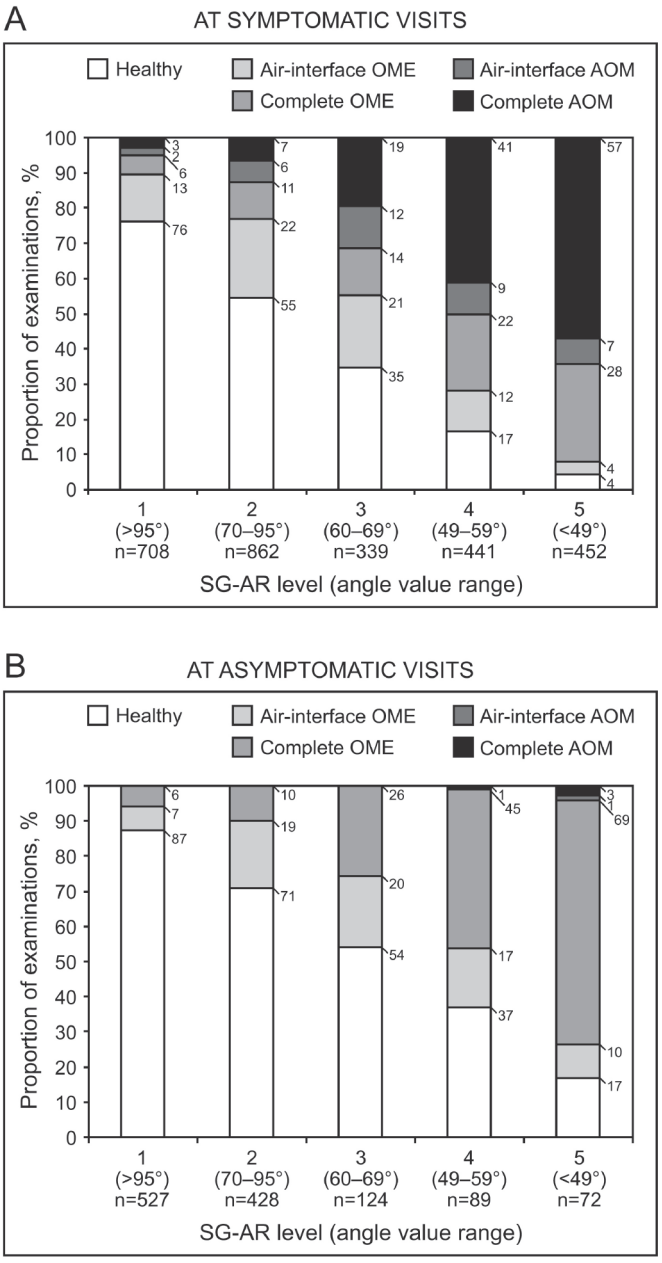


Figure 9. The proportions of otoscopic diagnoses in relation to successful SG-AR examinations obtained by physicians A) at symptomatic visits and B) at asymptomatic visits. From Original publication II (Pediatr Infect Dis J. 2012;31:1007-11). Published with the permission of the copyright holder.

Abbreviations: OME, otitis media with effusion; AOM, acute otitis media

5.4 Tympanometry and spectral gradient acoustic reflectometry performed by nurses in the exclusion of acute otitis media (III)

Of the 2123 visits included in Studies I-II, 1466 visits were related to acute symptoms. Of these 1466 symptomatic visits, the nurses performed tympanometry and/or SG-AR on one or both ears of the child at 459 visits (Table 12; Section 5.1). The frequency of AOM with pneumatic otoscopy by the study physician was 467/1782 (26%) of all tympanometric and/or SG-AR examinations performed by the nurse.

The nurses performed 670/890 successful tympanometric examinations. The three nurses succeeded in 96/138 (70%), 159/217 (73%), and 415/535 (78%) of performed tympanometric examinations, respectively. The negative predictive values of a type A tympanogram, grouped type A and C1 tympanogram, and any peaked tympanogram (type A, C1, C2, or Cs) were 95% (95% CI 91-97%), 94% (91-97%), and 93% (90-95%), respectively (Table 13; part of the data unpublished).

Table 13. The exclusion of acute otitis media (AOM) by nurses. The predictive values (with respective 95% confidence intervals [CI]) for the diagnostic test results with tympanometry (N=670) and spectral gradient acoustic reflectometry (SG-AR) (N=782) obtained by the nurses. Pneumatic otoscopy by the study physician served as the diagnostic standard; AOM was contrasted with non-AOM (i.e. healthy middle ear or otitis media with effusion).

	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Type C1, C2, Cs, and B vs. type A tympanograms[1]	95% (90-97%)	34% (30-38%)	32% (28-36%)	95% (91-97%)
Type C2, Cs, and B vs. type A and C1 tympanograms[1]	90% (85-94%)	54% (50-58%)	39% (35-44%)	94% (91-97%)
Flat (type B) vs. peaked tympanograms[1] (type A, C1, C2, and Cs)	83% (76-88%)	73% (69-76%)	50% (44-56%)	93% (90-95%)
SG-AR level 2-5 (≤95°) vs. level 1 (>95°) results	95% (91-98%)	26% (22-30%)	32% (28-36%)	94% (89-97%)
SG-AR level 3-5 (<70°) vs. level 1-2 (≥70°) results	79% (73-85%)	63% (59-67%)	44% (39-49%)	89% (86-92%)

[1]Classification of tympanogram types. A: tympanometric peak pressure >-100 daPa; C1: -100 to -199 daPa; C2: ≤-200 daPa; Cs: ≤-100 daPa and static acoustic admittance <0.2 mmho or width >300 daPa; B: flat tympanogram.

Of the 459 symptomatic visits, tympanometry was successful in both ears of the child at 302 (66%) visits. For the successful exclusion of AOM based on a diagnostic test result, the test result was required to be obtained from both ears of the child. Based on the exclusive test results of a type A tympanogram, grouped type A and C1 tympanogram, and any peaked tympanogram, the nurses could rule out AOM at 49 (11%), 94 (20%), and 143 (31%) of 459 visits, respectively (part of the data unpublished). However, of these visits with the exclusive test result, AOM was diagnosed with pneumatic otoscopy at 3/49 (6%), 6/94 (6%), and 11/143 (8%) of visits, respectively. Figure 10 shows a flow chart of the exclusion of AOM by nurses with the exclusive test result of grouped type A and C1 tympanograms. AOM was diagnosed with pneumatic otoscopy in 153/365 (42%) of visits where the nurses did not obtain the exclusive result from both ears of the child (Figure 10).

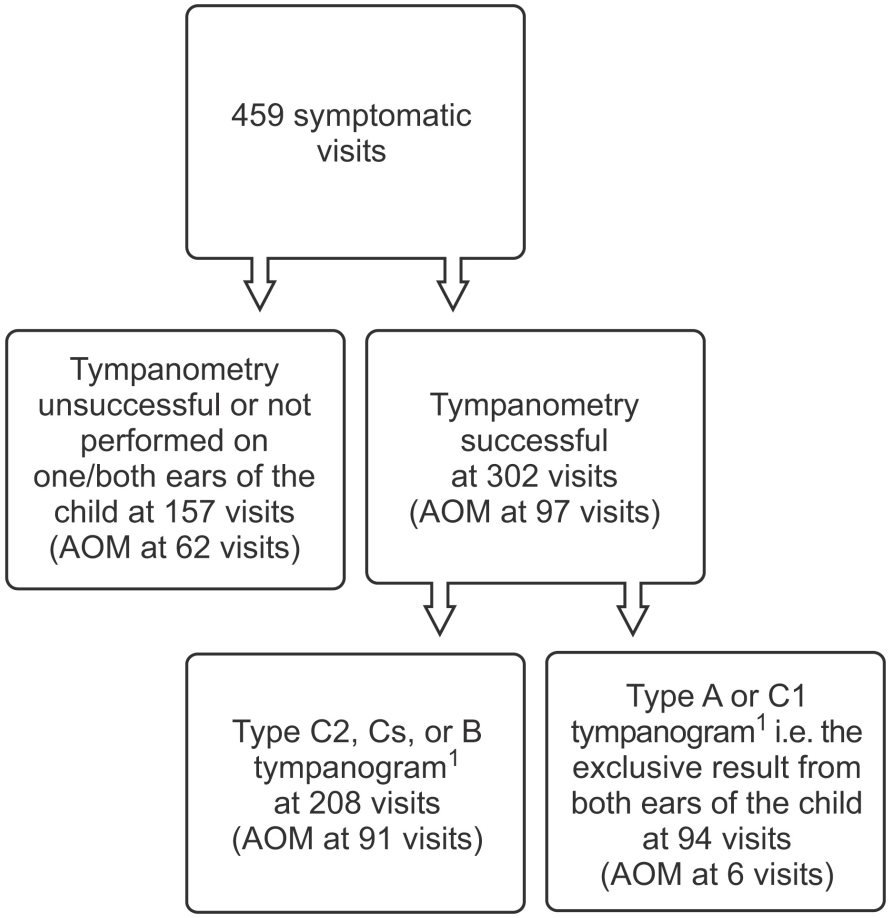


Figure 10. Flow chart of the exclusion of acute otitis media (AOM) based on tympanometry performed by the nurses at symptomatic visits (N=459). Type A or C1 tympanogram from both ears of the child was regarded as the exclusive result for AOM. From Original publication III (submitted to Scand J Prim Health Care). Published with the permission of the copyright holder.

[1]Classification of tympanogram types. A: tympanometric peak pressure >-100 daPa; C1: -100 to -199 daPa; C2: ≤-200 daPa; Cs: ≤-100 daPa and static acoustic admittance <0.2 mmho or width >300 daPa; B: flat tympanogram.

The nurses performed 782/892 (88%) successful SG-AR examinations. The three nurses succeeded in 112/140 (80%), 472/537 (88%), and 198/215 (92%) of performed SG-AR examinations, respectively. The negative predictive values of a SG-AR level 1 result and SG-AR level 1-2 result were 94% (95% CI 89-97%) and 89% (86-92%), respectively (Table 13).

Of the 459 visits, SG-AR was successfully performed on both ears of the child at 373 (81%) visits. The nurses obtained the exclusive result (i.e. level 1) from both ears of the child at 36/459 (8%) visits. Of these 36 visits, AOM was diagnosed with pneumatic otoscopy at 2 (6%) visits.

Tympanometry was unsuccessful or not performed on one or both ears of the child at 157/459 (34%) visits. Among these visits with unavailable tympanogram(s), the proportion of visits where the nurse could exclude AOM with SG-AR level 1 was calculated. When the exclusive result for AOM was a type A tympanogram, grouped type A and C1 tympanogram, or any peaked tympanogram, SG-AR level 1 result excluded AOM from the child at additional 8 visits, 11 visits, or 13 visits, respectively (with no additional diagnoses of AOM) (unpublished data).

5.5 Tympanometry and spectral gradient acoustic reflectometry performed by nurses in the exclusion of middle ear effusion (IV)

Of the 2123 visits included in Studies I-II, children were asymptomatic at 657 visits. Of these 657 visits, the nurses performed tympanometry and/or SG-AR on one or both ears of the child at 196 visits (Table 12; Section 5.1). The frequency of MEE with pneumatic otoscopy by the study physician was 206/753 (27%) of all tympanometric and/or SG-AR examinations performed by the nurse.

The nurses performed 272/373 (73%) successful tympanometric examinations. The three nurses succeeded in 35/58 (60%), 149/206 (72%), and 88/109 (81%) of the performed tympanometric examinations, respectively. The negative predictive values of a type A tympanogram, grouped type A and C1 tympanogram, and any peaked tympanogram (type A, C1, C2, or Cs) were 94% (95% CI 89-97%), 95% (91-97%), and 91% (86-94%), respectively (Table 14; part of the data unpublished).

Table 14. The exclusion of middle ear effusion (MEE) by nurses. Test characteristics (with respective 95% confidence intervals [CI]) for the diagnostic test results with tympanometry (N=272) and spectral gradient acoustic reflectometry (SG-AR; N=332). MEE was contrasted with healthy middle ear; diagnostic standard was pneumatic otoscopy by the study physician.

	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Type C1, C2, Cs, and B vs. type A tympanograms[1]	87% (77-93%)	65% (58-71%)	42% (34-51%)	94% (89-97%)
Type C2, Cs, and B vs. type A and C1 tympanograms[1]	84% (73-91%)	87% (82-91%)	66% (55-75%)	95% (91-97%)
Flat (type B) vs. peaked tympanograms[1] (type A, C1, C2, and Cs)	68% (55-78%)	91% (87-95%)	70% (57-80%)	91 % (86-94%)
SG-AR level 2-5 (≤95°) vs. level 1 (>95°) results	79% (69-86%)	45% (38-51%)	33% (27-40%)	86% (79-91%)
SG-AR level 3-5 (<70°) vs. level 1-2 (≥70°) results	52% (41-62%)	83% (78-88%)	52% (41-62%)	83% (78-88%)

[1]Classification of tympanogram types. A: tympanometric peak pressure >-100 daPa; C1: -100 to -199 daPa; C2: ≤-200 daPa; Cs: ≤-100 daPa and static acoustic admittance <0.2 mmho or width >300 daPa; B: flat tympanogram.

Of the 196 asymptomatic visits, tympanometry was successfully performed on both ears of the child at 119 (61%) visits. Corresponding to Study III, for the successful exclusion of MEE based on a diagnostic test result, the test result was required to be obtained from both ears of the child. Based on the exclusive test results of a type A tympanogram, grouped type A and C1 tympanogram, and any peaked tympanogram, the nurses could exclude MEE at 53 (27%), 81 (41%), and 86 (44%) of 196 visits, respectively (part of the data unpublished). However, of these visits with the exclusive result, MEE was diagnosed with pneumatic otoscopy at 4/53 (8%), 7/81 (9%), and 8/86 (9%) of visits, respectively. Figure 11 shows a flow chart of the exclusion of MEE by nurses with the exclusive test result of grouped type A and C1 tympanograms. MEE was diagnosed with pneumatic otoscopy at 64/115 (56%) of visits where the nurses did not obtain the exclusive result from both ears of the child (Figure 11).

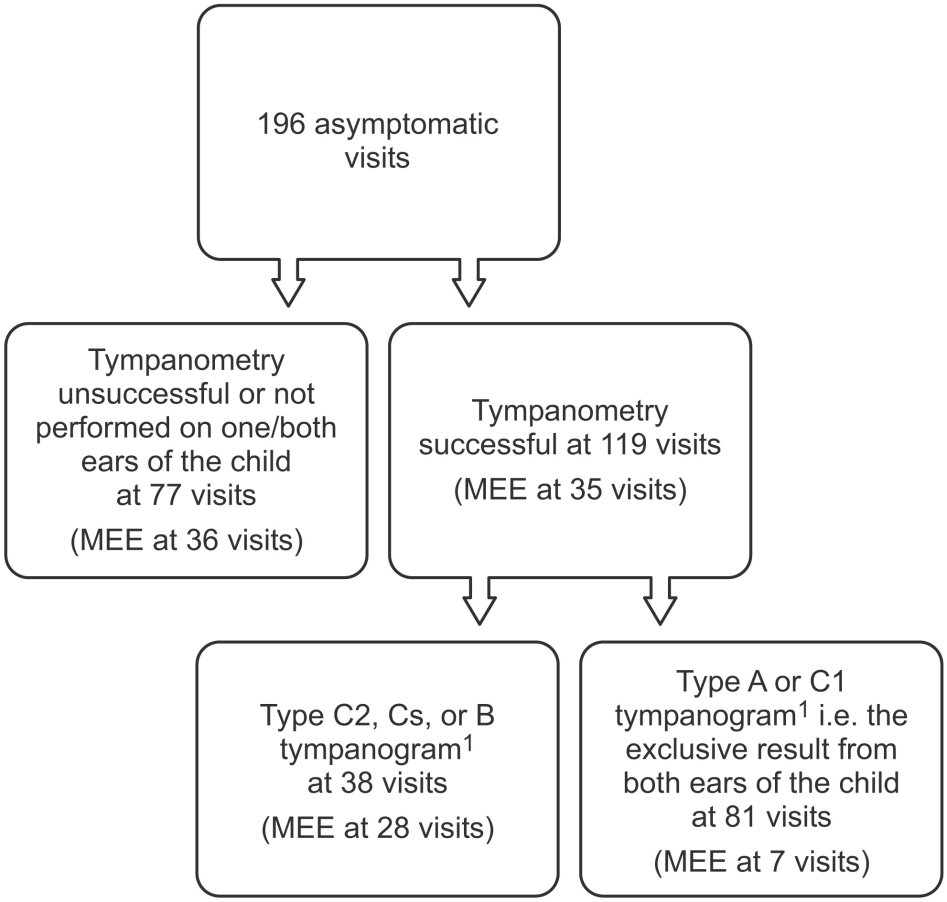


Figure 11. Flow chart of the exclusion of middle ear effusion (MEE) based on tympanometry performed by the nurses at asymptomatic visits (N=196). Type A or C1 tympanogram from both ears of the child was regarded as the exclusive test result for MEE. From Original publication IV (Scand J Prim Health Care 2015; Early online:1-6). Published with the permission of the copyright holder.

[1]Classification of tympanogram types. A: tympanometric peak pressure >-100 daPa; C1: -100 to -199 daPa; C2: ≤-200 daPa; Cs: ≤-100 daPa and static acoustic admittance <0.2 mmho or width >300 daPa; B: flat tympanogram.

The nurses performed 332/380 (87%) successful SG-AR examinations. The three nurses succeeded in 46/60 (77%), 183/208 (88%), and 103/112 (92%) of performed SG-AR examinations, respectively. The negative predictive values of a SG-AR level 1 result and level 1-2 result were 86% (95% CI 79-91%) and 83% (78-88%), respectively (Table 14).

Of the 196 visits, SG-AR was successfully performed on both ears of the child at 158 (81%) of visits. The nurses obtained the exclusive result (i.e. level 1) from both ears of the child at 29/196 (15%) of visits. Of these 29 visits, MEE was diagnosed with pneumatic otoscopy at 5 (17%) of visits.

6. DISCUSSION

The aim of the thesis was to investigate the diagnostic accuracy and success rates of tympanometry and SG-AR performed by physicians and nurses. In addition, the thesis estimated the proportion of symptomatic and asymptomatic visits where nurses obtained accurate diagnostic test results from both ears of the child in the exclusion of AOM and MEE, respectively.

6.1 Tympanometry performed by physicians (I)

The rationale of studying the accuracy of tympanometry in differentiating otoscopic diagnoses is based on the difficulty of diagnosing healthy middle ear, OME, or AOM. Pneumatic otoscopy is the recommended method for ear examination in primary health care (Rosenfeld et al. 2004). However, accurate diagnosis with pneumatic otoscopy requires substantial training and experience. In fact, the diagnostic accuracy of pneumatic otoscopy performed by inexperienced otoscopists is significantly lower compared to experienced otoscopists (Pichichero 2002, Steinbach et al. 2002). Less experienced otoscopists tend to focus on the child's symptoms and erythema of the tympanic membrane, whereas assessing the position and mobility of the tympanic membrane (i.e. the most important aspects regarding the diagnosis of AOM) is difficult for them (Steinbach et al. 2002, Blomgren and Pitkäranta 2003). Furthermore, even among experienced otoscopists, the diagnostic accuracy may differ (Paradise et al. 1976, Cantekin et al. 1980, Karma et al. 1989, Shaikh et al. 2011). Nevertheless, the accurate diagnosis of AOM is essential in minimizing unnecessary antimicrobial treatment. Tympanometry as a supplementary tool for AOM has been reported to reduce AOM diagnoses by 30% (Blomgren and Pitkäranta 2003). Thus, this study aimed to investigate the role tympanometry in the diagnosis of the otitis media spectrum.

The success rate of physicians with tympanometry was found to be 76%, and thus, one fourth of the tympanometric examinations failed or was not interpretable due to lack of cooperation of the young children. Previous studies have either reported success rates of 80% to 90%, or have analyzed only successful tympanograms and not reported unsuccessful examinations (Table 8; Section 2.4.5.3). In addition, the majority of these studies have included children older than 3 years of age. Chianese et al. (2007) studied the diagnostic accuracy of tympanometry in children 6-24 months of age and reported a success rate of 74%. For infants 2-11 months of age, Palmu et al. (1999) reported a tympanometric success rate of 94%. However, the success rate was significantly lower in infants older than 7 months compared to infants of less than 7 months of age. Thus,

the age from 6 to 24 months seems to be the major factor decreasing the success rate of tympanometric examinations.

At symptomatic visits, type B tympanograms were strongly associated with MEE (AOM or OME). Thus, type B tympanograms were accurate in predicting the presence of MEE. Corresponding diagnostic accuracy of type B tympanograms in predicting MEE in young children has been reported by Palmu et al. (1999) and Chianese et al. (2007). However, in the current study, approximately half of MEE was found to be AOM and half OME. Therefore, even though a type B tympanogram is an accurate predictor of MEE, pneumatic otoscopy is needed to evaluate the presence of acute inflammatory signs on the tympanic membrane. On the other hand, even type A tympanograms were not accurate in excluding MEE, because these tympanograms were associated with healthy middle ears in only 78% of ears. However, type A tympanograms may be accurate in excluding AOM because these tympanograms were associated with AOM in only 10% of ears (c-AOM in 6%). With type C1, C2, and Cs tympanograms, higher proportions of MEE were detected when compared to the study conducted by Palmu et al. (2001b). In their study, type C1 tympanograms were associated with MEE in 12% of ears; C2a (-200 to -295 daPa) in 20%; C2b (-300 to -395 daPa) in 29%, and Cs in 22% of ears. However, this current study is in agreement with their conclusion of negative pressure tympanograms being poor predictors for MEE. Moreover, when the prevalence of MEE is high (at acute sick visits), type C tympanograms cannot be used to reliably exclude MEE either.

At asymptomatic visits, type B tympanograms were associated with MEE in the majority of cases. Type A tympanograms were, and type C1 tympanograms seemed to be, accurate in predicting healthy middle ears. Corresponding to symptomatic visits, type C2 and Cs tympanograms predicted neither MEE nor a healthy middle ear.

Interestingly, when tympanometry showed a peaked tympanogram (type A, C1, C2, or Cs) in the presence of OME or AOM, only air-fluid interface (i.e. no full effusion) was seen in most cases. In contrast, type B tympanograms were mainly associated with full OME or full AOM. Corresponding to these results, Koivunen et al. (1997) found that type A tympanograms were associated with a healthy middle ear in the majority of cases. In addition, when a type A tympanogram was obtained in the presence of MEE, only a small amount (i.e. small mean weight) of MEE was found in their study. On the other hand, type B tympanograms were associated with a significantly higher mean amount of MEE (Koivunen et al. 1997). Furthermore, the amount of MEE has been shown to correspond to the severity of hearing impairment (Fiellau-Nikolajsen 1983, Koivunen et al. 2000). Thus, peaked tympanograms can be expected to be mainly associated with normal hearing (Dempster and MacKenzie 1991). On the other hand, approximately half of type B tympanograms might be associated with hearing impairment (Dempster and MacKenzie 1991).

To summarize the tympanometric test results, tympanometry is most useful in verifying the presence of MEE. Pneumatic otoscopy is needed to distinguish AOM from OME. At asymptomatic visits, type A tympanograms are accurate in predicting a healthy middle ear.

Even though tympanometry offers useful test results to support pneumatic otoscopy and has been shown to reduce the number of AOM diagnoses as an adjunctive tool for pneumatic otoscopy (Johansen et al. 2000, Blomgren and Pitkäranta 2003), the major problem with tympanometry seems to be its limited use in primary health care. Honkanen et al. (2002) studied the use of diagnostic tools in respiratory tract infections in Finnish primary health care. During one week in November, the use of tympanometry in AOM-related visits was recorded in 30 health centres. Strikingly, they found that tympanometry was used in only 1% (8/915) of children having AOM, even though tympanometry was already recommended by the evidence-based guidelines at that time. Thus, Honkanen et al. (2002) concluded that tympanometry is notably underused compared to the recommendations. Correspondingly, Lous et al. (2012) have noted that the use of tympanometry is highly skewed in primary health care, and surprisingly few general practitioners actually use tympanometry. Lous et al. (2012) studied the use of tympanometry in Danish primary health care and reported that nearly half of the followed clinics did not use tympanometry at all. A few general practitioners used tympanometry a little, and the most active general practitioners performed more than 500 tympanometric examinations per year. Similarly, some regions of Denmark used tympanometry significantly more often than other regions. When Lous et al. (2014) followed the proportion of clinics using tympanometry from 2007 to 2009, virtually no improvement was seen during these years. Therefore, it seems that even though tympanometry has been available for decades and the benefits of using tympanometry have been promoted, the implementation of tympanometry into primary health care has not been a success. The most commonly reported problems with tympanometry by general practitioners have been: understanding the meaning of the figures displayed by a tympanometer, obtaining a reliable tympanogram, and achieving an air-tight seal to the external auditory canal (Lous et al. 2012). Difficulties have been reported both in performing tympanometry and interpreting tympanometric test results. The most frequently reported reasons for not using tympanometry have been lack of training and that the device is not available or functioning (MacClements et al. 2002). Interestingly, Lous et al. (2012) found that a one-day course (of six hours) on the principles and use of tympanometry improved general practitioners' confidence with tympanometry, especially interpretation of obtained test results, and general practitioners' clinical skills in performing tympanometry. In Australia, a multimodal, interactive workshop was found to increase general practitioners' confidence in performing tympanometry and pneumatic otoscopy (Rosenkranz et al. 2012). However, even though the general

practitioners recognized the importance of these diagnostic skills, the 3-hour course did not increase their intention to use tympanometry and pneumatic otoscopy in the future. Thus, this study emphasized the importance of following up and supporting general practitioners in the use of tympanometry. To summarize, the two critical aspects with the implementation of tympanometry in primary health care seem to be: first, getting general practitioners motivated (i.e. interested in) using the device and second, getting general practitioners, who have started to use tympanometry, to maintain their tympanometric skills and routine use of tympanometry in ear-related visits.

In Finland, the barriers for the use of tympanometry by general practitioners are unknown (Kontiokari et al. 2000). In fact, several factors may limit the use of tympanometry among general practitioners. Education concerning tympanometry may be lacking in the basic medical school teaching. The relatively high cost of a tympanometer (approximately 2000-3000 euros) may limit the number of tympanometers that health centres can afford. In health centres where relatively few patients are young children, general practitioners may not acquire enough experience with tympanometry to maintain their tympanometric skills. Consequently, when general practitioners are uncertain with the use of tympanometry, their motivation to perform tympanometric examinations may be limited. Thus, the facilitating factors for the use of tympanometry in primary health care might include familiarizing the students with tympanometry already during medical school, i.e. teaching the use of tympanometry and emphasizing its importance. An important facilitator for implementing tympanometry in general practioners' routines could be to arrange short courses including several workshops on tympanometry to support and maintain the use of tympanometry (Rosenkranz et al. 2012). In addition, a tympanometer should be available in the general practitioners' rooms thus guaranteing that the device is easily available when needed and also in order to be used when only a relatively short time has been reserved for the visit.

6.2 Spectral gradient acoustic reflectometry performed by physicians (II)

Corresponding to Study I, the rationale of studying the usefulness of SG-AR derives from the difficulty of diagnosing a healthy middle ear, OME, or AOM. Thus, reliable adjunctive diagnostic tools to pneumatic otoscopy are needed.

The success rate of physicians with SG-AR was found to be 95%, which corresponds to the previous studies (Table 11; Section 2.4.6.3). Even in this most challenging age group of 6-35 months, high success rates are obtained with SG-AR because an air-tight seal to the external auditory canal is not required. Thus, based both on Studies I-II and the previous literature, the success rates of SG-AR are substantially higher compared to tympanometry.

At symptomatic visits, SG-AR level 5 results (<49˚) were accurate in detecting MEE. Corresponding to type B tympanogram in Study I, approximately half of MEE was AOM and half OME. This finding emphasizes the importance of pneumatic otoscopy in diagnosing AOM, because neither tympanometry nor SG-AR could distinguish AOM from OME. SG-AR level 4 (49-59˚) can also be considered to predict MEE at symptomatic visits. On the other hand, corresponding to type A tympanogram, even SG-AR level 1 result (>95˚) failed to exclude all MEE but seemed to exclude AOM. Further, corresponding to type C2 and Cs tympanograms, SG-AR levels 2 and 3 were ”diagnostic grey area” with approximately equal proportions of otoscopically diagnosed healthy middle ears and MEE. The usefulness of SG-AR levels 1, 4, and 5, and the diagnostic grey area of levels 2-3 are in accordance with previous studies (Barnett et al. 1998, Block et al. 1998, Teppo et al. 2006, Chianese et al. 2007, Linden et al. 2007).

At asymptomatic visits, corresponding to type B tympanogram in Study I, SG-AR level 5 seemed to predict MEE. On the other hand, corresponding to type A (and C1) tympanograms, SG-AR level 1 predicted healthy middle ear. Further, corresponding to type C2 and Cs tympanograms, SG-AR levels 2-3 predicted neither healthy middle ear nor MEE.

To summarize SG-AR results, SG-AR level 5 is accurate in predicting MEE and level 1 in predicting healthy middle ears in young outpatients. The wide diagnostic grey area (levels 2-3) limits the usefulness of SG-AR results.

The test results of SG-AR and tympanometry generally agree with each other, i.e. the devices show similar test results for an otoscopic diagnosis, and discrepant results seem to be rare. When comparing the usefulness of SG-AR and tympanometry, these devices clearly have different technical advantages and disadvantages. Substantially higher success rates are obtained with SG-AR than with tympanometry in young children. On the other hand, both of these devices have diagnostic test results which cannot be used to predict MEE or a healthy middle ear. However, SG-AR level 2-3 (or level 2-4) results are more frequent than type C2 and Cs tympanograms, which limits the use of obtained SG-AR results. To summarize, tympanometry succeeds less often than SG-AR but when tympanometric results are obtained, they are useful in the majority of cases. Even though SG-AR and tympanometric examinations are generally successful in the same (cooperating) children, the concurrent use of SG-AR and tympanometry is likely to add to the number of children with an accurate middle ear diagnosis. Thus, the use of both devices might be preferable. The use of these devices would be especially beneficial for those who are still developing their diagnostic skills, i.e. for young physicians (Blomgren and Pitkäranta 2005).

Even though SG-AR offers useful test results, is easily and rapidly performed, and pleasant even for young children, its use in primary health care is rare (Jensen and

Lous 1999). The greatest barrier for the use of SG-AR seems to be the overall lack of knowledge in primary health care concerning SG-AR and the lack of these devices. In fact, the key factors in the implementation of SG-AR and tympanometry in primary health care include: the importance of these techniques being accepted, general practitioners maintaining their motivation to use the devices, the organization (i.e. health centre) organizing and supporting the use of these devices, and that the use of these devices and the benefits obtained from their use being evaluated in the organization (Finch et al. 2013). To facilitate the implementation of both SG-AR and tympanometry, all these aspects would have to be markedly developed.

This study only compared the accuracy of SG-AR test results compared to different otoscopic diagnoses. When evaluating the overall clinical usefulness of test results of a diagnostic tool, different aspects of usefulness have to be considered (Sackett et al. 1991). A useful diagnostic tool answers to a clinically relevant question (e.g. does the child have a healthy middle ear or MEE). The obtained test results have to be accurate compared to the used diagnostic reference (i.e. pneumatic otoscopy in outpatient setting). A useful diagnostic tool would ideally differentiate between health and disease, and also distinguish borderline (equivocal) cases. In an optimal study design, the studied diagnostic test and the reference standard would be performed by different examiners. In this study, SG-AR, tympanometry, and pneumatic otoscopy were performed by the same study physician for practical reasons, i.e. only one study physician was working at a time. Furthermore, patients included in the study should represent the population to whom the obtained results are generalized, the study setting should be similar to the settings where the diagnostic tool is used, and the study groups should not differ concerning their baseline characteristics. Importantly, clinically useful diagnostic test results would be both reproducible (by the same performer and different performers) and easily interpreted (i.e. low observer variation) (Sackett et al. 1991). With a clinically useful diagnostic tool, a "normal" test result would be clearly defined, i.e. how a "normal" test result has been defined and what it means in clinical practice. Moreover, the instructions and possible special requirements for performing the test would have to be defined, and possible differences in performing the test in a study setting and in clinical practice would have to be noticed.

6.3 Tympanometry and spectral gradient acoustic reflectometry performed by nurses in the exclusion of acute otitis media (III)

The basis for studying the reliable exclusion of AOM performed by nurses is the extensive number of acute sick visits made due to suspected AOM. In many of these children, the overall condition is normal but the child has symptoms of RTI and possible nonspecific symptoms (such as irritability and night restlessness) which lead parents to

suspect AOM. If nurses could reliably rule out AOM in part of the children with a normal overall condition, then easy access of these children to a reliable ear evaluation might be enhanced, and the physicians's time might be saved for other duties. The specific aim was to analyze both the diagnostic accuracy of tympanometry and SG-AR performed by nurses and as a new practical perspective, the proportion of visits where accurate test results are obtained from both ears of the child.

The nurses' success rate with tympanometry was lower (75%) than most of the previously reported success rates (Koivunen et al. 1997, Palmu et al. 1999, Blomgren et al. 2007) but corresponded to the physicians' success rate in Study I. Factors affecting the nurses' success rate may include the young age of the children, the nurses' experience, the tympanometer chosen, and whether examinations (ears) or visits are analyzed. On the other hand, Chianese et al. (2007) have reported corresponding success rates in children of less than 2 years of age. Since young children are often quite difficult to examine, better success rates can be expected with older children (Koivunen et al. 1997). The nurses were inexperienced when starting to perform examinations, and they gradually became more experienced during the study. Thus, in clinical practice, nurses would perform better if they were already experienced with the devices when starting to perform examinations. Furthermore, the tympanometer (MicroTymp2) used in this study has been found slightly difficult to handle, and better success rates might be obtained with a more easily handled tympanometer (e.g. GSI tympanometers, Grason-Stadler, Eden Prairie, MN, USA) (Patricoski and Ferguson 2006).

Type A and C1 tympanograms (TPP >-200 daPa) and SG-AR level 1 result obtained by nurses were shown as accurate test results in excluding AOM. Even though a peaked tympanogram (type A, C1, C2, or Cs) as the exclusive result might seem to be useful, this entity includes type C2 and Cs tympanograms, which are associated with increased likelihood of MEE (Palmu et al. 2002, Smith et al. 2006). Based on this current study and Study I, C2 and Cs are "diagnostic grey area" which cannot be used to predict AOM or exclude it. Furthermore, since SG-AR level 1 results were rarely obtained from both ears of the child, SG-AR seems to be most useful as a supplementary device when tympanometry is unsuccessful or unavailable.

Type A and C1 tympanograms were obtained from both ears of the child only at one fifth of the symptomatic visits, which clearly limits the usefulness of excluding AOM with tympanometry. In the previous literature, the few studies reporting results of the exclusion of MEE by nurses have also been disappointing. Teppo et al. (2006) found that nurses could not reliably rule out MEE with SG-AR in young symptomatic children. Blomgren et al. (2007) concluded that on the basis of a brief teaching session, nurses could not be taught to reliably detect MEE with tympanometry in children undergoing tympanostomy tube placement. In contrast, this current study

showed that type A and C1 tympanograms tend to differentiate visits with and without AOM. Of the visits where nurses obtained bilateral exclusive test results, AOM was diagnosed with pneumatic otoscopy in 6%. In comparison, AOM was diagnosed with pneumatic otoscopy at 42% of the visits where bilateral type A or C1 tympanogram was not obtained by the nurses. Thus, these test results can be utilized in the exclusion of AOM.

In primary health care, trained nurses might be considered to rule out AOM when the primary concern of parents is suspected AOM and the child´s overall condition has been evaluated to be normal. Of great importance is that this study only investigated accurate exclusive test results and the proportion of visits where these test results were obtained from both ears. This study did not investigate nurses' skills in interpreting tympanograms or the implementation of the exclusion of AOM by nurses. Palmu (2002) has suggested that nurses might rule out AOM from children with RTI if bilateral tympanometry shows normal results, the child's overall condition is normal and he/she is afebrile, the parental concern is only AOM, and parents agree with this procedure. This kind of a health care process would have to be developed and validated before implementation (Palmu 2002). When symptomatic children attend primary health care, trained nurses might first complete a structured questionnaire, perform tympanometry, and give instructions concerning pain medication. If the child's overall condition was not normal, or AOM could not be ruled out with tympanometry or SG-AR, a physician would examine the child. A new examination of the child would have to be performed by a physician any time the symptoms of the child worsened. Importantly, the process should include a structured questionnaire excluding serious signs and conditions in the child.

Disappointingly, the implementation of excluding AOM by nurses would include several barriers, which would clearly reduce its usefulness. Health centres and emergency settings include a great number of nurses, who would have to learn the reliable use of tympanometry and interpretation of the obtained test results. In addition, they should be able to confirm that children do not have serious signs or conditions, i.e. they do not have a severe illness. Thus, many nurses might not want to participate in excluding AOM. Furthermore, even if nurses learned the use of tympanometry and interpretation of tympanograms, they might not have enough tympanometric examinations to maintain their skills and thus, nurses might lose their motivation to perform tympanometric examinations. Moreover, since accurate exclusive test results are rare from both ears, children would have to be examined first by a nurse and then by a physician in most cases. From the point of the health care system, a physician would have to be available to examine the children in whom the nurse could not rule out AOM. Taking all these facts into consideration, the exclusion of AOM by nurses may not be useful.

6.4 Tympanometry and spectral gradient acoustic reflectometry performed by nurses in the exclusion of middle ear effusion (IV)

The rationale for this study is based on the Finnish Current Care Guideline on the diagnosis and management of AOM (Heikkinen et al. 2010). Even though the success rate of tympanometry from both ears of the child at asymptomatic visits has not been studied, the Finnish Current Care Guideline states that routine ear controls after an AOM episode can be performed with tympanometry by physicians or nurses. If nurses could reliably perform part of routine ear controls after AOM, children's access to reliable ear examination might be faster, and physicians' time might be saved for other duties in primary health care.

Corresponding to Studies I and III, approximately three fourths of the tympanometric examinations were successful. Even though these tympanometric success rates are lower than most success rates reported in the previous literature (Table 8; Section 2.4.5.3), it is of importance that the success rate of the physicians in Study I and nurses in Studies III-IV correspond. Accordingly, the success rates of physicians and nurses with SG-AR correspond. Since nurses cannot be expected to obtain better success rates than physicians experienced with pneumatic otoscopy, the major factors reducing the tympanometric success rate seem to be the lack of cooperation of young children and the study setting. Since these study visits were part of a project examining the optimal diagnostics and management of AOM (Tähtinen et al. 2011), the study visits included several diagnostic procedures. Thus, tympanometric examinations could not be performed several times if the young child was struggling, and this might have reduced the tympanometric success rate.

Type A and C1 tympanograms obtained by the nurses were accurate test results in excluding MEE. This finding is in accordance with Study III where these test results were found to reliably exclude AOM. Somewhat surprisingly, the negative predictive values for different test results tended to be lower in this study compared to Study III. On the other hand, the frequency of MEE found in this study and the frequency of AOM in Study III were corresponding, approximately 25%. Furthermore, the number of performed examinations was lower in this study compared to Study III, and this may have resulted in slightly wider confidence intervals. Previously, Teppo et al. (2006) reported a negative predictive value of 98% for SG-AR angle values $\geq 100^{\circ}$ in excluding MEE. In their study, the frequency of MEE was lower (9%) which might explain the difference. As SG-AR level 1 results are relatively rare, SG-AR level 1 may best serve as a supplementary exclusive test result when tympanometry does not succeed or is unavailable.

Type A and C1 tympanograms were more often obtained from both ears of the child at these asymptomatic visits compared to symptomatic visits in Study III. These test

results could exclude MEE at less than half of asymptomatic visits and AOM at 20% of symptomatic visits. This difference is caused by the higher proportion of obtained type A and C1 tympanograms at asymptomatic visits compared to symptomatic visits. On the other hand, in the current study, type A and C1 tympanograms tended to differentiate visits with and without MEE. Of the visits where nurses obtained bilateral exclusive test results, MEE was diagnosed with pneumatic otoscopy in 9% compared to 56% at visits where bilateral type A or C1 tympanograms were not obtained. Thus, type A and C1 tympanograms obtained by nurses may serve as test results excluding MEE.

This study only investigated the accuracy of exclusive test results and the success rate of these examinations from both ears of the child when performed by nurses. This study did not investigate the nurses' skills to interpret tympanograms or the implementation of the process. Thus, if the exclusion of MEE performed by nurses was implemented, a health care process would have to be developed. Demonstrating the great importance of careful tympanometric training of nurses, Blomgren et al. (2007) reported relatively low diagnostic accuracy of nurses in detecting MEE with tympanometry. Blomgren et al. concluded that one training session was inadequate to qualify nurses for accurate use of tympanometry. However, in conflict with this, the nurses themselves reported that one teaching session had given them sufficient training, and that the use of tympanometry was simple. Thus, the technique and performance of nurses with tympanometry would have to be carefully evaluated to guarantee the reliable exclusion of MEE.

The implementation of excluding MEE by nurses would include several barriers. Health centres include great number of nurses, who would have to learn the reliable use of tympanometry and interpretation of obtained test results. However, when considering the acceptability of this kind of process from the nurses' point of view, examining healthy children might be easier than examining acutely sick children. In addition, routine ear controls might be performed by certain nurses, who would become experienced at using the technique. However, even if only a proportion of nurses performed routine ear controls, the number of these visits might be too low to maintain nurses' skills and motivation with tympanometry in a setting where the number of children in the population is low. Thus, this process would probably be useful only in settings with high frequency of routine ear controls. From the perspective of the family, the child would have to be examined first by a nurse and then by a physician at more than half of visits. Thus, if implemented, the usefulness of excluding MEE by nurses would have to be carefully analyzed. The facilitating factors for excluding MEE as performed by nurses might include well-organized training of nurses, frequent workshops to support and maintain nurses' tympanometric skills, and evaluation of the nurses' tympanometric performance and the usefulness of the process (i.e. which proportion of the routine ear controls nurses actually manage to perform).

6.5 Limitations and strengths of Studies I-IV

In Studies I-IV, pneumatic otoscopy instead of tympanocentesis was used as the diagnostic standard. However, since tympanocentesis is painful and used only in complicated cases of AOM, pneumatic otoscopy is the only diagnostic standard which was justified.

Concerning Studies I-II, SG-AR and tympanometry were performed before pneumatic otoscopy by the same physician who performed pneumatic otoscopy. Thus, SG-AR and tympanometric results may have influenced the evaluation of the pneumatic otoscopic findings. However, video-otoscopy was used to guarantee the objective evaluation of otoscopic findings, and interobserver agreement of physicians was analyzed and found to be excellent. Of note, this order of diagnostic procedures was selected to allow the evaluation of the true success rates of SG-AR and tympanometry performed by physicians and nurses. If pneumatic otoscopy and cerumen removal had been performed before SG-AR and tympanometry, the proportion of uncooperative children would have been substantially higher and would not have reflected the clinical practice in primary health care. In fact, this order of diagnostic ear examinations is also the order of examinations at primary health care visits.

Since Studies I-IV were part of a project investigating the optimal diagnostics and management of AOM, the study visits included several diagnostic procedures. Thus, SG-AR and tympanometry by nurses and physicians could not be performed several times if the child struggled during these examinations. Therefore, slightly higher success rates might be obtained at primary health care visits where only a few diagnostic procedures are performed. On the other hand, the challenges of performing several diagnostic procedures may be one of the barriers that cause tympanometry to be rarely performed in primary health care. Further, at visits in the study clinic, the children actually learned to know the nurses and physicians, and this might have increased the success of tympanometric and SG-AR examinations in some children.

As a limitation in Studies III-IV, the nurse performed examinations when she was available, i.e. was not handling other tasks in the project. Thus, more data could have been collected if the nurse had been present at all the study visits. In addition, only a few nurses performed SG-AR and tympanometric examinations. Demonstrating the everyday practice, the nurse who performed the lowest number of tympanometric examinations also had the lowest success rate. Thus, in clinical practice, nurses' success rates might improve when they become experienced with tympanometry. However, nurses in primary health care would be unlikely to become as experienced with tympanometry as the study nurses who performed tympanometry several times per day. Maintaining the nurses' skills in performing routine ear controls with tympanometry is of great importance and could be a barrier for the exclusion of MEE unless regular support is arranged.

The nurses' skills in interpreting tympanograms or the implementation of a health care process were not studied, and cannot be evaluated on the basis of this study. The children were examined in the study clinic at a primary health care level. However, the study clinic is likely to differ from a health centre, i.e. not all families are willing to participate in a study. Thus, the real clinical usefulness of routine ear controls performed by nurses would have to be studied in a health centre.

The major strength of Studies I-IV is the study population consisting of young outpatients of 6-35 months of age. These children were at the age where most AOM episodes are diagnosed. In addition, Studies I and II included more than 4000 performed examinations.

The quality of reference diagnostics by trained otoscopists was a further strength of Studies I-IV. Otoscopists were also analyzed as having excellent interobserver agreement. Furthermore, strict predefined diagnostic criteria on AOM and OME were used together with video otoscopy to guarantee the objective evaluation of otoscopic findings. Finally, the study population consisted of the whole spectrum of otoscopic findings: healthy middle ears, middle ears with only small amounts of MEE, middle ears full of MEE, middle ears with air-fluid interface AOM, and AOM in which the tympanic membrane was severely bulging.

7. SUMMARY AND CONCLUSIONS

The diagnosis of AOM is challenging in young, often uncooperative children less than 3 years of age. On the other hand, the incidence of AOM is highest among these children. In addition, the diagnoses of AOM and OME are complicated because they are not definitive diagnoses but form a spectrum of varying otoscopic findings. To clarify the definition of AOM, a bulging position of the tympanic membrane has been adopted as the main criterion for the diagnosis of AOM. Furthermore, tympanometry as a supplementary tool for pneumatic otoscopy may reduce false positive diagnoses of AOM.

In this thesis, type B tympanograms and SG-AR level 5 results (<49˚) obtained by physicians reliably predicted the presence of MEE. On the other hand, pneumatic otoscopy visualizing bulging and other acute inflammatory signs on the tympanic membrane was needed for diagnosing AOM. At symptomatic visits, pneumatic otoscopy was needed to verify a healthy middle ear. At asymptomatic visits, type A and C1 tympanograms (TPP >-200 daPa) and SG-AR level 1 result (>95˚) indicated a healthy middle ear.

The diagnostic accuracies of physicians and trained nurses with tympanometry and SG-AR corresponded. The more experience nurses had with these devices, the higher their tympanometric success rate. Type A and C1 tympanograms obtained by nurses were accurate in excluding AOM at symptomatic visits and MEE at asymptomatic visits. As a new practical perspective, the nurses obtained type A or C1 tympanogram from both ears of the child at 20% of symptomatic visits and 41% of asymptomatic visits. SG-AR level 1 results were rarely obtained from both ears of the child, which limits the usefulness of SG-AR.

As a message for policy makers, tympanometry and SG-AR are useful diagnostic tools to support pneumatic otoscopy, and their use should be encouraged especially when there is diagnostic uncertainty in pneumatic otoscopy. The nurses in the study clinic in outpatient setting obtained tympanometric results reliably excluding AOM at one fifth of symptomatic visits, and results excluding MEE at less than half of asymptomatic visits. Nurses' skills in interpreting tympanograms or the implementation of a health care process were not studied, and these would be interesting aims for future research in primary health care. The exclusion of AOM by nurses would probably have several barriers, including the rarity of exclusive test results, differentiating children with serious illnesses, and maintaining nurses' tympanometric skills. Further, since accurate exclusive test results are rare from both ears of the child, the majority of children would have to be examined first by a nurse and then by a physician. Thus, the exclusion of AOM performed by nurses may not be useful. On the other hand, nurses might be able to perform a proportion of routine ear controls (i.e. rule out MEE in healthy children)

in settings with high frequency of ear control visits. Concerning future research, the proportion of ear control visits that nurses can successfully perform in primary health care as well as the barriers and facilitators for the process would be interesting study aims. Furthermore, future research is required to investigate whether routine ear controls after an AOM episode are actually needed for normal hearing and development of speech in otherwise healthy children. Finally, uniform diagnostic criteria for AOM and OME would be crucial for optimal management and research.

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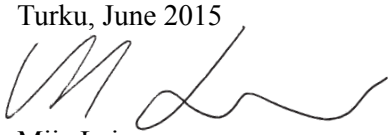

Miia Laine

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