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CHILDHOOD OTITIS MEDIA

Risk factors and surgical management

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Academic Dissertation

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To my Family

ABSTRACT

Background: Otitis media (OM) is one of the most common childhood diseases. Approximately every third child suffers from recurrent acute otitis media (RAOM), and 5% of all children have persistent middle ear effusion for months during their childhood. Despite numerous studies on the prevention and treatment of OM during the past decades, its management remains challenging and controversial. In this study, the effect of adenoidectomy on the risk for OM, the potential risk factors influencing the development of OM and the frequency of asthma among otitis-prone children were investigated.

Subjects and methods: One prospective randomized trial and two retrospective studies were conducted. In the prospective trial, 217 children with RAOM or chronic otitis media with effusion (COME) were randomized to have tympanostomy with or without adenoidectomy. The age of the children at recruitment was between 1 and 4 years. RAOM was defined as having $\geq$3 episodes of AOM during the last 6 months or $\geq$5 episodes of AOM during the last 12 months. COME was defined as having persistent middle ear effusion for 2-3 months. The children were followed up for one year. In the first retrospective study, the frequency of childhood infections and allergy was evaluated by a questionnaire among 819 individuals. In the second retrospective study, data of asthma diagnosis were analysed from hospital discharge records of 1616 children who underwent adenoidectomy or had probing of the nasolacrimal duct.

Results: In the prospective randomized study, adenoidectomy had no beneficial effect on the prevention of subsequent episodes of AOM. Parental smoking was found to be a significant risk factor for OM even after the insertion of tympanostomy tubes. The frequencies of exposure to tobacco smoke and day-care attendance at the time of randomization were similar among children with RAOM and COME. However, the frequencies of allergy to animal dust and pollen and parental asthma were lower among children with COME than those with RAOM. The questionnaire survey and the hospital discharge data revealed that children who had frequent episodes of OM had an increased risk for asthma.

Conclusions: The first surgical intervention to treat an otitis-prone child younger than 4 years should not include adenoidectomy. Interventions to stop parental smoking could significantly reduce the risk for childhood RAOM. Whether an otitis-prone child develops COME or RAOM, seems to be influenced by genetic predisposition more strongly than by environmental risk factors. Children who suffer from repeated upper respiratory tract infections, like OM, may be at increased risk for developing asthma.

TIIVISTELMÄ

Taustaa: Välikorvatulehdukset ovat yksi tavallisimmista lasten sairauksista. Arviolta joka kolmas lapsi sairastaa toistuvia akuutteja välikorvatulehduksia ja 5%:lla kaikista lapsista on pitkittyneitä jopa kuukausia kestäviä eritejaksoja välikorvissa. Lukuisista viimeaikaisista välikorvatulehdusten ehkäisyyn ja hoitoon keskittyneistä tutkimuksista huolimatta taudin hoitolinjat eivät ole vakiintuneet. Tässä väitöskirjassa selvitettiin kitarisan poiston vaikutusta välikorvatulehdusten ehkäisyssä. Lisäksi selvitettiin välikorvatulehduksen kehittymiseen johtavia riskitekijöitä. Koska välikorvatulehduksia sairastavat lapset altistuvat usein lukuisille ylähengitystieinfektioille, haluttiin selvittää niiden yhteyttä astman ilmaantuvuuteen.

Aineisto ja menetelmät: Väitöskirjatutkimus koostuu yhdestä satunnaistetusta seurantatutkimuksesta ja kahdesta retrospektiivisestä epidemiologisesta aineistosta. Satunnaistetussa osiossa 217 toistuvista korvatulehduksista tai liimakorvatautia sairastavaa lasta satunnaistettiin joko tärykalvoputkitusryhmään tai tärykalvoputkitukseen kitarisan poistoon yhdistettynä. Lapset olivat 1-4-vuotiaita. Toistuvina korvatulehduksina pidettiin vähintään kolmea akuuttia välikorvatulehdusta edeltävän 6 kuukauden aikana tai vähintään 5 tulehdusta edeltävän 12 kuukauden aikana. Liimakorvatauti määriteltiin pitkittyneenä vähintään 2-3 kuukautta kestäneenä välikorvaeritelöydöksenä. Tutkimuslasten seuranta-aika oli yksi vuosi. Ensimmäisessä retrospektiivisessä osiossa kysyttiin 819 tutkittavalta heidän lapsuuden aikaisia infektioitaan ja allergioitaan. Toisessa retrospektiivisessä osiossa analysoitiin HUS Silmäkorvasairaalan poistorekistereistä kitarisan poiston tai kyyneltiesondeerauksen läpikäyneen 1616 lapsen astmadiagnoosit.

Tulokset: Kitarisan poisto ei tuonut lisäarvoa akuuttien välikorvatulehdusten ehkäisemisessä. Vanhempien tupakointi havaittiin merkittäväksi riskitekijäksi toistuville välikorvatulehduksille, myös tärykalvoputkituksen jälkeen. Liimakorvatautia sairastavien lasten vanhemmilla oli vähemmän eläin- ja siitepölyallergioita ja astmaa kuin toistuvia välikorvatulehduksia sairastavien lasten vanhemmilla. Välikorvatulehduksia sairastavilla lapsilla todettiin enemmän astmadiagnooseja kuin verrokkilapsilla.

Johtopäätökset: Kitarisan poistoa ei suositella ensimmäiseksi leikkaustoimenpiteeksi alle 4-vuotiaiden lasten pelkkien välikorvatulehdusten ehkäisyssä tai hoidossa. Koska vanhempien tupakointi lisää lasten välikorvatulehdusten riskiä merkittävästi, tulisi vanhempien tupakoinnin lopettamista kannustaa ponnekkaasti. Atooppinen perimä näyttää vaikuttavan ympäristötekijöitä enemmän siihen sairastuuko välikorvatulehduksille altis lapsi toistuviin korvatulehduksiin vai liimakorvatautiin. Toistuvia ylähengitystieinfektioita kuten välikorvatulehduksia sairastavat lapset saattavat olla suuressa riskissä sairastua astmaan.

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ABBREVIATIONS

AOM	acute otitis media
CI	confidence interval
COME	chronic otitis media with effusion
ET	Eustachian tube
IL	interleukin
Ig	immunoglobulin
MALT	mucosa-associated lymphoid tissue
MEE	middle ear effusion
NNT	number needed to treat
OM	otitis media
OME	otitis media with effusion
OR	odds ratio
PCR	polymerase chain reaction
Pnc	*Streptococcus pneumoniae*, pneumococcus
QOL	quality of life
RAOM	recurrent acute otitis media
RCT	randomized controlled study
RR	relative risk, risk ratio
RSV	respiratory syncytial virus
URI	upper respiratory tract infection
WW	watchful waiting

ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by the Roman numerals I to IV.

I Hammarén-Malmi S, Saxen H, Tarkkanen J, Mattila PS: Adenoidectomy does not significantly reduce the incidence of otitis media in conjunction with the insertion of tympanostomy tubes in children who are younger than 4 years: a randomized trial. Pediatrics; 116:185-189, 2005.

II Hammarén-Malmi S, Saxen H, Tarkkanen J, Mattila PS: Passive smoking after tympanostomy and risk of recurrent acute otitis media. International Journal of Pediatric Otorhinolaryngology; 71: 1305-1310, 2007.

III Hammarén-Malmi S, Tarkkanen J, Mattila PS: Analysis of risk factors for childhood persistent middle ear effusion. Acta Oto-Laryngologica; 125: 1051-1054, 2005.

IV Mattila PS, Hammarén-Malmi S, Tarkkanen J, Saxen H, Pitkäniemi J, Karvonen M, Tuomilehto J: Adenoidectomy during early life and the risk of asthma. Pediatric Allergy and Immunology; 14: 358-362, 2003.

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1. INTRODUCTION

Otitis media (OM) is one of the most common medical problems of childhood. It is the leading cause for office visits (Teele et al. 1983), a common reason for prescribing antibiotics (McCaig and Hughes 1995) and the most frequent reason that children undergo surgery (Derkay 1993). Moreover, it causes both direct and indirect financial losses to the families and to the community, comprising approximately 5 billion dollars in the United States and 100 million euros in Finland annually (Bondy et al. 2000, Niemelä et al. 1999).

There are many challenges in the management of an otitis-prone child. Increasing antibiotic consumption has been shown to be related to the emerging phenomenon of antimicrobial resistance (Cristino 1999). Besides pain and other acute symptoms, OM episodes impair hearing because the middle ear is filled with effusion. Prolonged or fluctuating hearing impairment in early childhood may result in long-term consequences for speech and language development (Luotonen et al. 1996, Teele et al. 1990). Prevention of OM by risk factor modification is attractive because it diminishes the costs and the side-effects of antimicrobial therapy and surgery. Despite numerous studies on OM-related topics, many unanswered questions remain.

2. REVIEW OF THE LITERATURE

2.1. Otitis media in young children

2.1.1. Terminology, definitions and classification

During the past 30 years, much effort has been devoted to the terminology, definitions and classification of otitis media (OM). After the first international symposium specifically addressing middle ear diseases in May 1975 (Paparella 1976), an updating research conference has been held every fourth year. The data presented in Table 1 are based on panel reports of the seventh meeting in 1999 (Gates et al. 2002).

Table 1. Terminology and definitions of otitis media.

Term	Definition
Otitis media (OM)	Inflammatory condition of the middle ear, regardless of aetiology or pathogenesis
Acute otitis media (AOM)	Rapid onset of signs and symptoms of an acute infection of the middle ear with middle ear effusion
Otitis media with effusion (OME)	Inflammation of the middle ear with middle ear effusion without symptoms and signs of an acute infection
Middle ear effusion (MEE)	Liquid in the middle ear. The effusion may be serous, mucoid, purulent or a combination of these
Recurrent AOM (RAOM)	Three or more episodes of acute otitis media within the preceding 6 months or 4 or more episodes in a year (Bluestone and Klein 1995)
Chronic otitis media with effusion (COME)	Inflammation of the middle ear with middle ear effusion longer than 3 months without symptoms and signs of an acute infection

Classification. OM can occur in different forms of varying severity, and its physical appearance changes with time. Acute otitis media (AOM) and chronic otitis media with effusion (COME) represent the extremes of the continuum of OM. After the pain and other acute symptoms of AOM subside, inflammatory middle ear effusion (MEE) may persist from a few days to months. This form of OM is called otitis media with effusion (OME). Sometimes persistent MEE may present without a preceding episode of AOM (Alho et al. 1995a). Persistent MEE may be further classified by the duration of the effusion as acute (less

than 3 weeks), subacute (from 3 weeks to 3 months) or chronic (longer than 3 months)(Gates et al. 2002). Synonyms of COME include secretory otitis media and glue ear disease.

2.1.2. Epidemiology

Limitations when analysing data from various studies. Study designs, population selections, subject numbers and observation periods vary widely in different epidemiological studies. The occurrence of OM is measured differently; some studies consider only the number of symptomatic episodes of AOM, while others count the days when effusion is present in the middle ear. Most notably, the diagnosing techniques vary among studies. Some studies base their results on objective clinical findings, while others rely on information obtained from parents. Apparently, the incidence of OM varies from population to population and depends on socio-economic, environmental, genetic and lifestyle factors.

Otitis media – a disease of infancy and early childhood. In one study, OM was the most common diagnosis during office visits among children aged under 15 years, accounting for 12% of all diagnoses, and the number was even higher among 1- to 4-year-olds, comprising 18% of all diagnoses in the United States between 1993 and 1995 (Freid et al. 1998). Another large study conducted in Greater Boston, USA, showed that every third visit to primary care centres during the first five years of life was due to OM (Teele et al. 1983). OM was also the primary reason for dispensing antibiotics in the United States, accounting for 17-25% of all oral antibiotics prescribed in 1985, 1989 and 1992 (McCaig and Hughes 1995).

The occurrence of OM has also been estimated in a prospective study carried out in the United States. This study involved 2253 infants followed up until the age of 2 years. Both symptomatic and asymptomatic MEE were recorded by follow-up visits at least monthly. At least one episode of OM developed in 48% of infants by the age of 6 months, in 79% by the age of 1 year and in 91% by the age of 2 years (Paradise et al. 1997). Surveys of healthy children have shown that almost all children have had MEE at least once before school age, but it usually resolves without medical intervention within 3-5 months (Fiellau-Nikolajsen 1983, Lous and Fiellau-Nikolajsen 1981, Tos and Poulsen 1979a, Tos et al. 1979b, 1982, Williamson et al. 1994, Zielhuis et al. 1989, 1990b).

The peak incidence of AOM is found between the ages of 6 and 18 months (Alho et al. 1991a, Lundgren and Ingvarsson 1983, Sipilä et al. 1987, Teele et al. 1989). The proportion of children who have had at least one episode of AOM before 1 year of age has been reported to be 32-62%, and before 2 years of age 42-80% (Casselbrant et al. 1995, Teele et al. 1980, 1989). Surveys of Finnish children have verified that 28-45% experience at least one episode of AOM before

their first birthday (Alho et al. 1991a, Pukander et al. 1982b, Sipilä et al. 1987), and 71% before their second birthday (Alho et al. 1991a). Children who have had few or no AOM episodes by 3 years of age are unlikely to contract severe middle ear infections (Darrow et al. 2003).

Recurrent AOM is common, affecting nearly 20% of children by 1 year of age and approximately one-third of children by the age of 3 years (Sipilä et al. 1987, Teele et al. 1989). These children can be called 'otitis-prone' (Howie et al. 1975).

Persistent MEE leading to COME is most frequent at the age of 16 months to 2 years (Zielhuis et al. 1990a). The exact occurrence of COME is difficult to determine because many COME episodes may go undiagnosed (Faden et al. 1998). In a Finnish cohort study of 2512 children in the mid-1980s, cumulative incidence of COME up to the age of 24 months was 4.4%, with most children (84%) having had an episode of AOM before the onset of COME. However, in only half of the cases was COME definitively considered to be a direct continuation of a symptomatic AOM episode (Alho et al. 1995a).

Temporal trends in the incidence of OM. During the past decades, the incidence of childhood OM appears to be on the rise. This trend may also reflect changes in access to health care systems and in increased awareness of the disease. A retrospective review in the United States reported that the number of office visits due to OM among children under age 15 has more than doubled from 9.9 million in 1975 to 24.5 million in 1990 (Schappert 1992). A more recent survey also from the United States showed the same trend; in 1980, the annual office visit rate per population of 1000 was 250, whereas in 1992 this was 450 (McCaig and Hughes 1995). A Finnish retrospective study found a 68% increase in the occurrence of AOM among children under 10 years of age between the years 1978-1979 and 1994-1995 (Joki-Erkkilä et al. 1998).

The annual number of antimicrobial drugs prescribed for OM has also clearly increased. Altogether 11.9 million prescriptions were written due to of OM in the United States during 1980, and this figure rose to 23.6 million in 1992 (McCaig and Hughes 1995). Tympanostomy tube insertion rates in the United States have increased 4-fold between 1970 and 1990 (Daly et al. 1999a, Daly and Giebink 2000). The number of surgical procedures (adenoidectomy and/or tympanostomy tube insertion) for OM has risen in Finland during the last decades. It doubled between 1978-1979 and 1994-1995 (Joki-Erkkilä et al. 2000) and increased 1.5-fold between 1987 and 2002 (Haapkylä et al. 2006). According to the latter study, the number of tympanostomies has increased 2.6-fold from 1987 to 2002. In a study based on parental reporting, the proportion of children younger than 5 years with RAOM increased from 19% to 27% between

1981 and 1988. In this survey, the greatest increase occurred in infants younger than 12 months (Lanphear et al. 1997).

2.1.3. Pathogenesis of otitis media

The pathogenesis of OM is complex and multifactorial. OM is mainly an infectious disease, resulting from a continuous interplay between host immune responses and environmental microbial load. The Eustachian tubes (ETs), or more precisely their anatomy and function, have a crucial role in the pathogenesis of OM because microbes of the nasopharynx invade the middle ear through the ET. The microbial load is influenced by such environmental factors as day-care attendance, number of siblings and season, whereas the host immune responses are influenced by such factors as genetic predisposition, age and atopy. Infants' and young children's immune systems are immature and their ETs are structurally and functionally different from those of adults. When children are exposed to microbes that cause upper respiratory tract infections, OM is a common sequalae.

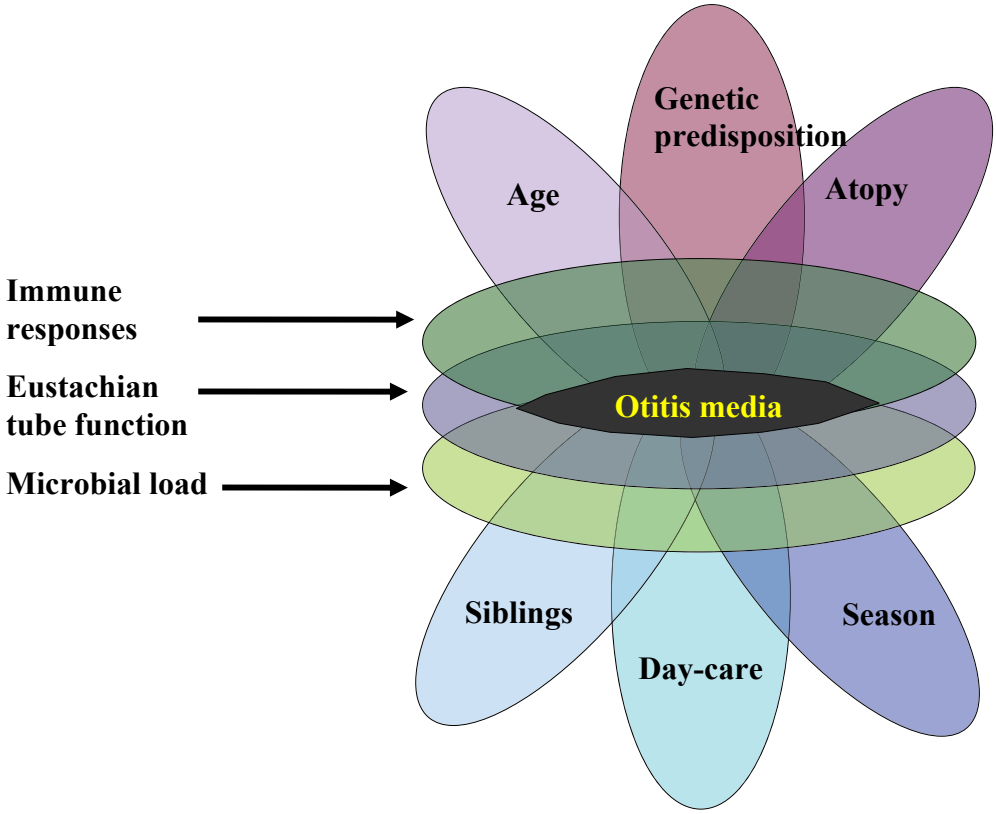


Figure 1. Pathogenesis of otitis media. Modified from Rovers et al. 2004.

2.1.3.1. Anatomy of the nasopharynx, Eustachian tube, middle ear and mastoid process

The nasopharynx lies behind the nasal cavities and above the soft palate. It is connected to the middle ear cavities by the ETs. The ETs are complex organs consisting of a lumen with mucosa, surrounding soft tissue, peritubal muscles and superior bony support. On the posterior wall of the nasopharynx and underneath the orifices of the ETs lies the nasopharyngeal tonsil, i.e. the adenoid, which is composed of abundant lymphoid tissue. The middle ear cavities are normally air-filled spaces free of microbes lying within the temporal bones (Bluestone and Klein 1995, Bluestone 1996). The ETs differ in length and angle between children and adults, being shorter and more horizontal in children aged under 7 years compared with adults (Ishijima et al. 2000, Proctor 1967, Sadler-Kimes et al. 1989).

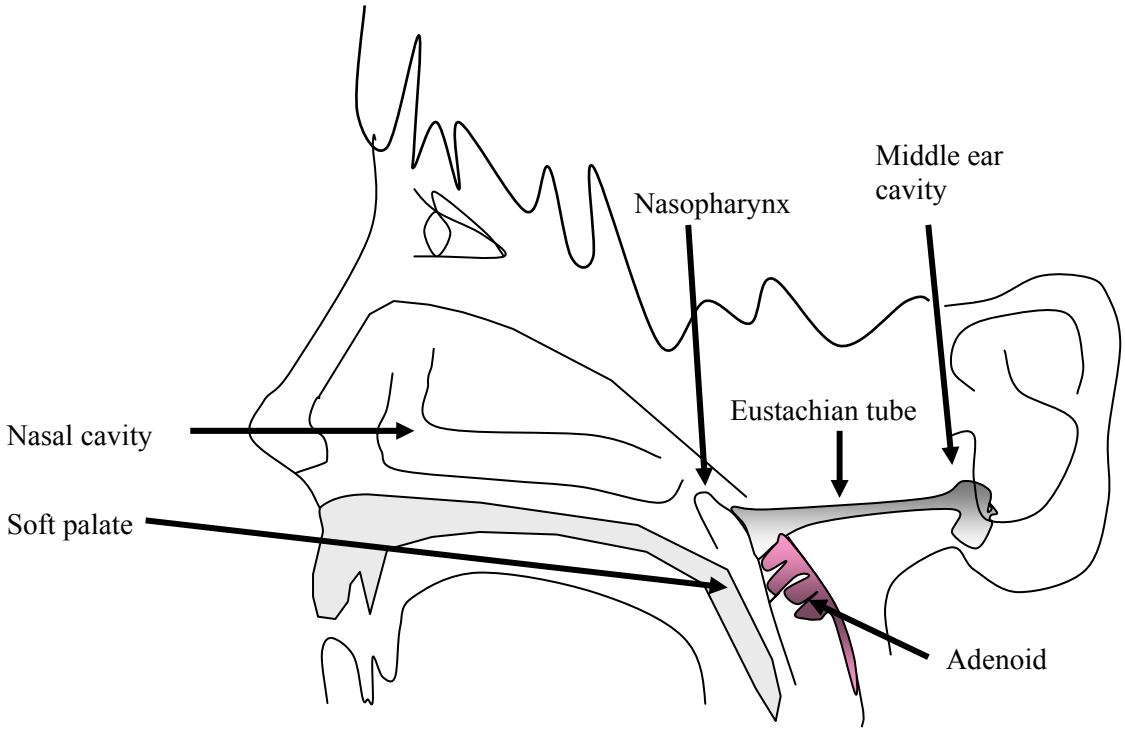


Figure 2. Anatomy of the nasopharynx, Eustachian tubes and middle ear.

The mucosal lining of ETs is similar to that of the nasal cavities and the nasopharynx, being characterized as a respiratory ciliated pseudo-stratified columnar epithelium with mucus-producing cells. This epithelium may continue into the anterior part of the middle ear cavity. Most of the epithelium of the middle ear and mastoid process consists of simple squamous or cuboidal cells, with a few mucus-producing elements (Michaels 1990). However, upon chronic inflammation, e.g. in COME, the epithelium of the middle ear undergoes progressive metaplasia with an increasing number of mucus-producing goblet cells (Rinaldo and Ferlito 2000).

2.1.3.2. Physiology and pathophysiology of the Eustachian tubes

The ETs have at least three physiological functions with respect to the middle ear: 1) pressure regulation and ventilation, 2) drainage of secretions produced in the middle ear and 3) protection from nasopharyngeal secretions, including pathogens, and from sound pressure.

The ETs are usually loosely closed. Swallowing, yawning or sneezing opens them momentarily, thereby permitting the air pressure between the middle ear cavities and the nasopharynx to equilibrate. Active dilatation of the lumen is induced mainly by contraction of the peritubal tensor veli palatini muscle (Huang et al. 1997). The ETs drain secretions produced in the middle ear and ET into the nasopharynx. This is achieved through mechanical opening of the ETs and more importantly by the active mucociliary function in the ETs and some areas of the middle ear mucous membrane (Bluestone and Klein 1995, Bluestone 1996).

The mucociliary system of the ETs and the secretions produced by epithelial cells both in the ET and in the middle ear create a highly effective barrier against invading pathogens. The molecules in the secretions include lubricating and virus-trapping mucins, surface-active surfactants and anti-microbial proteins that are part of the innate immune system (Lim et al. 2000).

Abnormal function of the ETs is considered one of the most important factors in the pathogenesis of OM in all age groups. Dysfunction of ETs can result from an impairment of any or all of their physiological functions. Mechanical obstruction may be caused by inflammation of the periluminar tissue due to infection or allergy. It can also be caused by an adenoidal mass or a tumour compressing their orifice. Functional obstruction, i.e. failure of the opening mechanism of ETs, can be related to the poor function of the tensor veli palatini muscle. This can be seen clearly in children with cleft palate. Functional obstruction may also be caused by dysfunction of the mucociliary system. In fact, children with immotile ciliary system (Kartagener´s syndrome) develop chronic sinusitis and OM easily (Mygind and Pedersen 1983). The mucociliary system may also be impaired by infections. Viral infections can cause

negative middle ear pressure that is associated with ciliary damage, disappearance of epithelial cells and increased accumulation of mucus and cellular debris into the tubal lumen (Giebink et al. 1987, Park et al. 1993). Respiratory allergy is another mechanism that can cause impairment of ET function. Function of the ETs may also be impaired by an abnormal position, shortness or patency of the tube (Bluestone 1996).

Even in otologically normal children aged 3-7 years, Eustachian tube function is poorer than in older children or adults (Bylander 1980, Stenström et al. 1991). Failure in the pressure regulation and ventilation of the middle ear can be related to less effective function of the tensor veli palatini muscle in children. Muscle function improves when the child becomes older, as both the amount and the stiffness of the ET cartilage support increase. The protective function also improves when the length and angle of the ET increase (Bluestone and Klein 1995).

2.1.3.3. Immune system

The main function of the immune system is to distinguish entities within the body as "self" or "non-self" and to eliminate those that are non-self. Microbes are the principal non-self entities. Structurally, the immune system is a network of lymphoid organs and interacting cells that work together. Functionally, the immune system can be divided into two parts: 1) the innate immune system, which is responsible for the initial recognition of the pathogen; its responses are non-specific and rapid, but do not develop immunologic memory and 2) the adaptive immune system, which has the ability to adapt to foreign antigens and to remember these upon a future challenge. The innate and adaptive immune systems are linked together by complex mechanisms of regulatory interactions.

2.1.3.3.1. Structure and function of the immune system

Lymphoid organs and their function. Lymphoid organs are positioned throughout the body. They are divided into two groups – primary and secondary. The primary lymphoid organs, i.e. the bone marrow and the thymus, are the sites of initial lymphocyte differentiation. Spleen, lymph nodes, and mucosa-associated lymphoid tissues (MALT) belong to the group of secondary lymphoid organs. The Peyer's patches of the gut and the Waldeyer's ring in the oropharynx are part of the MALT. The Waldeyer's ring, which includes the palatine (commonly called tonsils), nasopharyngeal (commonly called adenoid) and lingual tonsils, is the primary site of contact of pathogens of the upper respiratory tract with the lymphocytes (Paraskevas 2004).

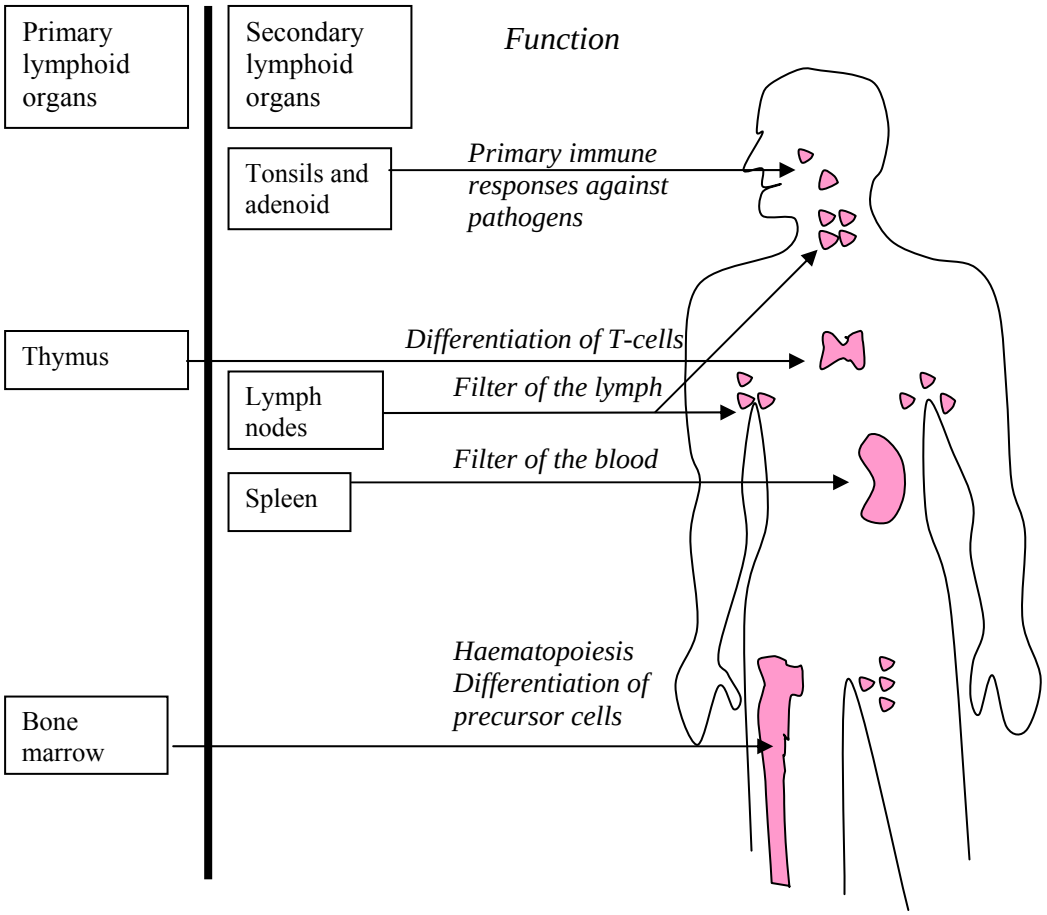


Figure 3. Lymphoid organs and their function.

Cells of the immune system and their function. Cells of the innate immune system form the first line of defence. They bind to the microbes by the so-called pattern recognition receptors and depending on the cell either destroy or process them further and present them to B- and T-lymphocytes (Skubitz 2004), which are central to all adaptive immune responses. Mature B-cells can differentiate into plasma cells, which produce soluble antigen receptors called antibodies, i.e. immunoglobulins (Ig), or into B-memory cells. Different immunoglobulins can bind to a particular antigen and participate in the elimination of foreign antigens. IgG is the major immunoglobulin in normal adult serum, accounting for 75% of the total pool, followed by IgA (15%), IgM (10%), IgD (<1%) and IgE (<1%) (Bluestone and Klein 1995, Roitt et al. 1998).

Mature T-cells can differentiate into various cell types and are categorized by their surface markers. A subset which carries the CD4 surface marker (Th cells) mainly helps or induces immune responses, and a subset that carries the CD8 marker (Tc cells) is predominantly cytotoxic. Furthermore, depending on the secreted cytokines the Th cells can be divided into two groups. Th1 cells secrete interleukin 2 (IL-2) and interferon-γ and interact with

phagocytes, helping them to destroy intracellular pathogens, e.g. viruses, bacteria and parasites. Th2 cells produce IL-4, IL-5, IL-6 and IL-10 and stimulate B-cells to start antibody production. Cytokines from Th1 cells inhibit the actions of Th2 cells, and vice versa. T-regulatory cells can regulate the responses of other T-cells. All T-cells generate their effects by releasing soluble proteins, cytokines, or by direct cell-cell interactions. B-memory cells can rapidly proliferate and differentiate into immunoglobulin-producing plasma cells upon a new contact with a previously encountered antigen (Paraskevas 2004). Cytokines, which regulate B- and T-cells, include interferons, interleukins, chemokines, colony-stimulating factors, tumour necrosis factors and various growth factors.

2.1.3.3.2. Local immunity in the nasopharynx and in the middle ear

The most prominent tissue containing lymphocytes in the pharynx is the adenotonsillar tissue. It contains lymphoid follicles, and its macroscopic structure resembles that of lymph nodes (Pajusto et al. 2005). Every child is born with adenotonsillar tissue confirming its important role since it has been preserved during evolution. However, the exact function of the adenotonsillar tissue as part of the immune system is incompletely understood. Of interest is the anatomical location of the adenoid and the tonsils. The adenoid is critically located in the nasopharynx to confront inhaled antigens, whereas the tonsils are located in the oropharynx, an ideal location to meet digested agents. The size of the human adenoid reaches its maximum at the age of 7-10 years, after which it gradually undergoes almost complete involution, typically being very small or absent in adults (Vogler et al. 2000). The behaviour of the tonsils follows a similar pattern, except that the involution is less evident. Children who have undergone adenoidectomy, tonsillectomy or both do not lack any immunological functions and are apparently healthy. This suggests that adenotonsillar tissue may have its most important functions during the first months of life, when adenotonsillar surgery is seldom performed.

Plasma cells in the salivary glands and in the epithelium lining the respiratory tract generate IgA. Two IgA molecules combine with another protein known as the secretory component, and the complex (SIgA) is transported through the cell and into the lumen. These complexes form the first-line barrier against invading microbes (Bluestone and Klein 1995, Roitt et al. 1998).

Infection in the middle ear during AOM is accompanied by the accumulation of MEE. MEE contains neutrophils, macrophages, lymphocytes, immunoglobulins, complement, immune complexes of antigen and antibody and various chemical mediators of inflammation (Bluestone and Klein 1995). The resolution of MEE is thought to occur via the recognition of pathogens by specific immunoglobulins that help neutrophils and other phagocytic cells to digest and

eliminate them. These phagocytic processes may be hindered by the formation of a microbial biofilm, which consists of microbial exopolysaccharides and host molecules, such as fibrin and cellular debris. The formation of such biofilms is hypothesized to prolong the clearance of MEE, which in turn may lead to the formation of COME. The formation of biofilm makes it difficult to isolate the pathogen by bacterial culture (Ehrlich et al. 2002, Lim et al. 2000, Post 2001).

2.1.3.3.3. Immune status of children

Maternal IgG is actively transported across the placenta during gestation, and its concentration is similar at birth as in adults. It disappears gradually by the age of 6-8 months. Some maternal IgA is acquired from breast milk. IgM, IgG and IgA productions start slowly around birth. Thereafter, immunoglobulin concentrations continue to increase during childhood, reaching adult levels at 2-7 years (Roitt et al. 1998). This phenomenon may reflect the fact that children do not generate a good serum immune response to polysaccharide antigens prior to the age of 2 years, as pneumococcal capsular polysaccharide vaccination studies have demonstrated (Kalm et al. 1986). Local IgA activity seems to be significantly lower in children than in adults, suggesting that local immunity is not fully developed in young children (Lindberg et al. 1993).

2.1.4. Microbiology

2.1.4.1. Colonization of the nasopharynx

Bacteria colonize the nasopharynx of infants soon after birth. Most of the bacteria of the nasopharyngeal normal flora, such as *Streptococcus viridans* are non-pathogenic, but some are potentially pathogenic. Of these, *Streptococcus pneumoniae* (*S. pneumoniae,* pneumococcus, Pnc), non-typable *Haemophilus influenzae (H. influenzae)*, and *Moraxella catarrhalis (M. catarrhalis)* are the most important.

Otitis-prone children tend to be colonized by pathogenic bacteria more often than non-otitis-prone children (Bernstein et al. 1993, Dhooge et al. 2000, Freijd et al. 1984). The rate of colonization by pathogenic bacteria predicts the onset and persistence of OM, as shown in studies among Australian Aboriginal infants (Leach et al. 1994, Smith-Vaughan et al. 1997). The earlier the child gets colonized with pathogenic bacteria, the higher the risk for OM. Infants colonized by pathogenic bacteria at less than 3 months of age are at an increased risk for OM (Faden et al. 1997).

The circumstances necessary for an organism colonizing the nasopharynx to gain access to the middle ear with inflammatory disease are uncertain but likely include co-infection with viruses (Bluestone and Klein 1995, Murphy 2000). *H. influenzae* colonization, as measured by concentration of bacteria in the nasopharynx, has been reported to be increased in cotton rats infected with respiratory syncytial virus (RSV) (Patel et al. 1992), and the same result was found in chinchillas with pneumococcal colonization and influenza A virus (Tong et al. 2000). Viruses have been reported to increase the adherence of bacteria to human epithelial cells in vitro (El Ahmer et al. 1999b, Håkansson et al. 1994, Jiang et al. 1999), as well as in adult volunteers (Fainstein et al. 1980). Pneumococcal colonization, as measured by the density of growth in the nasopharynx, has been reported to be increased in adult patients infected with influenza A virus (Wadowsky et al. 1995). These studies show that viral infections strongly influence the nasopharyngeal colonization of pathogenic bacteria.

2.1.4.2. Pathogenic viruses and bacteria

OM is a polymicrobial infection involving any of the respiratory tract viruses and bacteria (Chonmaitree 2000a, Gitiban et al. 2005). For a long time, AOM was considered a purely bacterial infection and COME a sterile condition. The development of new techniques for the isolation and identification of microbes, especially the sensitive polymerase chain reaction (PCR) techniques, has changed these rates during the last decades. Combining the results of five surveys on aetiology of AOM (Figure 4), that used conventional detecting methods, bacteria alone are found in more than 60% of MEEs, viruses and bacteria together in less than 10% of MEEs, viruses alone in less than 5% of MEEs and no detectable pathogens in ca. 25% of MEEs (Canafax et al. 1998, Chonmaitree et al. 1986, 1990, 1992, Heikkinen et al. 1999). When novel PCR methods are used the numbers change; a recent study found at least one respiratory tract pathogen in nearly all MEEs (Figure 5) (Ruohola et al. 2006). For COME, no corresponding distribution results are available. The proportion of viral and bacterial OM infections varies depending on the population studied and on the inclusion criteria applied. The causative agent cannot be predicted by symptoms, by otoscopic finding of the tympanic membrane (TM) or by colour, volume or viscosity of MEE (McCormick et al. 2000, Palmu et al. 2004, Rodriguez and Schwartz 1999).

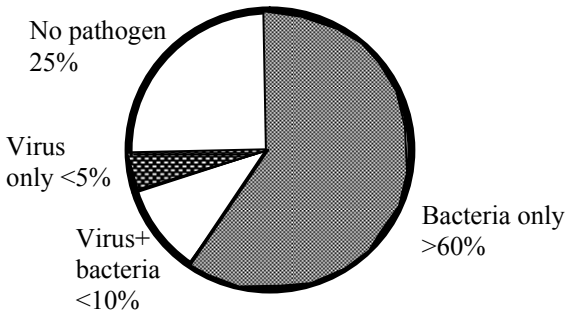


Figure 4. Distribution of microbes by culture and/or isolation in AOM. (Canafax et al. 1998, Chonmaitree et al. 1986, 1990, 1992, Heikkinen et al. 1999)

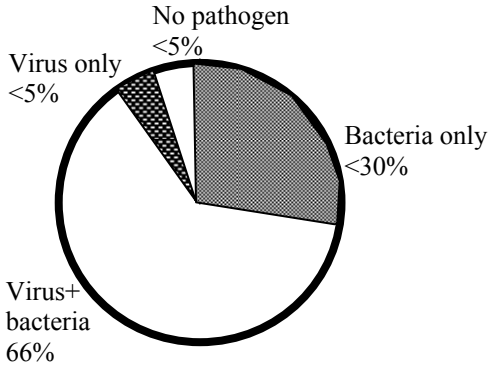


Figure 5. Distribution of microbes by PCR in AOM. (Ruohola et al. 2006)

2.1.4.2.1. Viruses

Epidemiological data support a strong association between upper respiratory tract infections (URIs) and AOM (Heikkinen 1994, Henderson et al. 1982, Koivunen et al. 1999, Ruuskanen et al. 1989). The seasonal variation in the occurrence of AOM parallels that of URI (Pukander et al. 1982a, Ruuskanen et al. 1989, Vesa et al. 2001). High rates of AOM have been found during outbreaks of respiratory virus infections caused by RSV, influenza A, influenza B and adenovirus (Arola et al. 1990b, Peltola et al. 2003, Ruuskanen et al. 1989). Especially URIs caused by RSV in children under 2 years of age are associated with AOM (Sagai et al. 2004). The occurrence of AOM peaks in the youngest age groups, who suffer from 6-8 URIs annually, and it decreases after the age of 2-3 years, as also the URIs become less prevalent (Pukander et al. 1982a). URIs are common worldwide, and they are mostly viral diseases (Mäkelä et al. 1998).

Role of viruses in the pathogenesis of AOM. Viruses play an important preceding role in the development of AOM, either alone or especially with bacterial pathogens. Viral infection induces the release of inflammatory mediators and cytokines from epithelial cells in the nasopharynx (Noah et al. 1995, Saito et al. 1997), and this may provoke ET dysfunction (Doyle et al. 1990). Tympanometric studies of children with URI demonstrated abnormal negative middle ear pressures as a result of ET dysfunction (Moody et al. 1998, Sanyal et al. 1980, Winther et al. 2002). Similar results were also observed in experimental viral challenge studies of adult volunteers (Buchman et al. 1994, Doyle et al. 1994). Chinchilla models of AOM have shown that Influenza A virus infection causes damage to the cilia of ET epithelial cells, which reduces ciliary activity, causing accumulation of mucus and cellular debris in tubal lumen. This occlusion of the ET promotes negative middle ear pressure and development of AOM (Chung et al. 1993, Giebink et al.

1987, Park et al. 1993). In a recent study by Gitiban, RSV infection caused similar effects in chinchilla and mouse models (Gitiban et al. 2005). Some viruses, particularly influenza A virus, are known to induce polymorphonuclear leukocyte dysfunction (Abramson and Wheeler 1994). Several studies have documented numerous changes in the systemic immune and inflammatory parameters during infections with rhinovirus, RSV or influenza virus A (Gentile et al. 2001, Hsia et al. 1990, Ruuskanen and Ogra 1993). These studies suggest that viruses may also produce changes in the host defence functions to escape immune surveillance. An AOM study that determined the occurrence of respiratory viruses in the MEEs of virus-positive URIs identified RSV more frequently (74%) than parainfluenza (52%) and influenza viruses (42%) in the MEEs of children infected by that particular virus (Heikkinen et al. 1999). This finding suggests that RSV actively invades the middle ear, while the others are passively carried into the middle ear by nasal secretions. More research is, however, needed to shed light on the mechanisms involved.

Viral pathogens detected from MEE. Before the 1980s, laboratory techniques could isolate viruses from MEE in less than 5% of cases, and hence, viruses were concluded not to be an important cause of AOM (Klein and Teele 1976). Since then, more sophisticated culture techniques and the development of antigen detection methods have increased the proportion of viruses detected in MEEs of children with AOM to 20% (Arola et al. 1990c, Chonmaitree et al. 1986, 1990, 1992, 1996, Chonmaitree and Henrickson 2000b, Klein et al. 1982). The development of PCR-based assays for several respiratory viruses has increased the rates of viral detection up 42-72% (mean 52%) (Chonmaitree and Henrickson 2000b, Monobe et al. 2003, Pitkäranta et al. 1998a). For COME, the number of reports detecting viruses is very small; the proportion of virus-positive MEEs in COME is less than 10% using conventional methods (Arola et al. 1990a) and ca. 30% using PCR methods (Pitkäranta et al. 1998b). Several viral pathogens have been detected in MEEs. These include RSV, rhinovirus, influenza A and B viruses, adenovirus, parainfluenza virus and enterovirus (Ruuskanen et al. 1991). RSV seems to be the most common virus detected in AOM, resulting in approximately half of the virus-positive MEEs using either conventional or PCR methods (Arola et al. 1990c, Chonmaitree et al. 1990, 1992, 1996, Chonmaitree and Henrickson 2000b, Klein et al. 1982, Monobe et al. 2003, Pitkäranta et al. 1998a). The next most common viruses are rhinovirus, adenovirus and influenza A virus (Henderson et al. 1982, Monobe et al. 2003, Ruuskanen et al. 1989). The predominant viruses detected by PCR in the rare virus-positive MEEs of COME were rhinovirus (63% of virus-positive MEEs), RSV (27%) and coronavirus (10%) (Pitkäranta et al. 1998a).

2.1.4.2.2. Bacteria

In the first half of the 20th century — in the pre-antibiotic era — β-haemolytic group A *Streptococcus pyogenes* (*S. pyogenes* ,group A Streptococcus, GAS) was the pathogen most frequently isolated from people with AOM, especially in cases where AOM was a complication of scarlet fever or acute tonsillitis (Valentine 1924). Since the 1950s, this pathogen has been replaced by *S. pneumoniae*, *H. influenzae and M. catarrhalis*, which are nowadays the main bacterial pathogens in OM all over the world and in all age and race groups (Bluestone et al. 1992, Casselbrant et al. 1995, del Castillo et al. 1996, Fujita et al. 1983, Karma et al. 1987, Trujillo et al. 1989). Pathogenic bacteria can be cultured in 71% of MEE samples in AOM (Table 2), and in 68% of MEE samples in COME (Table 3). PCR-based amplification techniques detect much higher proportions; bacterial DNA can be found in 92% of MEEs in AOM and in 77-94% of MEEs in COME (Gok et al. 2001, Hendolin et al. 1997, Post et al. 1995). *S. pneumoniae* is most frequently isolated from MEE of patients with AOM (Table 2); whereas *H. influenzae* is most commonly found in aspirates from patients with COME (Table 3). Other pathogens causing OM include group A Streptococcus, *Staphylococcus aureus (St. aureus), Pseudomonas aeruginosa, Alloiococcus otitidis,* other Gram-negative bacteria such as *E. coli and Klebsiella*, as well as some anaerobic bacteria, such as *Fusobacterium, Bacteroides and Peptostreptococcus* (Bluestone and Klein 1995).

Table 2. Bacteria in acute otitis media.

Bacteria isolated from 10247 MEEs in children with AOM		
	Mean (%)	Range (%)
Positive bacterial culture	71	56-95
Distribution of bacteria		
S. pneumoniae	26	19-43
H. influenzae	21	9-36
M. catarrhalis	10	1-24
St aureus	2.8	1-17
Streptococcus A, GAS	2.4	0.1-5
Pseudomonas aeruginosa	2.1	0.3-4
Other*	17	1.3-31

Based on reports of Bluestone et al. 1992, Casselbrant et al. 1995, Chonmaitree et al. 1990, del Castillo et al. 1996, Gehanno et al. 2001, Karma et al. 1987b, Kilpi et al. 2001, Luotonen et al. 1981, Rodriquez and Schwartz 1999, Ruuskanen et al. 1989, Trujillo et al. 1989.

*****Other includes *E. coli, Klebsiella* and anaerobic bacteria as well as coagulase-negative staphylococci and diphteroids, but the numbers are too small to determine proportions (the last two are considered contaminants).

Table 3. Bacteria in chronic otitis media with effusion.

Bacteria isolated from 4932 MEEs in children with COME		
	Mean (%)	Range (%)
Positive bacterial culture	68	24-70
Distribution of bacteria		
H. influenzae	15	8-22
S. pneumoniae	7	5-16
M. catarrhalis	10	3-16
Other*	36	0-38

Based on reports of Bluestone et al. 1992, Gok et al. 2001, Hendolin et al. 1997, Jero et al. 1996, Post et al. 1995.

*Other includes *St. aureus, Alloiococcus otitidis, Streptococcus viridans* and *Pseudomonas aeruginosa*.

Streptococcus pneumoniae. Pnc is the most important pathogen of OM. It is cultured in approximately 26% of MEEs in AOM patients (Table 2), and in 7% in OME patients (Table 3). There are more than 90 types of pnc based on capsular polysaccharide type but relatively few types are responsible for most OM cases. The most common types are 3, 6, 14, 18, 19 and 23 (Bluestone and Klein 1995). During immune defence against pneumococcus the generation of capsular polysaccharide antibodies is important. Knowing the type distribution is imperative when developing optimal vaccines against pneumococcus as this distribution is different in different countries (Kilpi et al. 2001, Orange and Gray 1993).

Recently, there has been a notable change in penicillin resistance in many countries. In Europe, the most difficult situations are in France (Gehanno et al. 2001) and in Spain (Schito et al. 2000), where 50-90% of pneumococci show decreased susceptibility to penicillin. In the United States, these figures are high, the proportion being 75% in the worst areas (Poole 1998, Sutton et al. 2000, Wald et al. 2001, Whitney et al. 2000). In Finland, most of the cultured strains are still fully susceptible to penicillin, with a prevalence of only 11% of penicillin-intermediate and penicillin-resistant strains in 2004 (Finnish Study Group for Antimicrobial Resistance 2005).

Haemophilus influenzae. *H. influenzae* is cultured in approximately 21% of MEEs in AOM (Table 2) and in 15% of those in COME (Table 3). Most strains lack a polysaccharide capsule and are called non-typable *H. influenzae*. *H. influenzae* is associated with recurrent AOM (Kilpi et al. 2001) and with COME (Bluestone et al. 1992). The occurrence of β-lactamase-producing *H. influenzae* has increased during previous decades in most countries (Gehanno et al. 2001, Manninen et al. 1997). In most European countries, 14-24% of strains produce β-lactamase

(Kilpi et al. 2001, Manninen et al. 1997, Schito et al. 2000), whereas in France almost 70% of *H. influenzae* strains produce β-lactamase (Gehanno et al. 2001).

Moraxella catarrhalis. *M. catarrhalis* (previously *Branhamella catarrhalis*) was considered non-pathogenic until the 1980s. Nowadays, it is cultured in 10% of MEE both in AOM (Table 2) and in COME (Table 3). The vast majority of strains produce β-lactamase (Bluestone et al. 1992, Kilpi et al. 2001, Manninen et al. 1997).

2.1.5. Clinical course of otitis media

Most children have symptoms of viral URI a couple of days before AOM (Heikkinen 1994). The first symptoms of ear ache usually appear during late evening or at night, when the child is in a supine position so the pressure increases in the middle ear. After pain and other acute symptoms of AOM have subsided, inflammatory MEE may persist from a few days to months. Effusions resolve at a relatively slow rate, the median duration being 2-3 months (Fiellau-Nikolajsen 1983, Lous and Fiellau-Nikolajsen 1981, Zielhuis et al. 1990b). At 2 weeks after the onset of AOM, 70% of children had MEE, 40% after a month, 20% after 2 months and 10% after 3 months, according to studies by Teele et al. (1980, 1989). According to a recent study of children with AOM monitored daily with tympanometry, normal tympanograms were obtained after a median time of 7.5 days (range 1-58 days) (Renko et al. 2006).

2.1.6. Diagnosis

The basic element in the diagnosis of OM is inspection of the tympanic membrane and most importantly assessment of the middle ear with pneumatic otoscope. Inspection of the tympanic membrane is a subjective method and therefore prone to individual errors. Tympanometry is more objective method and can also be used to evaluate the middle ear, although there are many technical difficulties when examining infants. Earwax and suboptimal patient compliance add to the complexity of the physical examination. Thus, diagnosing OM, particularly in small children, can be challenging even for specialists.

A diagnosis of AOM must meet three criteria: 1) rapid onset, 2) acute symptoms and signs suggestive of middle ear infection and 3) presence of MEE (Finnish Current Care Guidelines 1999, updated 2004, American Academy of Pediatrics et al. 2004). Otorrhoea not caused by external otitis as the only sign is also diagnostic for AOM. A diagnosis of COME is defined as the presence of effusion in the middle ear without signs and symptoms of acute ear infection (American Academy of Family Physicians et al. 2004).

2.1.6.1. Symptoms and signs of otitis media

The most common local symptom of AOM is otalgia (i.e. ear ache), appearing 73% of attacks (Pukander 1983). Other local symptoms and signs include otorrhoea (i.e. discharge from the ear canal), hearing loss, vertigo, nystagmus, tinnitus and in very rare cases swelling around the ear and facial paralysis (Bluestone and Klein 1995). Of children with AOM, 28-40% do not have any ear-related symptoms (Heikkinen and Ruuskanen 1995, Niemelä et al. 1994). Systemic symptoms and signs of AOM comprise fever, irritability, headache, apathy, loss of appetite, vomiting and diarrhoea, which are also symptoms of viral URI (Heikkinen and Ruuskanen 1995, Kontiokari et al. 1998a, Niemelä et al. 1994). The severity of the symptoms should be also evaluated. Non-severe illness is defined as mild otalgia and fever less than 39°C, and severe illness as moderate to severe otalgia and fever $\geq$39°C (American Academy of Family Physicians et al. 2004, American Academy of Pediatrics et al. 2004).

Local symptoms and signs of COME are hearing loss, feeling of fullness in the ear, a 'popping' sensation and occasionally dizziness, tinnitus and vertigo (Bluestone and Klein 1995). Sometimes children with OME, without any obvious symptoms, are diagnosed after routine hearing assessment screens (American Academy of Family Physicians et al. 2004).

2.1.6.2. Physical examination to verify middle ear effusion

According to a meta-analysis, pneumatic otoscopy with tympanometry gave the highest sensitivity scores in MEE diagnostics, as tested by myringotomy (Takata et al. 2003).

Pneumatic otoscopy. Pneumatic otoscopy with adequate illumination is the basic examination method of OM (Finnish Current Care guidelines 1999, updated 2004, American Academy of Family Physicians et al. 2004). The position, colour, degree of translucency and mobility of the tympanic membrane are evaluated. The obstructing cerumen must first be removed. Normal eardrum is in neutral position. Mild retraction of the tympanic membrane indicates negative middle ear pressure or effusion, or both. Severe retraction occurs when there is a high negative pressure in association with MEE in the middle ear. Increased pressure or effusion, or both, in the middle ear cause bulging of the tympanic membrane. The normal eardrum is pearl-white and is usually translucent. Red, pink, white, yellow and blue colours occur with OM. The normal eardrum moves briskly with slight positive and negative pressure. Poor mobility is highly suggestive of OM.

Tympanometry. Tympanometry can be used as an invaluable aid in diagnosis. It is used to identify MEE and to measure middle ear pressure. The device has a soft probe that seals the

ear canal tightly, a sound generator, a microphone to detect the returning energy and a vacuum pump that alters the pressure. Tympanometry measures acoustic admittance, i.e. the ease of sound energy flow from the air medium, a with high admittance/low impedance, to the liquid medium of the cochlea, with a relatively low admittance/high impedance. The tympanic membrane and middle ear act as a transformer. Sound energy has a maximal admittance from the ear canal into the middle ear when the air pressure on both sides of the eardrum is equal. The resulting curve of this measurement is a tympanogram, a graphic presentation of the acoustic admittance of the middle ear as a function of altered air pressure. It has an air pressure from –400 daPa to +200 daPa on the x-axis and static admittance on the y-axis. The highest peak is called the tympanometric peak. Its position on the x-axis indicates tympanometric peak pressure. It is an indirect estimate of pressure in the middle ear. Normally, the peak pressure is at 0 daPa. The basic types of tympanogram are as follows: type A curve indicating normal middle ear pressure, type B curve (flat peak/no peak) indicating decreased or low admittance suggestive of MEE and type C curve (peak is in the negative zone) suggesting negative middle ear pressure (Figure 6) (Bluestone and Klein 1995).

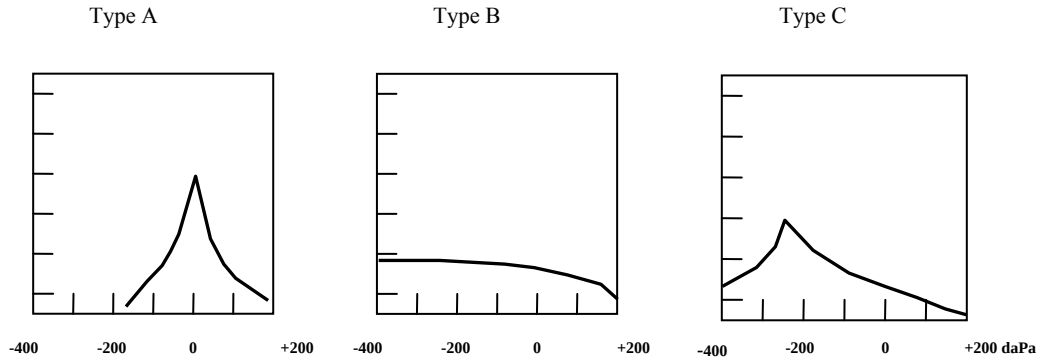


Figure 6. Basic types of the tympanogram. Adapted from Bluestone and Klein 1995.

2.1.6.3. Other diagnostic methods

Assessment of hearing. OM causes moderate conductive hearing loss, the average loss being 27 dB (Fria et al. 1985). This hearing loss is usually reversible after resolution of the effusion. When MEE is diagnosed, hearing testing is recommended after persistence for 3 months or longer or at any time if language delay, learning problems or a significant hearing loss is suspected (American Academy of Family Physicians et al. 2004). Depending on the child's age and ability to cooperate, either behavioural or non-behavioural tests can be used. There are several types of behavioural tests to suit all ages, for example, play audiometry and conventional audiometry. The most available and widely used non-behavioural test is the auditory brain stem response (Bluestone and Klein 1995).

Tympanocentesis. When determination of the aetiological agent is needed, a needle aspiration of the MEE for microbiological study can be performed (Bluestone and Klein 1995).

2.1.7. Complications

Despite the apparent increase in the prevalence of AOM during the past decades, the severity of the disease seems to have diminished. At present, less than 0.5% of AOM cases are associated with serious complications, compared with up to 40% early in the last century (Faden et al. 1998). The most frequent, albeit less serious, complication of OM is hearing loss. The hearing loss may potentially have linguistic, developmental and other social consequences if the disorder is bilateral and of long duration (Luotonen et al. 1996, Teele et al. 1990). Apparently, the hearing loss in general has a very small if any long-term effect on the linguistic development of a child (Paradise 1998, Roberts et al. 2004, Rovers et al. 2004).

Serious complications of OM can be divided into intratemporal and intracranial sequelae, of which the former are more common. Intratemporal complications include acute and chronic perforation of the tympanic membrane, mastoiditis, facial nerve paralysis, cholesteatoma, adhesive otitis media, tympanosclerosis and ossicular discontinuity and fixation (Bluestone and Klein 1995). Acute mastoiditis is the most commonly found acute intratemporal complication of OM. In the 1950s the occurrence of mastoiditis was quite high, up to 17% among children who did not receive antibiotics (Bluestone 2000, Rudberg 1954). The incidence of mastoiditis at present is very low in developed countries. It is reported to be 3.8/100 000 person-years in the Netherlands, which is one of the countries with the lowest antimicrobial prescription rate, compared with 1.2-2/100 000 person-years in countries with prescription rates of up to 100% (Van Zuijlen et al. 2001). Facial paralysis can also be associated with AOM. The incidence of facial paralysis in association with AOM is reported to be 5/100 000 person-years (Ellefsen and Bonding 1996).

Intracranial complications are rare and are mainly the sequelae of untreated mastoiditis. These complications include meningitis, extradural abscess, subdural empyema, brain abscess and lateral sinus thrombosis (Bluestone and Klein 1995).

2.2. Risk factors for otitis media in children

Several large epidemiologic studies have been carried out to elucidate the risk factors for OM. There are two types of risk factors: host-related and environment-related (Table 4).

Table 4. Risk factors for otitis media.

Host-related risk factors	Environment-related risk factors
Young age	Respiratory infections
Genetic predisposition	Day-care outside home
Male gender	Number of siblings
Allergy	Season
	Parental smoking
	Use of pacifier
	Short duration of breastfeeding

2.2.1. Host-related risk factors

2.2.1.1. Young age

According to a large cohort study conducted in Finland in the late 1970s, the highest annual incidence rates of AOM are found in infants younger than 2 years (Pukander et al. 1982a). Annual incidence rates were 47/100 child-years for the age group 0-1 year, 51 for the age group 1-2 years and 36 for the age group 2-3 years, after which the rates gradually decreased. When the age group 10-15 years was chosen as a reference group, the relative risk (RR) of contracting AOM was 18 times higher during the first year of life, 20 times higher during the second year of life and 14 times higher during the third year of life (Table 5) (Pukander et al. 1982a). The younger the child is at her/his first episode of AOM, the higher the risk for recurrent episodes (Alho et al. 1991b, Howie et al. 1975, Marchant et al. 1984, Teele et al. 1989). Especially the onset of AOM before 6 months of age is highly predictive for recurrent episodes (Harsten et al. 1989).

2.2.1.2. Genetic predisposition including gender

The most powerful evidence of a genetic predisposition for OM has been obtained from twin and triplet studies (Casselbrant et al. 1999, Casselbrant and Mandel 2005, Kvaerner et al. 1997, Rovers et al. 2002). A positive family history may increase the risk for OM up to 2.6-fold (Table 5) (Daly et al. 1999b, Uhari et al. 1996a). AOM incidence, particularly regarding recurrent AOM, seems to be higher in boys than in girls (Pukander et al. 1982b, Sipilä et al. 1987, Teele et al. 1989). Male gender

was associated with AOM in all age cohorts in a study by Teele et al. (1989), odds ratios (ORs) were 1.7 in the cohort of 0-1 year and 2.1 in that of 0-3 years. Male sex is also a clear risk factor for COME, OR being 2.17 (Alho et al. 1995b).

2.2.1.3. Allergy

Children with cow's milk allergy have an elevated risk for OM, RR 2.14 (Table 5) (Juntti et al. 1999). Respiratory allergy in not very common in infants, but it may play a role in the pathogenesis of OM in older children (Fireman 1997). The role of allergy may involve several mechanisms, such as inflammatory swelling of the ET, nose and nasopharynx.

Table 5. Studies on host-related risk factors for otitis media.

Study	Design	Number of subjects	Age of subjects	Outcome	Comparison groups	RR or OR (95% CI)
Young age						
Pukander et al. 1982a	population-based cohort	146822		AOM	age 0-1 year vs. 10-15 years	RR 18.3
					age 1-2 years vs. 10-15 years	RR 20.1
					age 2-3 years vs. 10-15 years	RR 14.3
Genetics						
Uhari et al. 1996	meta-analytic review	1240		AOM	positive vs. negative family history	RR 2.63 (1.86-3.72)
Daly et al. 1999b	cohort	596	0-6 months	AOM		RR 1.5-1.7 (1.1-2.5)
Teele et al. 1989	cohort	877	0-1 years	AOM	male vs. female	OR 1.70 (1.21-2.38)
	cohort	698	0-3 years	AOM		OR 2.10 (1.31-3.35)
Alho et al. 1995b	cohort	2512	0-2 years	COME		OR 2.17 (1.37-3.44)
Allergy						
Jäntti et al. 1999	case-control	260	9-11 years	RAOM	cow's milk allergy vs. no allergy	RR 2.14 (1.21-3.78)

2.2.2. Environment-related risk factors

2.2.2.1. Respiratory infections

URIs can be considered the most important predisposing factor for OM (Table 6). In children younger than 6 months, RR is reported to be as high as 7.5 (Daly et al. 1999b). The estimated risk of AOM in children with URI ranges between 26% and 43% (Henderson et al. 1982, Koivunen et al. 1999, Ruuskanen et al. 1989). The highest risk (41-54%) for AOM seems to be within 4 days of the onset of URI (Heikkinen 1994, Koivunen et al. 1999).

Recurrent exposure to infectious virus microbes can occur in day-care centres as well as in large households. Day-care outside the home is the single most important environmental risk factor for OM (Table 6). RR varies between 1.7 and 2.45 for AOM (Daly et al. 1999b, Uhari et al. 1996a) and is 1.36 for OME (Dewey et al. 2000). OR varies between 1.49 and 4.01 for AOM and 1.9 and 2.56 for OME (Rovers et al. 1999). Children with older siblings have an increased risk for AOM, RR is 1.33 (Uhari et al. 1996a). A strong positive relationship appears to exist between the occurrence of OM and the extent of exposure to other children whether at home or in day-care. The number of children seems to be an important risk factor, probably due to increased exposure to respiratory viruses and OM pathogens (Paradise et al. 1997, Rovers et al. 1999).

Differences exist in the occurrence of AOM and COME depending on the season (Alho et al. 1991a, 1995b, Sipilä et al. 1988) Sipilä et al. (1988) found a 2-fold risk for AOM in winter compared with in summer, whereas Alho et al. (1991a) reported a 2.5-fold higher incidence rate in the early spring and late autumn than in summer (Table 6). Risk for COME is higher in autumn than in summer, with an OR of 1.99 (Table 6) (Alho et al. 1995b). During the winter months, people gather indoors, which may facilitate transmission of microbes. AOM follows the appearance of winter respiratory viruses, such as RSV and influenza virus.

2.2.2.2. Parental smoking

A positive relationship between the occurrence of OM and household exposure to tobacco smoke has been found in many studies (Etzel et al. 1992, Kraemer et al. 1983, Owen et al. 1993, Paradise et al. 1997, Pukander et al. 1985, Reed and Lutz 1988, Sipilä et al. 1988, Tainio et al. 1988). In some studies, the association has been less clear (Alho et al. 1995b, Casselbrant et al. 1995, Daly et al. 1999b, Harsten et al. 1989).

According to a large meta-analysis, parental smoking is associated with increased risk for OM (Table 6). RRs were 1.66 and 1.76 for AOM and RAOM, respectively (Uhari et al. 1996a). For

OME, the RR was 1.58 (Dewey et al. 2000). Several mechanisms may account for the increase in risk. Cigarette smoke deteriorates mucociliary clearance, thus facilitating bacterial colonization (Stanley et al. 1986, Wanner 1985). There also seems to be an increased adherence of bacteria to epithelial cells in smokers as compared with non-smokers (El Ahmer et al. 1999a, Piatti et al. 1997). In addition, tobacco smoke induces inflammation, causing epithelial injury (Willemse et al. 2005).

An inverse correlation exists between household smoking and socio-economic status (Paradise et al. 1997). Thus, low socio-economic status may indirectly influence the risk for OM.

2.2.2.3. Use of pacifier

The use of a pacifier has been reported to slightly increase the risk for AOM and RAOM (Table 6). RR was 1.24 for AOM (Uhari et al. 1996a) and 2.9 for RAOM (Niemelä et al. 1995). The mechanism is, however, unknown. Because the use of a pacifier apparently does not increase the occurrence of respiratory viral infections (Niemelä et al. 1995), the effect may lie in the alteration of the pressure equilibrium between the middle ear cavity and the nasopharynx. This may be explained by a change in the oral microbial flora caused by the pacifier, producing a foreign body reaction in the mouth.

2.2.2.4. Breastfeeding

Short duration of breastfeeding, i.e. less than 3 months, increases the risk for AOM (Alho et al. 1990, Duffy et al. 1997, Teele et al. 1989). The protective function of breastfeeding against OM is dependent of the dose/time period of breastfeeding such that the risk for RAOM is higher among children fully breastfed for 4-6 months than in those fully breastfed for over 6 months, OR 1.95 (95% CI 1.06-3.59) (Chantry et al. 2006, Duncan et al. 1993). There are several possible explanations for the protective effect of breastfeeding. Firstly, the effect may be purely mechanical, since breastfed infants are held in a different position than bottle-fed infants. Secondly, human milk contains large amounts of antibodies; the high levels of secretory IgA, in particular, may offer passive protection against infections via mucosal defence (Hanson et al. 1985, Hanson 1999). Thirdly, breast milk contains factors of the innate immune system, which may mediate the protective effect (Hanson 1998).

Table 6. Studies on environmental risk factors for otitis media.

Study	Design	Number of subjects	Age of subjects	Outcome	Comparison groups	RR or OR (95% CI)
Respiratory infections						
Daly et al. 1999b	cohort	596	0-6 months	OM	URI vs. no URI	RR 7.5 (5.4-10.3)
Uhari et al. 1996	meta-analytic review	1972		AOM	day-care outside the home vs. home care	RR 2.45 (1.51-3.98)
Rovers et al. 1999	review of 17 studies			AOM		OR 1.49 (1.10-2.02)-4.01(1.69-9.54)
				OME		OR 1.9 (1.1-3.2)-2.56 (1.17-5.57)
Daly et al. 1999b	cohort	596	0-6 months	AOM		RR 1.7 (1.3-2.3)
Dewey et a. l2000	cohort	1290	8-43 months	OME		OR 1.36 (1.02-1.82)
Uhari et al. 1996	meta-analytic review	1972		AOM	>1 siblings vs. no siblings	RR 1.33 (1.29-2.85)
Daly et al. 1999b	cohort	596	0-6 months	OM		RR 1.4 (1.1-1.7)
Dewey et al. 2000	cohort	1290	8-43 months	OME		OR 1.52 (1.23-1.88)
Sipilä et al. 1988	cohort	1294	0-25 months	AOM	Winter vs. summer	RR 2.0
Alho et al. 1991a	cohort	2512	0-2 years	AOM	spring and autumn vs. summer	RR 2.5
Alho et al. 1995b	cohort	2512	0-2 years	OME	autumn vs. summer	OR 1.99 (1.11-3.55)
Parental smoking						
Uhari et al. 1996	meta-analytic review	1784		AOM	yes vs. no	RR 1.66 (1.33-2.06)
		1954		RAOM		RR 1.76 (1.36-2.28)
Dewey et al. 2000	cohort	1290	8-43 months	OME	maternal smoking <10 cigarettes/day vs. 0	OR 1.23 (0.82-1.84)
					10-19 cigarettes/day vs. 0	OR 1.58 (1.09-2.29)
					20+ cigarettes/day vs. 0	OR 0.75 (0.45-1.27)
Use of pacifier						
Niemelä et al. 1995	cohort	129	0-2 years	RAOM	use of pacifier vs. no use	RR 1.6 (0.6-4.1)
		138	2-3 years	RAOM		RR 2.9 (1.2-7.3)
Uhari et al. 1996	meta-analytic review	4110		AOM		RR 1.24 (1.06-1.46)
Breast feeding						
Uhari et al. 1996	meta-analytic review	2548		AOM	>3 months vs. 0 months	RR 0.87 (0.79-0.95)

2.3. Management of otitis media

The main goal in the management of OM is to lessen its impact on the quality of life (QOL) of both children and their families. Distinguishing AOM from COME is fundamental to proper management OM. Specific goals in the management of each episode of AOM are to reduce symptoms (especially pain - the most common symptom) and to prevent complications – e.g. mastoiditis. A specific goal in the management of RAOM is to reduce the frequency of AOM episodes. Specific goals in the management of COME are restoration of normal hearing and avoidance of middle ear sequelae, e.g. tympanic membrane perforation, retraction pocket and cholesteatoma. Long-term sequelae of hearing loss in COME are currently under debate and include adverse effects on speech, language, cognitive and psychosocial development. To determine the effect of any management options, number needed to treat (NNT), i.e. the number of patients who need to be treated to prevent one adverse outcome, is often used.

2.3.1. Prevention

Prevention of OM has been the focus of much research. Possibilities to prevent OM include modification of risk factors, use of vaccines and use of other substances, such as xylitol; however, none of these is ideal alone, and thus, should be used in combination to achieve optimal results.

2.3.1.1. Modification of risk factors

Prevention of OM by risk factor modification sounds attractive because it avoids the costs and the unwanted side-effects of antimicrobial therapy and surgery. Modifying the environmental risk factors for OM could be a feasible approach.

As day-care outside the home is one of the most important risk factors for OM, decreased group size or improved infection control in day-care centres could result in lower prevalence of OM. There are few randomized trials that have estimated the effect of improved infection control in day-care centres (Carabin et al. 1999, Roberts et al. 2000, Uhari and Möttönen 1999). In these Canadian, Australian and Finnish trials, day-care personnel were advised to improve hand-washing and toy-cleaning. The occurrence of URI episodes were compared with that in control centres. There was a significant decrease in the occurrence of URI as well as in the occurrence of AOM (Carabin et al. 1999, Roberts et al. 2000, Uhari and Möttönen 1999).

In a randomized controlled trial (RCT) of parental counselling on pacifier use, the occurrence of AOM was 29% lower in children in the intervention group than in those in the control

group. In the intervention group, pacifier use was decreased 21% compared with the control group. The children who did not use a pacifier continuously in either of the groups had 33% fewer AOM episodes than children who did (Niemelä et al. 2000).

The promotion of breastfeeding, discouragement of parental smoking and restriction of the use of pacifiers are all potential ways of preventing OM; however, no controlled intervention studies have yet been published.

2.3.1.2. Vaccination

Since viral URI usually precedes AOM, developing a vaccine against the most common respiratory viruses would be ideal. Viral vaccines are difficult to develop because of the constant modification of viral surface proteins. The first inactivated influenza vaccine was developed and proven to be efficacious during World War II (Zangwill and Belshe 2004). The inactivated trivalent intramuscular influenza vaccine in use today has been shown to be effective in preventing AOM in children. Its use decreased the occurrence of AOM in children by 31-36% during an influenza epidemic (Clements et al. 1995, Heikkinen et al. 1991). Influenza vaccine is recommended for children aged 6-23 months in the United States and in Canada, but few other countries have adopted similar policies. Vaccination has been shown to be cost-effective in all Finnish children (Salo et al. 2006), and starting in autumn 2007 will be provided to all children 6-35 months of age as part of a national vaccination programme (Finnish National Public Health Institute 2007). An intranasal live-attenuated influenza virus vaccine reduced febrile AOM episodes by 30-47% (Belshe et al. 1998, Marchisio et al. 2002). This vaccine is currently available to persons 5-49 years of age in the United States (Zangwill and Belshe 2004). Inactivated RSV vaccines were introduced as early as in the 1960s, but their impact was disappointing (Kapikian et al. 1969, Kim et al. 1969). New vaccine types for RSV are continuously being studied (Anderson 2000, Wright et al. 2000).

As *S. pneumoniae* is one of the most common bacterial pathogens causing OM, much effort has been focused on pneumococcal vaccines during the last decades. The first polysaccharide-based vaccines (tetravalent, hexavalent) that were effective in adults were introduced during World War II (Austrian 2000). Polyvalent vaccines (14-valent) were developed in the 1970s. They were capable of reducing pneumococcal AOM by half (Mäkelä et al. 1980), but had low efficacy among children younger than 2 years (Karma et al. 1985, Koskela et al. 1986). The 23-valent polysaccharide vaccine still in use was developed in the 1980s, but its preventive potential was disappointing in the youngest age group. A novel conjugate pneumococcal vaccine that contains a carriage protein for capsular polysaccharide against seven of the most frequent OM serotypes is immunogenic also among infants. Results from the randomized

Californian vaccination trial of 38 000 children showed a 6% reduction in the prevalence of AOM (Black et al. 2000). Similar results were found in the Finnish Otitis Media Vaccine Trial, the reduction of serotype-specific AOM being as high as 57%, but the total reduction rate against any AOM was only 6% (Eskola et al. 2001). New vaccine types containing virulence proteins of *S. pneumoniae* are under development (Briles et al. 2000).

The development of vaccines against non-encapsulated *H. influenzae* and *M. catarrhalis* is difficult because these are both mucosal surface pathogens and their surface antigens are variable. It is also a demanding task to find a suitable animal model of infection that could predict human efficacy. However, some vaccine candidates are being investigated (McMichael 2000, McMichael and Green 2003, Poolman et al. 2000).

2.3.1.3. Xylitol

Xylitol is a five-carbon sugar alcohol referred to as birch sugar. Xylitol inhibits the growth of *S. pneumoniae* (Kontiokari et al. 1995) and the attachment of both pneumococci and *H. influenzae* on nasopharyngeal epithelial cells (Kontiokari et al. 1998b). In two randomized placebo-controlled clinical trials, xylitol was effective in preventing AOM (Uhari et al. 1996b, 1998). The occurrence of AOM in a 3-month trial was 40% (95% CI 10.1-71.1%) lower among children receiving chewing gum than in the control group, and 30% (95% CI 4.6-55.4%) lower when xylitol syrup was used. The mean ages of subjects were 4.6 years (range 1.5-6.7 years, SD 1.3) and 2.2 years (range 0.8-6.6 years, SD 1.0) in the gum and syrup groups, respectively (Uhari et al. 1998). These results cannot be extrapolated to the youngest age group (6-18 months), which has the highest risk for AOM. Interestingly, xylitol consumed only during URI episodes did not prevent AOM (Tapiainen et al. 2002). To prevent OM, xylitol should be used five times a day continuously (Hautalahti et al. 2007).

2.3.1.4. Other approaches

Several miscellaneous agents to prevent OM have been attempted with more or less unsuccessful results. Intranasal fluticasone propionate administered during viral URIs had no effect in preventing AOM (Ruohola et al. 2000). Intranasal oligosaccharides to prevent bacterial adherence and OM were also unsuccessful (Ukkonen et al. 2000). On the other hand, probiotics (Hatakka et al. 2001), α-haemolytic streptococci (Roos et al. 2001), immunoglobulins (Englund and Glezen 2000) and antiviral treatment (Whitley et al. 2001) showed some effect in preventing AOM. However, all of these findings require confirmation.

2.3.2. Non-surgical management

2.3.2.1. Watchful waiting

In the pre-antibiotic era, watchful waiting (WW) and myringotomy were the only treatment options for OM. As antibiotics and operative procedures have adverse effects, general interest towards more conservative options has increased. WW means observation without antibacterial agents or surgical intervention. However, it should not be equated with no treatment. All children should receive adequate analgesics and a careful and scheduled re-evaluation.

Watchful waiting in AOM and Quality-of-Life (QOL) outcomes. A recent RCT, including 223 children, showed that WW is an acceptable alternative to immediate antibiotic treatment for children older than 6 months with non-severe AOM (McCormick et al. 2005). Parental satisfaction and parent/child QOL outcomes were the same between the two groups regardless of treatment. Key factors in this strategy were assessment of AOM severity, parent education, management of AOM symptoms, access to follow-up care and use of antibiotics when needed.

Watchful waiting in AOM and symptomatic relief. The natural history of an individual episode of AOM is quite favourable. According to a large meta-analysis of 11 RCT control groups, 61% (95% CI 50-72%) of children managed without antibiotics had symptomatic relief within 24 h of AOM diagnosis (Rosenfeld and Kay 2003). Another large meta-analysis using data pooling of nearly 40 trials suggests that around 80% (95% CI 70-90%) of children had spontaneous clinical relief within 2-14 days of AOM diagnosis (Rovers et al. 2004). In order to prevent one child from experiencing pain 2-7 days after presentation, 15-17 children must be treated with antibiotics, i.e. NNT equals 15-17 (Del Mar et al. 1997, Glasziou et al. 2004). Correspondingly, to prevent one child from experiencing pain and/or fever 2-7 days after presentation (Takata et al. 2001) or from experiencing a prolonged (7-14 days) course of AOM (Rosenfeld et al. 1994), NNT equals 7 with initial antimicrobials. In children older than 6 months presenting with AOM without fever (>37.5°C) or vomiting, immediate antibiotics made little difference to distress by day 3 compared with children in the WW group (20% vs. 27%), and poor outcome was unlikely (Little et al. 2002).

Watchful waiting in AOM and complication rates. In developed countries, AOM appears to have rather similar intratemporal or intracranial complication rates whether antibiotics are prescribed or withheld. The rates of complications among children in control and treatment groups were quite similar according to two reviews (1 of 843, 0.12% vs. 2 of 932, 0.21%)

(Glasziou et al. 2004, Rosenfeld and Kay 2003). According to a report by Van Zuijlen et al. (2001), the potential increase in the incidence of mastoiditis is only two cases per 100 000 person-years (from 1.2–2 cases to 3.8 cases) with restrictive use of antibiotics.

Watchful waiting in COME and language development. A recent individual patient data meta-analysis of 7 RCTs by Rovers et al. (2005) compared the effect of short-term ventilation tubes against WW in OME. The effect on mean time spent with effusion, mean hearing levels and language development was assessed. Language development was studied in 381 children. No significant differences were present in language development between the children treated with ventilation tubes and the children in the WW group at the 6- to 9- and at 12- to 18-month follow-ups. Another current meta-analysis, the Cochrane Systematic Database Review of 17 studies (Lous et al. 2005), proved that early insertion of grommets had no impact on language development or cognition in otherwise healthy children with long-standing OME and hearing loss. In another RCT study of otherwise healthy children younger than 3 years who had persistent OM (n=429), early insertion of tympanostomy tubes was compared with delayed (6–9 months) intervention (Paradise et al. 2001, 2003b, 2005). The proportion of children in the late-treatment group who had effusion more than 50% of the time (first 12 months) was approximately three times higher than that in the early-treatment group (44% vs. 14%), and during the first 24 months the respective proportion was approximately two times higher (28% vs. 14%). However, no significant differences were observed between the two groups on any developmental outcomes at the ages of 3, 4, 6 and 9-11 years (Paradise et al. 2001, 2003b, 2005, 2007). Moreover, comparison of subgroups with different continuity or laterality of MEE or even moderate hearing loss also showed no differences on any developmental outcomes (Paradise et al. 2003a).

2.3.2.2. Antibiotics

Penicillin was the first antibiotic discovered, described by Alexander Fleming in 1929. Since then antibiotics have been used to treat a wide variety of bacteria-caused illnesses, including OM (Forsius 1995). Today, AOM is the most frequent reason for antibiotic prescriptions in children (McCaig and Hughes 1995), accounting for over 60% of all antibiotics in children (Finkelstein et al. 2001). There is a wide variation in prescribing antibiotics for AOM between different countries. According to a large questionnaire study, the differences varied from 31.2% in the Netherlands to 98.2% in Australia, New Zealand and the United States (Froom et al. 1990, 1997).

Selection of a particular antimicrobial agent is based on clinical and microbiological efficacy against the three major pathogens, low frequency of side-effects, convenience of dosing and

cost. Although there are several drugs with approval for use in the treatment of AOM, amoxicillin remains the current drug of choice. It is effective, safe and relatively inexpensive (American Academy of Pediatrics et al. 2004, Dowell et al. 1999, Finnish Current Care Guidelines 1999, updated 2004). The dosage of amoxicillin is 40 mg/kg divided into two daily doses for 5-7 days. Second-choice antibiotics include amoxicillin-clavulanate, sulfafurazole combined with trimethoprim and macrolide (Finnish Current Care Guidelines 1999, updated 2004). In North America, the recommended dosage of amoxicillin is 80-90 mg/kg divided into two daily doses because of the high number of resistant pneumococci (American Academy of Pediatrics et al. 2004).

Evidence from systematic reviews suggests that antibiotics today may provide only a modest benefit. The biggest problem among modern treatment trials is that the end–point is usually symptomatic relief. Since viruses cause similar symptoms as bacteria in AOM, it is difficult to get results that favour antibiotics. There is a clear lack of placebo-controlled studies that have duration of MEE as the end-point. Selective prescription of antibiotics for children with AOM requires discrimination between subgroups of children who would, and would not benefit from antibiotics. Identifying these subgroups is problematic because most studies exclude children younger than 2 years and those with severe symptoms.

Antibiotics in AOM and prevention of prolonged course. Rovers et al. (2006) conducted an individual patient data meta-analysis of six randomized trials including 1643 children aged 6 months to 12 years and came to the conclusion that antibiotics are beneficial in children aged less than 2 years with bilateral AOM and in children with otorrhoea; NNT is 3-4 to prevent a prolonged course (= residual pain or fever).

Antibiotics in preventing RAOM. Antimicrobials that are used in the treatment of AOM have also been used for prevention of RAOM. However, according to large meta-analyses by Rosenfeld and Kay (2003) and Williams (1993), the impact is rather small. The difference in the incidence density of AOM was 0.11-0.12 episodes per patient–month (NNT equals 8-9): i.e. 8-9 children need to be treated with antibiotic prophylaxis for one month in order to prevent a single AOM episode.

Antibiotics in COME. Antibiotics appear to have a very limited effect on COME. No long-term effect of antimicrobial therapy on OME has been shown (Mandel et al. 1987, Rosenfeld and Post 1992, Williams et al. 1993).

Antibiotics cause unwanted side-effects such as diarrhoea, stomach pain and allergic reactions, including rash. The massive use of antibiotics has also increased bacterial resistance to antibiotics as well as increased expenses.

2.3.3. Surgical management

Although careful observation and medical treatment remain the first-line approach to the management of OM, surgical options should be considered, especially in children experiencing suppurative complications of AOM, RAOM or persistent OME. Optimal surgical outcomes are most likely to occur when the right child has the right surgery. The question the becomes which children should be offered surgical treatment and when.

Surgical management and QOL. The impact of any surgery in the management of OM on the QOL seems to be very good. According to a prospective questionnaire-based study of 123 children with either RAOM or COME, the mean percentage change in total ear symptom score was a 74.5% improvement at the 1-month follow-up and 59.8% at the 6-month follow-up after any surgical intervention. Of the caregivers, 91% would have their children undergo surgery at the 1-month follow-up and 84% at the 6-month follow-up, if they had to make the same decision again (Richards and Giannoni 2002).

2.3.3.1. Myringotomy

Myringotomy or incision of the tympanic membrane was first described by Sir Ashley Cooper in 1802 (Bluestone and Klein 1995). It was a very popular procedure until antimicrobial agents came into wide use in the 1940s.

The rationale of myringotomy is to provide short-term ventilation of the middle ear space and to decrease the pain that the pressure causes in the middle ear.

Nowadays, myringotomy is reserved for selected cases, including children younger than 3 months, critically ill children, children with severe otalgia, children with continued symptoms despite appropriate antibiotic therapy, children with suppurative complications and immunodeficient children (Bluestone and Klein 1995).

2.3.3.2. Tympanostomy

Myringotomy with insertion of tympanostomy tubes is currently the most common surgical procedure performed in children that requires general anaesthesia (Owings and Kozak 1998).

Politzer invented the use of tympanostomy tubes almost 150 years ago, in 1862. Since 1954, these tubes have become increasingly popular, after being reintroduced by Armstrong. After incision of the anterosuperior part of the tympanic membrane, the MEE is aspirated, and the

tympanostomy tube inserted (Bluestone and Klein 1995). There are many different tube designs and materials available. These can be divided into two general types according to the intended time to remain in the tympanic membrane, namely short-term (e.g. Donaldson) and long-term (e.g. T-tubes). Donaldson tubes are a common type used in Finland. Materials vary from metals, such as titanium and gold, to plastics, silicon and hydroxyl-apatite (Isaacson and Rosenfeld 1996).

The rationale of tympanostomy is to restore ventilation and pressure regulation in the middle ear. Tympanostomy tubes allow drainage of MEE. This reduces pain caused by the pressure of the purulent effusion during attacks of AOM and improves hearing in children with COME. In addition, tympanostomy tubes may reduce the damage caused by the inflammatory effusion to the middle ear mucosa and the mucociliary lining of the ET. In a middle ear with no effusion, tympanostomy tubes may prevent the generation of negative middle ear pressure when the function of the ET is impaired during an acute URI. This may inhibit aspiration of nasopharyngeal microbes into the middle ear cavity, and thus theoretically preventing episodes of OM.

Considerable variation in the frequency of the tympanostomy tube operation is seen both between countries and between different districts in the same country. Tube insertion rates vary from 2 per 1000 children younger than 15 years annually in the UK, to 8 in Canada and to 9 in the United States. In the Netherlands, 20 per 1000 children younger than 12 years receive tympanostomy tubes annually (Schilder et al. 2004). In Finland, this rate is 6 per 1000 children younger than 16 years (Haapkylä et al. 2006). There were more than 500 000 procedures done in the United States in 1996 (Owings and Kozak 1998). According to a population-based retrospective study conducted in Ohio, of children younger than 24 months, 30.1% underwent a ventilation tube insertion procedure (Myer and France 1997). In Finland, the total number of procedures in 2002 was 5058. Of these children, 2,309 (45.6%) were younger than 3 years and 1831 (36.2%) were 3-6 years old. An estimated 1.4% of children under 3 years and 1.0% of children under 7 years receive tympanostomy tubes in Finland (Haapkylä et al. 2006).

The procedure has been controversial for many years. Opinions regarding the benefits and disadvantages vary greatly. The appropriate indications for grommet insertion remain unclear. The primary indications for the operation are restoration of normal hearing in children with long-standing (>3-6 months) bilateral OME and prevention of RAOM. Other indications for grommets include treatment of suppurative complications of OM as well as the maintenance of normal middle ear pressure in the treatment of atelectasis of the tympanic membrane, retraction pocket and postoperatively in tympanoplasty (Bluestone and Klein 1995).

Tympanostomy and QOL. The QOL measurements have demonstrated a significant benefit in children treated with tympanostomy tubes. In a prospective study of 248 children scheduled for insertion of bilateral tympanostomy tubes, 79% experienced improved QOL in shortly, i.e. a few months, after the procedure (Rosenfeld et al. 2000a).

Tympanostomy and AOM occurrence. A large meta-analysis of several randomized trials has shown the objective benefits of tubes with regard the occurrence of RAOM (Rosenfeld 2000b). Insertion of tubes reduced AOM incidence by 1.75 episodes per child-year (95% CI 0.44-3.93), and the risk declined by 49% relative to controls (95% CI 21-76%) in children with RAOM. In children with either RAOM or COME, the figures were 1.0 episodes less per child-year (95% CI 0.41-1.58) and a 56% decline in the RR to controls (95% CI 21-76%), and in children with COME 0.29 episodes less per child-year (95% CI 0.15-0.43) and a 64% decline in the RR to controls (95% CI 21-76%) (Rosenfeld 2000b).

Tympanostomy and time spent with effusion. Three large meta-analyses and one RCT determined the objective benefits of tubes on the time spent with effusion in children with RAOM or COME. The first meta-analysis showed that insertion of tubes reduced time spent with MEE by 163 days per child-year (95% CI 11-220 days), and the risk in children with COME declined by 73% relative to controls (95% CI 54-67%). The corresponding figures in children with either RAOM or COME were 115 days per child-year (95% CI 11-220 days), and a reduced RR 67% (95% CI 54-67%) (Rosenfeld 2000b). The second meta-analysis, the Cochrane Systematic Database Review of 17 studies (Lous et al. 2005), revealed that children treated with grommets spent 32% less time (95% CI 17-48%) with effusion during the first year of follow-up than children with non-surgical treatment. The third meta-analysis, an individual patient data meta-analysis (Rovers et al. 2005) of 7 RCTs of 557 children, showed that during a follow-up period of 12 months, the mean time spent with effusion was 19.7 weeks (95% CI 17.6-21.9 weeks) in children treated with ventilation tubes and 37 weeks (95% CI 34.9-39.1 weeks) in the WW group ($p = 0.0001$).

In one RCT of otherwise healthy children younger than 3 years who had persistent OM (n=429), early insertion of tympanostomy tubes was compared with a delayed intervention of 6-9 months (Paradise et al. 2001). The proportion of children in the late-treatment group who had effusion more than 50% of the time (first 12 months) was approximately three times (14% vs. 44%), and during the first 24 months approximately two times (14% vs. 28%) that of the early-treatment group.

Tympanostomy in COME and mean hearing levels. Two large meta-analyses have shown objective benefits of tubes on hearing levels in children with COME. An individual patient

data meta-analysis (Rovers et al. 2005) of 7 RCTs including 574 children showed that the mean hearing level in children treated with ventilation tubes was 26.6 dB (SE 1.0) compared with 31.1 dB (SE 1.0) in the WW group (p = 0.001) at the 6-month follow-up. At the 12- and 18-month follow-ups, no differences were found between the groups. According to a Cochrane Systematic Database Review on 17 studies (Lous et al. 2005), myringotomy with insertion of grommets has a short-term effect on hearing in children with COME. Hearing levels improved on average about 9 dB (95% CI 4-14 dB) at 6 months and 6 dB (95% CI 3-9 dB) at 12 months after the operation.

Disadvantages of tympanostomy. Regular follow-up care is required to ensure that the tubes are functional and that the hearing loss has been corrected and also to prevent further complications. According to a meta-analysis of data from 134 articles by Kay et al. (2001), the sequelae from tympanostomy tubes are common but are generally transient. The most common sequela after the tube placement is otorrhoea, affecting 17% of intubated ears (Kay et al. 2001). Of children, 16% had an early transient otorrhoea (2 weeks after the procedure); this figure rose to 26% for the entire period of intubation (delayed otorrhoea). Other common sequelae are obstruction (7% of all ears), granulation tissue (5%), premature extrusion (4%) and medial displacement (0.5%) (Kay et al. 2001). The need to avoid immersion in water is controversial, as equivalent rates of otorrhoea are present in swimmers and non-swimmers (Becker et al. 1987, Goldstein et al. 2005). Sequelae after tube extrusion include tympanosclerosis (32% of ears), focal atrophy (26%), retraction pocket (3.1%), cholesteatoma (0.7%) and tympanic membrane perforations (2.2% with short-term tubes) (Kay et al. 2001). Tubes often lead to long-term anatomical changes in the tympanic membrane, such as tympanosclerosis, changes in mobility and retraction pockets, which may be the first step in the genesis of an acquired cholesteatoma. A 14-year follow-up study of long-term sequelae of tympanostomy tubes by Valtonen et al. (1999, 2005a, 2005b) included 305 children aged 5-16 months who underwent tympanostomy tube placement. Repeated tube insertion was performed once in 60%, twice in 27% and thrice in 14% of all children. Those with OME received repeated tubes significantly more often than those with RAOM. Two-thirds of the ears were healed 5 years after the tube insertion, and this figure increased to 91% 14 years after the procedure. Five years after tympanostomy, 39 patients (16%) had tympanic membrane retraction, and this figure fell to 23 (10%) 14 years after tube insertion. Twenty children had OME 5 years after the tube insertion, and more than half of these i.e. 11 children, were healed 14 years after the tube insertion. Eleven children (4.6%) had perforation at the end of the first follow-up at 5 years and five children (2.1%) at the end of the 12-year follow-up. Of the 6 children who had healed at the end of follow-up, 3 had done so shortly after surgery and 3 spontaneously during the second follow-up. The hearing level of healed ears was comparable with that of age-matched normal ears. Hearing losses were infrequent, of slight grade and when present,

almost exclusively conductive and related to unsuccessful otological outcomes (Valtonen et al. 2005b). This long-term follow-up study confirms the early tympanostomy procedure is safe and patients healed after 5 years do not require further follow-up. From the viewpoint of hearing, repeated tympanostomy tube insertion for RAOM or OME early in life is a safe treatment (Valtonen et al. 2005b).

Tympanostomy and need for re-operation. Approximately 20% of children who have had tympanostomy tubes have OME relapse after tube extrusion, possibly requiring additional surgery (Boston et al. 2003).

2.3.3.3. Adenoidectomy

Adenoidectomy was probably performed for the first time in the late 1800s, when Hans Wilhelm Meyer of Copenhagen, Denmark, proposed that adenoid vegetations were responsible for nasal symptoms and impaired hearing. Adenoidectomy and tonsillectomy operations were routinely performed simultaneously, commencing in the early part of the 1900s, when the tonsils and adenoid were considered reservoirs of microbes that caused many different types of diseases (Curtin 1987, Thornval 1969).

Adenoidectomy is nowadays performed under general anaesthesia using velotraction of the soft palate under visual control using a mirror. In Finland, the most common technique is to remove adenoid tissue with a Beckmann ring curette and the residual tissue of Rosemüller with forceps.

The rationale for adenotonsillar surgery is to remove a chronically infected tissue. Absolute indications for adenoidectomy include adenotonsillar hyperplasia with obstructive sleep apnoea, failure to thrive and suspicion of malignant disease. Relative indications include OM and chronic rhinosinusitis (Darrow and Siemens 2002). Chronic nasopharyngeal infection is thought to promote middle ear infection by providing a source of pathogenic microbes that constantly regurgitate to the middle ear through the ETs.

As with the tympanostomy tube procedures, marked variation is present in the frequency of adenoidectomies both between countries and between different districts in the same country. According to the year 2002 figures from the Finnish National Research and Development Centre for Welfare and Health, the annual rate is 10 per 1000 children younger than 16 years. The total number of adenoidectomies was 9447; 51.7% (n=4880) of the children were younger than 3 years, and 32.2% (n=3046) were 3-6 years (Haapkylä et al. 2006). In the United States, approximately 129 000 adenoidectomies were performed in 1996. The procedure was

reported to be the 7th most common procedure done in children under 15 years of age (Owings and Kozak 1998). Annual adenoidectomy rates vary from 1.7 per 1000 children younger than 15 years in Canada to 10 in the Netherlands and 13 in Finland (Schilder et al. 2004).

Adenoidectomy and AOM incidence. A meta-analysis of two RCTs (n=99 and n=304) has shown the objective benefits of adenoidectomy on the occurrence of RAOM (Rosenfeld 2000b). The procedure reduced the incidence of AOM by 0.32 episodes (95% CI, 0.03-0.61 episodes) per child-year for a 3-year period, but only in children with prior tubes (Paradise et al. 1990, Paradise et al. 1999). Most of the children in these RCTs were older than 3 years. A recent Finnish RCT (n=180) on children aged 10-24 months with RAOM found no benefit from adenoidectomy as the first surgical procedure compared with placebo and chemoprophylaxis (Koivunen et al. 2004).

Adenoidectomy in COME and time spent with effusion. Rosenfeld's meta-analysis (2000b) showed how adenoidectomy reduced the MEE duration by 35 days per child-year (95% CI 23-47 days) during the 3-year follow-up, but only in children with prior tubes (Paradise et al. 1990, 1999). Other studies of children older than 2-4 years with prolonged MEE have reported similar results (Gates et al. 1987, Maw and Bawden 1993).

Adenoidectomy and need for subsequent tubes. The relative risk of needing future tubes decreased by about 50% when adenoidectomy was performed for RAOM after tube extrusion (Paradise et al. 1990) or for COME in children aged 4 years or older (Gates et al. 1987).

Disadvantages of adenoidectomy. Complications after adenoidectomy appear to occur in 0.5-5% of patients (Coyte et al. 2001, Crysdale and Russel 1986, Paradise et al. 1999). These include anaesthesia-related complications such as nausea, vomiting and malignant hyperthermia, and operation-related complications, such as haemorrhage and transient velopharyngeal insufficiency.

2.3.3.4. Adenoidectomy in conjunction with the insertion of tympanostomy tubes

There are few studies that compare the effect of tympanostomy tubes vs. tympanostomy combined with adenoidectomy in the management of OM. One large retrospective analysis of hospital discharge records of over 37 000 children in Canada showed that tympanostomy tube insertion and adjuvant adenoidectomy reduced the likelihood of reinsertion of tympanostomy tubes (RR 0.5, 95% CI 0.4-0.8, $p<0.001$) and re-hospitalization for conditions related to OM (RR 0.5, 95% CI 0.5-0.6, $p<0.001$) (Coyte et al. 2001). The effect was age-related; the benefit was apparent in 2-year-olds and greatest among children 3 years of age or older (Coyte et al.

2001). The weakness of this study is that it did not differentiate the duration or type of OM. Another recent RCT of 137 children showed that in children younger than 2 years with RAOM, concurrent adenoidectomy during the insertion of tympanostomy tubes did not confer a major advantage over the insertion of tympanostomy tubes alone (Mattila et al. 2003).

3. AIMS OF THE STUDY

Management of childhood OM is challenging. There is an ongoing debate about the differences between management strategies. The purpose of this study was to clarify the effect of surgical procedures on the management of OM. In addition, risk factors for childhood OM and the frequency of asthma in otitis-prone children were evaluated.

The specific questions addressed were as follows:

1. Does adenoidectomy decrease the risk for OM in otitis-prone children younger than 4 years who have not previously received surgical intervention?

2. What are the risk factors associated with recurrence of OM after the insertion of tympanostomy tubes?

3. What are the risk factors associated with persistent MEE?

4. What is the frequency of other diseases, such as asthma, among otitis-prone children?

4. MATERIALS AND METHODS

4.1. Study designs and patients

4.1.1. Prospective randomized controlled trial (I, II, III)

The study participants were recruited from children referred to the Department of Otorhinolaryngology, Helsinki University Central Hospital, Finland, between January 2001 and December 2002 for any OM related reason. Children qualified for enrolment if they were aged 1-4 years with a history of OM and without previous adenotonsillar surgery or placement of tympanostomy tubes. History of OM was defined as 3 or more episodes of AOM during the preceding 6 months, 5 or more AOM episodes during the preceding 12 months, or COME as judged by examination with a pneumatic otoscope 2-3 months before tympanostomy in the outpatient clinic of the Department of Otorhinolaryngology and at the time of recruitment. The number of OM episodes was obtained by interviewing the parents and from the primary care patient records. The exclusion criteria were asthma, craniofacial abnormalities, cleft palate, diabetes or other immune dysfunction. In addition, children who were judged to require removal of adenoids because of symptoms of nasal airway obstruction resulting in obstructive breathing, obstructive sleep apnoea symptoms or continuous mouth breathing were excluded. Of the 1385 children evaluated, 296 qualified for enrolment. The guardians of 217 eligible children gave their signed consent. The mean age of the children was 1.9 years (median 1.7, range 1.0-3.9 years). They were randomized in blocks of 8 to receive Donaldson silicon tympanostomy tubes in both ears either in conjunction with adenoidectomy (n=109) or without adenoidectomy (n=108). All procedures were performed under general anaesthesia using standard techniques.

4.1.2. Retrospective studies (IV)

Two surveys were carried out. Survey A consisted of 819 Finnish individuals who had previously served as a control cohort in a childhood diabetes study conducted in 1986-1989. They were a random representative of age- and sex-matched children (370 girls, 449 boys) selected from the Finnish National Population Registry (Tuomilehto et al. 1992). Of the 819 questionnaires, 483 (59%) were returned in survey A. The mean age of the respondents was 18.3 years (range 10.7–27.5 years); 243 were females and 240 males.

Survey B comprised children from the hospital discharge records of the Departments of Ophthalmology and Otorhinolaryngology, Helsinki University Central Hospital, Finland, who were born after 1 January 1992 and had undergone either adenoidectomy or probing of the

nasolacrimal duct due to congenital obstruction before 1 January 2000. A total of 1616 children who had undergone adenoidectomy served as cases and 161 children who had undergone probing of the nasolacrimal duct served as controls. Of these children, 1001 were boys and 776 girls. Their mean age at the end of follow-up was 6.2 years (range 2.1-9.0 years).

4.2. Methods

4.2.1. Data collection by patient diaries (I, II, III)

The participants of the randomized trial were given a patient diary to document all episodes of AOM and other respiratory infections during the 12-month follow-up. The parents were advised to visit a primary care doctor whenever their child had symptoms of acute URI or they suspected OM. They were also advised to ask the doctor to record the data of that visit in the patient diary. The diaries were easy to use; each page included questions regarding the signs of AOM, followed by multiple-choice answer fields. Definitions of AOM were provided on every page. The definition of AOM included acute symptoms, such as fever, nasal discharge, cough or irritability, in combination with MEE. When the tympanostomy tube was patent, MEE was defined as a draining ear. If the tympanostomy tube was not patent, acute MEE was asked to be evaluated by a pneumatic otoscope. If the diaries were not filled in properly, the study physician contacted the primary care centre, with the permission of the parents, to obtain the missing data.

4.2.2. Data collection by questionnaires (I, II, III, IV)

Prospective trial: The guardians of the participants filled in a structured questionnaire at the beginning of the trial. It included questions about the number of siblings living in the same household, day-care, parental smoking and parents' history of asthma, their allergies to pollen and animal dust and parents' education. Parental smoking was defined as 20 cigarettes or more per week. After the follow-up, smoking habits were enquired about in more detail. The average number of cigarettes smoked per day was recorded, as was whether tobacco was also smoked indoors, exposing the child directly to tobacco smoke. If one of the parents had university or comparable academic education, the family was considered to be of a high socio-economic class. The family was considered to be of a lower socio-economic class if the above criterion was not fulfilled.

Retrospective trial: The questionnaire in survey A was designed to detect the frequency of adenoidectomy, infections, allergy and asthma in childhood.

4.2.3. Data collection from asthma register (IV)

Asthma diagnosis of the children in retrospective survey B was retrieved from the nationwide register of the Social Insurance Institution of Finland. This register includes individuals eligible for reimbursement of the costs of drugs used to treat asthma since 1 January 1992, i.e. includes all children of the study. A more detailed description of the criteria for reimbursement of asthma medication can be found in the original article (IV).

4.2.4. Sample size in the randomized study

An estimated 10% of the children in the adenoidectomy group and 30% in the tympanostomy group would likely develop RAOM. With a significance level of 5% and a power of 95%, the minimum required number of children in each group was 97 (total thus 194). To cover possible drop-outs, this number was increased to 215. The final number was 217 on the last recruitment day of 20 December 2002.

4.2.5. Statistical methods

I: The difference in the number of OM episodes between the randomization groups was compared by the use of univariate Student's *t*-test. Risk for recurrent episodes of OM ($\geq$3 episodes) was evaluated by multivariate logistic regression analysis adjusted by gender, age, number of siblings, previous number of OM episodes 12 months before surgery, parental smoking and clinical diagnosis of either RAOM or COME.

II: Mean numbers of OM were calculated for the children of both smoking and non-smoking parents, and the statistical significance of the difference was tested by Student's *t*-test. The effect of parental smoking on the risk for RAOM was evaluated by multivariate logistic regression analysis adjusted by gender, age, day-care, previous number of OM episodes 12 months before surgery, clinical diagnosis of RAOM or COME, socio-economic class and whether or not adenoidectomy was performed in conjunction with the insertion tympanostomy tubes.

III: Factors associated with the risk for COME were evaluated by logistic regression analysis.

IV: Risk for asthma and atopy in survey A was tested by multivariate logistic regression analysis adjusted by sex and age. Risk for asthma in survey B was estimated by the use of the Cox proportional hazards method adjusted by sex and age.

4.2.6. Ethical considerations

The Ethics Review Committee of Helsinki University Central Hospital approved the protocols of all studies. The Social Insurance Institution of Finland and the Ethics Review Committee of the Finnish National Health Institute approved the protocols of retrospective surveys.

5. RESULTS

5.1. Effect of adenoidectomy on the risk for otitis media in children younger than 4 years (I)

Of the 217 children recruited, 198 completed the one-year follow-up. The two study groups were similar in gender distribution, mean age at operation, number of siblings, history of AOM episodes, frequency of parental smoking and frequency of persistent MEE. The detailed flowchart and baseline characteristics of participants are shown in the original paper (I).

Table 7. Comparison of the two randomization groups.

	Adenoidectomy and tympanostomy	Tympanostomy	OR (95% CI)
All children, n	102	96	
Total no. of OM episodes	176	138	
Mean no. of OM episodes (SD)	1.7 (1.8)	1.4 (1.5)	
Children with RAOM, n	28	17	1.66 (0.80-3.46)
Frequency of reinsertion of tympanostomy tubes	8	10	

No significant difference was present between the randomization groups in the mean number of OM episodes during the 12-month follow-up (Table 7). Even when the groups were subdivided by the number of episodes of OM before randomization, by the clinical diagnosis of RAOM or COME or by the age of the patient, concurrent adenoidectomy provided no benefit.

Adenoidectomy also provided no benefit in decreasing the risk for recurrence of OM, as defined by $\geq$3 episodes during the one-year follow-up. In addition, there was no significant difference between the randomization groups in the frequency of reinsertion of tympanostomy tubes (Table 7).

5.2. Parental smoking as a risk factor for recurrent acute otitis media after the insertion of tympanostomy tubes (II)

Of the 394 parents whose children completed the one-year follow-up and whose smoking habits were known, 158 (40%) were smokers. Data on the smoking habits of two fathers were missing. During the previous 12 months prior to enrolment, the reported numbers of AOM episodes were similar between the children of smoking parents (mean number 5.6, SD 2.0) and those of non-smoking parents (mean number 5.7, SD 1.9).

Table 8. Comparison of children with smoking parent(s) and non-smoking parents.

	Smoking parent(s)	Non-smoking parents	OR (95% CI)
Children, n	104	94	
Mean number of AOM episodes	1.81	1.34	$p<0.05$
Number of RAOM children	20	4	5.36 (1.76-16.3)

During the follow-up, the number of AOM episodes was associated with parental smoking (Table 8). The difference in the mean number of OM episodes was significant ($p<0.05$). Especially, RAOM was present more often among children of smoking parents than among those of non-smoking parents.

Gender and age of the child, day-care outside the home during the follow-up period, the number of OM episodes during the 12 months prior to the enrolment, initial clinical diagnosis of RAOM or COME, socio-economic class of the family and whether the child had undergone adenoidectomy in conjunction with the insertion of tympanostomy tubes were entered as independent variables to control for possible confounding factors. As maternal and paternal smoking habits were strongly associated with each other, two sets of analyses were performed; 1) maternal smoking (yes/no), but not paternal smoking (analysis set 1) and 2) paternal smoking (yes/no), but not maternal smoking (analysis set 2) were entered with the independent variables.

Table 9. Multivariate analysis of the factors associated with the risk for RAOM.

Factor	OR (95% CI)	p
Analysis set 1 Maternal smoking (yes/no) n=182	4.15 (1.45-11.9)	<0.0082
Analysis set 2 Paternal smoking (yes/no) n=181	2.45 (0.85-7.07)	

The results showed that maternal smoking was a significant risk factor for RAOM even after the insertion of tympanostomy tubes (Table 9).

5.3. Risk factors for childhood persistent middle ear effusion (III)

Of the 217 children recruited to the prospective trial, 214 returned the completed questionnaires. Of these, 159 had RAOM and 55 had COME. Data on asthma and allergy were obtained from 304 parents of children with RAOM and from all 110 parents of children with COME. The asthma and allergy status of 14 parents of children with RAOM was missing.

Children with COME and those with RAOM appeared to be similar in terms of their mean number of siblings and their history of day-care outside the home. No difference was present in the frequency of parental smoking between the two groups.

The results showed that frequencies of pollen and animal dust allergies were lower among the parents of children with COME than among the parents of children with RAOM (Table 10).

Table 10. Frequencies of asthma, pollen and animal dust allergies among the parents of children with COME and RAOM.

	Parents of children with		
	COME	RAOM	
Characteristic	Frequency % (n)	Frequency % (n)	OR (95% CI)
Asthma	6 (7/110)	11 (33/303)	0.54 (0.23-1.25)
Pollen allergy	16 (17/108)	27 (80/298)	0.50*(0.28-0.89)
Animal dust allergy	11 (12/108)	21 (63/298)	0.49*(0.25-0.94)
Asthma or pollen or animal dust allergy	20 (22/108)	34 (101/297)	0.49*(0.30-0.83)

*p<0.05.

5.4. Frequency of asthma among otitis-prone children (IV)

Survey A showed that adenoidectomy before the age of 4 years was associated with asthma and with allergy to animal dust (Table 11).

Table 11. Frequency of asthma and allergy by adenoidectomy status, survey A.

Characteristic	No adenoidectomy Frequency % (n)	Adenoidectomy before the age of 4 Frequency % (n)	OR (95% CI)	p
Asthma	5.8 (21/359)	15 (7/47)	3.19 (1.25-8.13)	<0.05
Allergy to animal dust	19.9 (65/341)	36 (13/44)	2.50 (1.27-4.95)	<0.01

Survey B showed that adenoidectomy before the age of 7 years was associated with an increased risk for asthma compared with the control group without adenoidectomy (Figure 7). If adenoidectomy was performed before the age of 4 years, the OR of asthma risk was 6.74 (95% CI 2.99-15.2, p<0.001). If it was performed between the ages 4–7 years, the OR was 4.36 (95% CI 1.85-10.4, p<0.001). An association existed between asthma and adenoidectomy, even before adenoidectomy had actually been performed. Children with RAOM had a higher risk for asthma (OR 7.52, 95% CI 3.34-16.9, p<0.001) than children with MEE (OR 3.27, 95% CI 1.39-7.63, p<0.01).

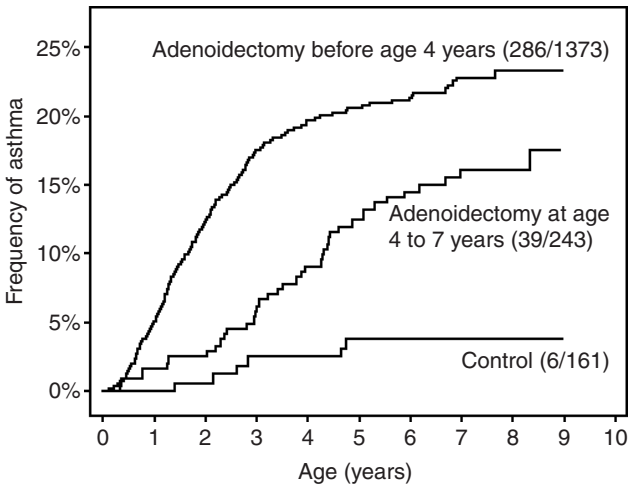


Figure 7. Cumulative frequency of asthma by age.

6. DISCUSSION

6.1. Effect of adenoidectomy on the risk for otitis media in children younger than 4 years

Otitis media is a common reason for seeking medical advice for children. For RAOM and COME, surgical management is an option if conservative management does not help. RAOM and COME are frequent indications for adenoidectomy, which is among the top ten operative procedures in children. Of the 989 adenoidectomies performed at the Department of Otorhinolaryngology, Helsinki University Central Hospital, during the two-year period of 1997-1998, 628 (63%) were performed on children younger than 4 years, and the most common reason (85%) for the surgery was OM (Mattila et al. 2001).

The indications for adenoidectomy are not uniform and the rates vary greatly between countries (Schilder et al. 2004). Some studies suggest that adenoidectomy would be beneficial in RAOM (Paradise et al. 1990) and especially in COME (Gates et al. 1987, Maw and Bawden 1993). However, these studies have been conducted mainly in children older than 4 years. In two recent Finnish studies on children aged 10-24 months, adenoidectomy as a sole procedure compared with antibiotics or placebo and adenoidectomy combined with the insertion of tympanostomy tubes compared with tubes alone showed no major advantage in preventing RAOM (Koivunen et al. 2004, Mattila et al. 2003). The latter study was not a real RCT, as the children were enrolled after the result of the randomization was disclosed to parents. In addition, the 95% CIs in both of the studies were relatively wide, suggesting a lack of efficacy.

The purpose of this study was to test whether adenoidectomy in conjunction with the insertion of tympanostomy tubes offers any major advantage over tubes alone in decreasing the risk for AOM in children younger than 4 years. The study was conducted in accordance with the CONSORT Statement recommendations for RCTs (Moher et al. 2001). The number of OM before recruitment was obtained from primary care medical records and by interviewing parents. However, both under- and overdiagnosing of OM commonly occurs and cannot be fully ruled out. After the allocated operations, the parents of the participants received a patient diary to document all OM episodes during the one-year follow-up. The children had one visit to the study physician at the study hospital one month after the operation. In addition, the parents were contacted by telephone once or twice during the follow-up to assess compliance. By contacting the primary care units, the data on the number of OM episodes during the follow-up became more reliable.

Children with adenoid hyperplasia causing obstructive symptoms, as judged by continuous mouth breathing, were excluded because adenotonsillar surgery among children with obstructive sleep disorders has been shown to result in significant improvement in the QOL (De Serres et al. 2002, Goldstein et al. 2002).

The results showed that adenoidectomy at the time of insertion of tympanostomy tubes did not provide any benefit in preventing AOM episodes in children younger than 4 years who have not previously received tympanostomy tubes. The age of the child, the presence of COME at the time of surgery or the frequency of OM episodes prior to surgery did not affect the outcome.

The results of this study are in line with those of Paradise et al. (1999), confirming that adenoidectomy does not help much in preventing AOM among children who have not received tympanostomy tubes earlier. The findings are also in line with the results of Koivunen et al. (2004) and Mattila et al. (2003), suggesting that adenoidectomy confers no major advantage in preventing RAOM.

Coyte et al. (2001), by contrast, reported that adenoidectomy reduces the occurrence of OM based on a retrospective analysis of hospital discharge records of more than 37 000 children. Their analysis revealed that children who had adenoidectomy combined with the insertion of tympanostomy tubes fared better, as measured by hospitalizations and repeated operations related to OM, than children, who received tympanostomy tubes alone as the first surgery. However, their analysis may have been biased, as children who had adenoidectomy as the first procedure were older at the time of surgery than children who underwent the insertion of tympanostomy tubes alone as their first procedure. Younger children who received tympanostomy alone may have been at a higher risk for OM than the older children who received adenoidectomy with concurrent tympanostomy, leading to a result favouring adenoidectomy.

The present results suggest that the effect of adenoidectomy as the first option for preventing OM in children younger than 4 years is rather modest. As adenoidectomy obviously does not solve the whole OM problem, alternative options need to be evaluated. To understand the factors leading to OM, knowledge of the risk indicators is required. This is essential since eliminating the risk factors may be effective in preventing OM.

6.2. Parental smoking as a risk factor for recurrent acute otitis media after the insertion of tympanostomy tubes

Prevention of OM by risk factor modification is attractive because it avoids the costs and the side-effects of the surgical methods. As the host-related risk factors, i.e. age, genetic predisposition and gender, cannot be modified, one could assume that modifying the environmental risk factors could lessen the possibility of contracting OM.

Environment-related risk factors comprise exposure to respiratory infections in day-care outside the home and/or in large households including season-related factors, parental smoking, short duration of breast feeding and use of a pacifier (Uhari et al. 1996a). Number of siblings and season are clearly factors that cannot be manipulated. Day-care outside the home is very common, especially in Finland where most mothers work full- or at least part-time. Smaller group sizes and improved hygiene are possible ways to decrease the risk of respiratory infections in day-care (Uhari and Möttönen 1999). Mothers are encouraged to breastfeed their babies at least 6 months as well as to decrease the use of a pacifier, which may theoretically decrease the risk of OM. One of the major risk factors that can be modified is parental smoking. However, no reports are available of the effect of parental smoking on the occurrence of AOM episodes after the insertion of tympanostomy tubes.

The intention of this study was to gain information about the effect of risk factors on the occurrence of AOM episodes after the insertion of tympanostomy tubes. Children participating in the randomized study received tympanostomy tubes at the beginning of the trial.

Participants were selected on the basis of their history of OM. The pre-enrolment history of OM of the children who were exposed to passive smoking was similar to those who were not exposed. However, after the enrolment and the insertion of tympanostomy tubes, the adverse effect of parental smoking could be observed.

The smoking habits of the parents were obtained by two questionnaires, one at the beginning and the other at the end of the trial. Most parents reported smoking exclusively outdoors. However, it may have been difficult for some parents to admit that they also smoked indoors, thus directly exposing their child to tobacco smoke. The children were obviously exposed to direct tobacco smoke much more often than reported. The proportions of smoking mothers (35%) and smoking fathers (46%) in this study were much higher than the average daily smoking prevalences of Finnish adults (18% of women and 26% of men) (Statistics Finland 2006). One possible explanation is that recruitment in this study selected those families with a

lower socio-economic status who are attended to by the municipal health care system, while those with a higher socio-economic status prefer the private sector. This fact does not, however, lessen the impact of smoking as a risk factor for contracting OM.

The results of this study showed that maternal smoking is associated with an over 4-fold increase in the risk of RAOM after tympanostomy. This figure is much higher than reported previously (Uhari et al. 1996a). It should, however, be noted that the study children represent a population with a high risk of OM and the result does not necessarily reflect the risk for OM at the population level.

The results of this study are in agreement with those of Maw et al.(1992), who evaluated the effect of parental smoking after adenotonsillar surgery in children with OME. They found that passive smoking is associated with a decreased clearance of MEE after surgery for OM.

These findings give a highly reliable estimate of the detrimental effect of parental smoking on the risk for RAOM after the insertion of tympanostomy tubes. This information can be used to encourage parents to stop smoking, but rates of counselling at medical offices may be low (Tanski et al. 2003, Winickoff et al. 2003).

Childhood OM presents with at least two distinct, albeit overlapping, forms. Some children have a rather indolent persistent MEE (COME), while others experience RAOM with healthy middle ears between the acute episodes. These two clinical presentations may have unique risk factors. Therefore, factors that lead to the development of either COME or RAOM need to be evaluated. This is crucial to gain a better understanding of the pathogenesis of OM.

6.3. Risk factors for childhood persistent middle ear effusion

The factors leading to COME instead of RAOM are largely unknown. Environmental factors, such as exposure to tobacco smoke, number of siblings, and day-care attendance, have previously been reported to increase the overall risk of AOM (Uhari et al. 1996a). Family and twin studies have shown that also genetic predisposition affects the risk of AOM (Casselbrant et al. 1999, Kvaerner et al. 1997, Rovers et al. 2002). Genetic predisposition has an impact on the risk for allergy and asthma as well (Laitinen et al. 2004). Possibly, genetic predisposition or some genetic factors modulate the immune response type of the child, which in turn may have an effect on the development of either COME or RAOM.

The goal in this study was to determine factors that influence the risk for persistent MEE in COME. Both environmental risk factors and genetic predisposition were evaluated. As the

immune response type per se is difficult to evaluate, the frequencies of allergy and asthma among parents of children with COME and RAOM were assessed. In this trial, approximately every fourth child had COME.

The distinction between COME and RAOM is not always clear, as even children with long-standing episodes of MEE may have effusion-free intervals and are thus misdiagnosed as suffering from RAOM. This bias could not fully be ruled out in this study. The diagnosis of COME was based on the findings of COME by the referring primary care physician as well as on MEE present at the insertion of tympanostomy tubes. Of the 57 referred children suspected of having COME, 55 had effusion in the middle ear at the insertion of tubes, confirming the diagnosis of COME rather valid.

The present results indicate that environmental factors might not play a major role in whether a child develops COME or RAOM. No significant difference was present between children with COME and those with RAOM in terms of numbers of siblings, exposure to environmental tobacco smoke and day-care attendance. On the other hand, a genetic predisposition to allergy or asthma, i.e. parental allergy or asthma, appeared to be more often associated with RAOM than with COME. Asthma and allergy are diseases, that are mediated by Th2 immune type responses. Th2 responses are characterized by the production of allergen-specific IgE antibodies and antibody-mediated responses in general (Del Prete 1992). This supports the hypothesis that Th2 immune responses may prevent the development of COME by efficient production of microbe-specific antibodies that augment the elimination of microbes in the middle ear. Although this is highly hypothetical, such antibodies may play an important role in the resolution of MEE.

6.4. Frequency of asthma among otitis-prone children

Otitis-prone children are a special population when considering the frequency of URIs they contract. Asthma is a common disease in childhood, being the most predominant chronic disease among Finnish children under 16 years of age (prevalence ~5%) (Finnish Current Care guidelines 2000, updated 2006). Inflammation of the airways is the main sign in asthma patients. This inflammation is produced by a mixture of allergy, viral respiratory infections and airborne irritants. Persistent IgE-mediated hypersensitivity reactions occur in children up to 7 years of age who have had severe RSV infections during infancy (Tuomilehto et al. 1992).

The purpose of these two surveys was to evaluate the frequency of asthma among otitis-prone children who had undergone adenoidectomy.

Survey A was a questionnaire-based study. The basic intention was not to evaluate whether adenoidectomy per se would influence the risk of asthma, but to estimate the risk of asthma in otitis-prone children. Questionnaire-based studies are known to often be biased because the answers are be modified by accuracy of memory or misunderstandings, etc. In addition, only 59% of the questionnaires in this study were returned, which is a rather low proportion. Another survey was therefore conducted.

Survey B was based on patient records. The operation code for adenoidectomy and the diagnosis for that precise procedure were easy and reliable to reveal, the most difficult part was to find out the real reason for the operation. Otitis-prone condition in children has been the most common indication for adenoidectomy during recent decades in Finland, the predominant otitis-related diagnoses being RAOM and COME.

Both surveys showed that adenoidectomy at an early age was associated with an increased risk for asthma. Adenoidectomy performed because of RAOM was associated with a higher risk for asthma than adenoidectomy performed because of COME, suggesting that children who suffer from repeated infections have an increased risk for childhood asthma.

The association observed between asthma and adenoidectomy is in concordance with the results of Bager et al. (2002), who found an increased risk of atopy in women who had had measles during the first year of life or measles, rubella, varicella and mumps during the first 2 years of life. These individuals apparently had experienced frequent respiratory tract infections very early in life, thus resembling the children who had undergone adenoidectomy at an early age in the present survey. Also rhinovirus infections exacerbate symptoms of asthma (Folkerts et al. 1998). It is thus possible that repeated infections might provoke asthma

symptoms in a child with subclinical bronchial hyperreactivity, thereby increasing the risk for fully developed asthma.

The result of this study and those of Bager et al. (2002) differ from the findings of some other studies. Illi et al. (2001), Bodner et al. (1998) and Strachan et al. (1989, 2000) reported that exposure to microbes decreased the risk of atopy. Illi et al. (2001) found a reduced occurrence of asthma among children with a frequent runny nose during early life, and the other authors observed an inverse association between risk of atopy and family size (Bodner et al. 1998, Strachan 1989, 2000). This apparent discrepancy may be explained by the magnitude or type of exposure. Present knowledge about the underlying causative mechanisms is very weak and contradictory, and thus further studies are needed.

6.5. Impact of this study and future prospects for prevention of otitis media

This study illustrated some factors that are associated with the pathogenesis of childhood OM. The results confirm earlier findings that the surgical management of the otitis-prone child should not include adenoidectomy if nasopharyngeal obstruction is absent. In fact, during the last few years the clinical practice of adenoidectomy has changed, and the number of adenoidectomies in Finland has decreased, especially among children younger than 4 years. This study also showed that parental smoking is a significant risk factor for OM. As the general attitude in society towards smoking has become quite negative, the supportive results of this study could be used to encourage parents of young children to quit smoking. Future prospects in the successful management of OM should include better diagnostic methods, more effective preventive tools and improved knowledge about genetic factors.

7. CONCLUSIONS

The present survey addressed the effect of adenoidectomy in conjunction with the insertion of tympanostomy tubes on subsequent episodes of OM. Adenoidectomy of otitis-prone children younger than 4 years did not significantly prevent subsequent episodes of OM. This result is in line with previously published reports.

An important aspect of treating otitis-prone children is to identify risk factors associated with less favourable outcome. Parental smoking emerged as the most important factor in this study. This information is important in that it may encourage parents to quit smoking, thereby improving their health as well as that of their children.

The pathogenesis of persistent MEE is obscure. This study aimed to find features of this condition by comparing clinical characteristics of children with persistent MEE with those of children with RAOM. As persistent MEE often begins after an acute episode of OM, it shares the same risk factors as RAOM, such as day-care attendance and parental smoking. Consequently, no difference in traditional risk factors for OM between these two child populations was found. Surprisingly, a significant difference emerged in the frequency of asthma and animal dust allergy between parents of these two child populations. Although this finding requires confirmation, it suggests that genetic predisposition strongly influences the pathogenesis of persistent MEE, presumably by influencing the immune response type of the child.

Otitis-prone children often live in an environment that exposes them to recurrent URIs. This may predispose them to other diseases such as asthma. This study evaluated the risk of asthma in otitis-prone children receiving surgical treatment for OM. The risk for asthma was greatly increased in otitis-prone children. Recurrent and excessive exposure to respiratory microbes may predispose to both OM and asthma. This finding stresses the importance of paying attention to respiratory function when treating an otitis-prone child.

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