Tiia Kujala

ACUTE OTITIS MEDIA IN YOUNG CHILDREN

RANDOMIZED CONTROLLED TRIALS OF ANTIMICROBIAL TREATMENT, PREVENTION AND QUALITY OF LIFE
TIIA KUJALA

ACUTE OTITIS MEDIA IN YOUNG CHILDREN
Randomized controlled trials of antimicrobial treatment, prevention and quality of life

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University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu; Oulu University Hospital
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

The purpose of this study was to evaluate the effect of antibiotic treatment and surgery on acute otitis media (AOM), and to evaluate quality of life (QoL) among children with AOM and their parents.

To evaluate the effectiveness of antibiotics, a total of 82 children with AOM were randomized for antibiotic or placebo treatment for 7 days. The duration of middle ear effusion was measured by daily tympanometry screenings at home over 2 weeks. Duration was also measured at clinical visits, including at entry, after 3 days, after 7 days, and then weekly until both ears were healthy according to pneumatic otoscopy or otomicroscopy, or for a maximum of 2 months. Among the group receiving antibiotics, middle ear effusion disappeared 2.0 weeks earlier than among those receiving placebo (P<0.02). On day 14, 69% of children in the antibiotic group and 38% in the placebo group had normal tympanometry findings (P =0.02). On day 60, 5% of children in the antibiotic group and 24% in the placebo group had persistent middle ear effusion (P=0.01).

The effect of surgery was assessed by randomly assigning 300 children with recurrent AOM, aged 10 months to 2 years, into 3 groups: 1. to receive ventilation tubes (VTs), 2. to receive VTs and adenoidectomy and 3. non-surgery. Follow-up of children occurred at clinical visits every 4 months for a 1-year period. If children suffered from upper respiratory symptoms or their parents suspected AOM during this period they were encouraged to receive additional follow-up care. Intervention was considered unsuccessful if a child had 2 AOM episodes in 2 months, 3 episodes in 6 months or persistent effusion lasting for 2 months. Intervention failed in 34% of children in the non-surgery group, 21% in the VT group (P=0.04 compared to non-surgery) and 16% in the group with VT and adenoidectomy (P=0.004 compared to non-surgery).

QoL was assessed among 159 children participating in the study on the effect of surgery in children with recurrent AOM. We used disease-specific (Otitis Media-6) and generic instruments (Child Health Questionnaire-50) to measure QoL among children with AOM and their parents, and the effect of surgery on QoL. Children with AOM and their parents had a significantly poorer QoL than healthy children. QoL improved significantly at 1-year follow-up, but it did not reach the level observed in healthy children. Surgery did not have any additional impact on QoL.

Keywords: adenoidectomy, anti-bacterial agents, child, infant, middle ear ventilation, otitis media, pediatric, quality of life, recurrence, tympanostomy
Tiivistelmä

Työn tavoitteena oli tutkia antibiootin ja kirurgian vaikutusta äkilliseen välikorvatulehdukseen sekä tutkia välikorvatulehduskaupun ja heidän vanhempiensa elämänlaattaa.

82 äkillistä välikorvatulehdusta sairastavaa lasta satunnasti valittiin saamaan joko antibiootti- tai lumelääkettä. Välikorvaeritteen poistumista seurattiin kotona päivittäisillä tympanometriamittauksilla kahden viikon ajan. Seuran takäynnit olivat yhden, kolmen ja seitsemän päivän kuluttua sekä viikoittain, kunnes korvat olivat todettu terveiksi pneumaattisella otoskoopilla tai korvamikroskoopilla tai kahden kuukauden seuranta-aika päättyi. Välikorvaerite poistui kaksi viikkoa aikaisemmin antibiootti- tai lumelääkkeellä (P<0.02). Tympanometria normalisoitui kahden viikon kuluttua 69 %:lla antibiootiryhmästä ja 38 %:lla lumelääkeryhmästä (P=0.02). 60 päivän kuluttua välikorvaeriti oli 5 %:lla antibioottiryhmästä ja 24 %:lla lumelääkeryhmästä (P=0.02).

Kirurgian vaikutavuutta toistuviksi äkillisiksi välikorvatulehdusiin tutkittiin satunnastamalla 300 10–24 kk:n ikäiset lasta saamaan ilmastoointiputket tai sekä ilmastoointiputket että kitarisa- poisto tai ei kumpaankaan. Seuran takäynnit olivat neljän kuukauden välein vuoden ajan tai aina kun lapset sairastuivat ylähengitysotstulehduseen tai vanhemmat epäiliivät välikorvatulehdusta. Interventio katsottiin epäonnistuneeksi (äkillisikä välikorvatulehduskaus 2 / 2 kk, 3 / 6 kk tai jatkuva erite 2 kk) 34 %:lla ilman kirurgiaa hoidetuista lapsista, 21 %:lla ilmastoointiputkiryhmän lapsista (P=0.04 verrattuna ilman kirurgiaa hoidettuihin) ja 16 %:lla lapsista, joille tehtiin sekä kitarisa-poisto että asetettiin ilmastoointiputket (P=0.004 verrattuna ilman kirurgiaa hoidettuihin). Eämänlaadun, äkillisen välikorvatulehduseen sekä siihen liittyvän kirurgian välitöntä selvittettiin 159 lapsella, jotka osallistuivat kirurgian vaikuttavuutta selvittävään tutkimukseen. Eämänlaadua mitattiin sekä tautikohtaisilla (Otitis Media-6) että yleistä elämänlaatu (Child Health Questionnaire-50) mittauksilla kyselylomakkeilla. Äkillistä välikorvatulehdusta sairastava lapsilla ja heidän vanhemmillaan oli merkittävästi huonompi elämänlaatu kuin terveillä. Eämänlaatu paranee merkittävästi vuoden seuranta-aikana, mutta ei saavuttanut terveiden tasoa. Kirurgia ei tuonut mitään lisäähyötyä elämänlaatuun.

Asiasanat: antibiootit, elämänlaatu, kitarisa, lapset, tärykalvo, välikorvatulehdus
With love to my Family
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Oulu, May 2015

Tiia Kujala
### Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
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<tr>
<td>AOM</td>
<td>acute otitis media</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CHQ</td>
<td>Child Health Questionnaire</td>
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<td>ET</td>
<td>Eustachian tube</td>
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<td>H. influenzae</td>
<td><em>Haemophilus influenzae</em></td>
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<td>M. catarrhalis</td>
<td><em>Moraxella catarrhalis</em></td>
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<tr>
<td>MEE</td>
<td>middle ear effusion</td>
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<tr>
<td>NNT</td>
<td>number needed to treat</td>
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<tr>
<td>OM</td>
<td>otitis media</td>
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<tr>
<td>OM-6</td>
<td>Otitis Media-6 questionnaire</td>
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<tr>
<td>OME</td>
<td>otitis media with effusion</td>
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<tr>
<td>PCV-7</td>
<td>heptavalent pneumococcal conjugate vaccine</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>RAOM</td>
<td>recurrent acute otitis media</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>RD</td>
<td>rate difference</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk, risk ratio</td>
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<tr>
<td>SA</td>
<td>static admittance</td>
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<tr>
<td>S. pneumoniae</td>
<td><em>Streptococcus pneumoniae</em></td>
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<tr>
<td>S. pyogenes</td>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td>TM</td>
<td>tympanic membrane</td>
</tr>
<tr>
<td>TPP</td>
<td>tympanic peak pressure</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>URI</td>
<td>upper respiratory tract infection</td>
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<td>US</td>
<td>United States</td>
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<tr>
<td>VT</td>
<td>ventilation tube, tympanostomy tube</td>
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List of original publications

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1 Introduction

Acute otitis media (AOM) is one of the most common diseases among children. Two-thirds of all children suffer at least 1 episode of AOM by age of 3 and one-third suffers from recurrent episodes (Teele et al. 1989). On average time spent with middle ear effusion (MEE) is 2.5 months during the first year of life and 2 months during the second (Paradise et al. 1997, Teele et al. 1989). MEE causes hearing loss of almost 30 dB (Bluestone 2003), and may impact negatively on speech development, education, and behavior (Roberts et al. 2004, Rovers et al. 2000).

Antibiotics are commonly used in the treatment of AOM, which is the most frequent reason for antimicrobial treatment among children (McCaug et al. 2002, Schappert 1992). Antibiotic overuse and the threat of emerging multi-resistant bacterial strains are of concern. Many studies have suggested that AOM can be resolved without antibiotics and guidelines for the treatment of AOM now include observation options. However, most of these studies have not recorded the duration of MEE and thus hearing loss. The main aim of treating AOM should be to eradicate bacteria from the middle ear and to normalize hearing.

AOM causes a great deal of harm to children and their parents and could lead to impaired quality of life (QoL). QoL among children and parents may be influenced by treatment choice. When a child suffers from persistent MEE, ventilation tubes (VTs), with or without an adenoidectomy, can be used to avoid hearing loss. The effect of this type of surgery is unclear in recurrent AOM (RAOM), primarily because the inclusion criteria and the results of previous studies have varied. The effect of these treatment options on QoL is also unclear.
2 Review of the literature

2.1 Terminology and definitions

Otitis media (OM) is an inflammation of the middle ear. The term includes a variety of medical conditions with different signs and symptoms, but without reference to etiology or pathogenesis. AOM is defined as rapid onset of the signs and symptoms of middle ear inflammation, together with MEE and upper respiratory tract infection (URI) symptoms (American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media 2004, Bluestone & Klein 2007b). Synonyms such as acute suppurative OM and purulent OM are commonly used. RAOM is defined as the appearance of 3 or more well-documented and separate AOM episodes in the preceding 6 months or 4 or more episodes in the preceding 12 months with at least 1 episode in the past 6 months (Dowell et al. 1998, Rosenfeld 2003). MEE without the signs and symptoms of acute infection is called OM with effusion (OME) (Bluestone 2003), which is considered to be chronic if it persists for more than 12 to 16 weeks (Berman 1997, Bluestone & Klein 2007b, Karma et al. 1987, Klein et al. 1989). OME may occur either after an episode of AOM or spontaneously because of poor Eustachian tube (ET) function (Rosenfeld 2004). Histologically OME is a chronic inflammatory condition, characterized by inflammation in the middle ear mucosa and overproduction of mucin (Kubba et al. 2000). Other terms for OME include secretory otitis, glue ear, serous OM and mucoid OM. These 2 forms of OM may be considered segments of a disease continuum (Paradise et al. 1993). When MEE spills through tympanic membrane (TM) perforation or VTs, it is called otorrhea.

2.2 Epidemiology

OM is the most common cause of pediatric health care visits and the most frequent reason children consume antibiotics or undergo surgery (Marom et al. 2014). A worldwide systematic review of 21 WHO regional areas from 2005 to present estimated that there are 709 million new cases of AOM annually (Monasta et al. 2012). In 2005, global incidence (new episodes per hundred people per year) was highest in the age group 1–4 (61%) and in the first year of life (45%) (Monasta et al. 2012).
In a recent study of children under 6 years of age in Germany, Italy, Spain, Sweden, and the United Kingdom (UK), the incidence of AOM was 268 per 1000 people in 2007-2008 and 256 between 2008 and 2010 (Liese et al. 2014). In a study from the United States (US), office visits for children with OM increased by 175% from 1975 to 1990 (Schappert 1992), but showed a 30% decrease between 2004 and 2011 (Marom et al. 2014). Also, the rates of RAOM decreased by 28% from 2001 to 2011 (Marom et al. 2014).

In Finland the estimated total number of AOM episodes was 200,000 in 1982 and increased to 500,000 in 1997 (Niemelä et al. 1999); the occurrence of AOM increased by 68% between 1978-1979 and 1994-1995 (Joki-Erkkilä et al. 1998). The number of surgical procedures for OM doubled between 1978-1979 and 1994-1995, and increased by 1.5-fold from 1987 to 2002 in Finland (Haapkylää et al. 2008).

Differences in AOM incidence between countries may be the result of true differences, differences in healthcare systems, social structure and/or diagnostic procedures between physicians. The recent decline in AOM may be due to the introduction of the pneumococcal conjugate vaccine, which appears to have decreased the number of individuals suffering from OM in many studies (Fletcher & Fritzell 2012, Hoffman et al. 2013, Marom et al. 2014).

2.3 Pathogenesis

2.3.1 Anatomical and physiological factors

The middle ear is a cavity containing the ear ossicles, with the ET placed anteriorly, the mastoid air cells posteriorly, TM laterally between the middle and external ear, and the inner ear medially. Other important nearby structures are the skull base/brain and meninges superiorly and the sigmoid sinus posteriorly. The nasopharynx lies behind the nasal cavities and above the soft palate. The nasopharynx is connected to the middle ear cavities by the ETs. The nose, nasopharynx, ETs, middle ear cavities and mastoid air cells are a continuum covered by respiratory mucosa. The ETs regulate air and sound pressure by actively opening when swallowing, yawning or sneezing, and then by passively closing. Changes in body position affect the degree of opening and closing of the ET. The best opening of the ET is achieved by swallowing when in a sitting position and the worst when in a head-down position (Okubo & Watanabe 1990).
The ET also allows the secretions of the middle ear to drain into the nasopharynx with the assistance of secretory cells and the mucociliary defense system and prevents the secretions of the nasopharynx from entering the middle ear (Bluestone 1996).

Young children are susceptible to AOM as a result of the immaturity of the ET (Bluestone 2008). ETs mature by 7 years of age. The ET is shorter, more flexible and horizontal in young children. Children affected by MEE are more likely to have a floppy ET that responds poorly to pressure changes than children without OM (Bluestone et al. 1974, Stenstrom et al. 1991). Also craniofacial anomalies, Down syndrome and cleft palate are associated with ET dysfunction. The nasopharyngeal dimensions have been shown to be smaller in children with OM than those in healthy children (Renko et al. 2007).

### 2.3.2 Viruses

AOM occurs most frequently as a consequence of viral URI (Chonmaitree & Heikkinen 1997, Chonmaitree et al. 2008, Henderson FW et al. 1982, Pukander et al. 1982a), which leads to nasopharyngeal inflammation, ET inflammation and dysfunction, negative middle ear pressure (Arola et al. 1990) and the movement of secretions from the nasopharynx into the middle ear. Viral infection of the nasopharynx creates an environment that promotes bacterial attachment and colonization, adhesion to cells, and invasion of the middle ear (Murphy et al. 2013). In a recent study, human rhinovirus (58% vs. 42%), human bocavirus (52% vs. 20%), polyomaviruses (36% vs. 15%), parainfluenza viruses (29% vs. 9%), adenovirus (25% vs. 6%), and respiratory syncytial virus (28% vs. 9%) were detected significantly more often in the nasopharynx of children with a history of RAOM compared to healthy children (Wiertsema et al. 2011).

Some viruses get to the middle ear passively along with nasal secretions, while others seem to actively invade the middle ear cavity (Heikkinen & Chonmaitree 2003). The most commonly verified virus in MEE during AOM is respiratory syncytial virus. Other important agents are rhino-, influenza- and adenoviruses, along with entero-, parainfluenza- and coronaviruses (Arola et al. 1990, Coker et al. 2010, Heikkinen et al. 1999, Okamoto et al. 1993). The advent of the polymerase chain reaction technique has dramatically increased the detection rates of viruses in MEE specimens. Presence of the virus in MEE has been found to slow down the recovery of AOM (Arola et al. 1990, Chonmaitree et
al. 1990); the rhinovirus especially has been associated with a poor bacteriologic outcome for AOM treated with antibiotics (Sung et al. 1993).

Over 60% of symptomatic URI episodes were complicated by AOM in children 3 years or younger (Chonmaitree et al. 2008). More than half of AOM episodes were diagnosed during the first 4 days and 75% during the first week of a viral URI. The incidence of AOM is highest on days 3 and 4 (Heikkinen & Ruuskanen 1994, Koivunen et al. 1999).

2.3.3 Bacteria

**Nasopharynx**

*Streptococcus pneumonia* (*S.pneumoniae*), *Haemophilus influenzae* (*H. influenzae*), and *Moraxella catarrhalis* (*M. catarrhalis*) colonize the nasopharynx from early infancy and are considered part of the normal flora (Faden et al. 1997). An increased rate of colonization at 3 months of age may identify a subpopulation of children that are at increased risk of OM (Faden et al. 1997). The prevalence of colonization with these pathogens differs by age and is highest during early childhood when over 60% of children are colonized at some point (Casey et al. 2010, Faden et al. 1997, Syrjänen et al. 2001). However, only 40% of children have these pathogens in their nasopharynx at the age 11 to 15 years (Stenfors & Räisänen 1990).

Like nonpathogenic bacterial flora colonizing the nasopharynx, pathogenic bacteria do not cause symptoms until there are changes in the nasopharyngeal milieu. During periods of URI, and in particular during AOM, colonization with middle ear pathogens increases significantly (Faden et al. 1991, Syrjänen et al. 2001). This increase is especially prominent among otitis prone children (Faden et al. 1991) and in children in day-care (Aniansson et al. 1994). Chronic biofilm colonization of the adenoids may act as a reservoir for bacteria entering the middle ear in OM (Saafan et al. 2013). Almost all middle ear pathogens derive from the pathogens colonizing the nasopharynx, but not all nasopharyngeal pathogens enter the middle ear to cause AOM.
**Middle ear effusion**

Bacteria and/or viruses can be detected in the MEE in up to 96% of AOM cases (66% bacteria and viruses together, 27% bacteria alone and 4% viruses alone) (Ruohola et al. 2006). Bacterial pathogens have been reported in 84% of the MEE of AOM (Bluestone & Klein 2007a). Common bacteria in AOM are *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (Chonmaitree & Heikkinen 1997) and to a lesser extent *Staphylococcus aureus* and *Streptococcus pyogenes* (*S. pyogenes*) (both about 5%). The distributions of these three main bacteria in MEE of AOM are all about 25% in Finland (Kilpi et al. 2001).

*S. pneumoniae* is likely to have a more severe clinical picture of AOM and more suppurative complications (Kilpi et al. 2001), and a study of children with AOM has demonstrated a close connection between it and the influenza virus (Heikkinen et al. 1999). *H. influenzae* is associated with RAOM (Kilpi et al. 2001) and with AOM with conjunctivitis (Barkai et al. 2009). AOM attributable to *M. catarrhalis* rarely progresses to acute mastoiditis or intracranial infections (Lieberthal et al. 2013). *S. pyogenes* usually occurs in older children, but has been shown to cause a greater degree of inflammation, more spontaneous rupture of the TM and more acute mastoiditis compared to other bacterial pathogens (Segal et al. 2005).

### 2.3.4 Immunology

Immaturity of the immune system may also contribute to AOM. The airway epithelium is the first line of defense against respiratory viruses and bacteria. The local mucosal defense consists of mechanical, innate and acquired/adaptive systems. The mucociliary system and the mucus produced by the secretory cells in the ET form a barrier against pathogens and protect the epithelium; dysfunction of this system is an important risk factor for OM (Lim et al. 2000). When respiratory viruses and bacteria interact with airway epithelial cells, antimicrobial molecules such as lysozyme, lactoferrin, beta defensins and the surfactant proteins are induced as part of an innate immune response and influence the adaptive immune system (Vareille et al. 2011). Defects in the expression or regulation of these molecules may also be a major risk factor for OM (Lim et al. 2000). Waldeyer's ring belongs to the mucosa-associated lymphoid tissue, which forms the primary defense against pathogens at the entry of the upper respiratory tract. The lymphoid cells of the adenoid can recognize and destroy
nasopharyngeal pathogens. Adenoids participate in the local defense by supplying secretory IgA and phagocytic cells (Ivarsson & Lundberg 2001). Deficiency in secretory IgA coating of the nasopharyngeal bacteria may contribute to the otitis prone condition (Stenfors & Räisänen 1993).

2.4 Risk factors

There are host- and environment-related risk factors for AOM (Hoffman et al. 2013) (Table 1). Young age is the most important risk factor for AOM (Alho et al. 1991, Teele et al. 1989); the occurrence of AOM peaks in children 6-12 months of age (Alho et al. 1991, Rye et al. 2011a, Sipilä et al. 1987, Teele et al. 1989). Before 1 year of age, 42%-79% of children experience at least 1 episode of AOM and about 71%-91% of children have AOM by the age of 24 months (Alho et al. 1991, Paradise et al. 1997, Sipilä et al. 1987, Teele et al. 1989). By 1 year of age, 17% of children had 3 or more AOM episodes (Sipilä et al. 1987, Teele et al. 1989). Half of all children younger than 2 years who have been treated for AOM will experience a recurrence within 6 months (Damoiseaux et al. 2006). Experiencing the first episode of AOM at a young age predisposes children to suffering a recurrence (Hoffman et al. 2013, Howie et al. 1975, Teele et al. 1989); of the children with an AOM onset before 6 months of age, 80% developed frequent episodes of AOM (Harsten et al. 1989).

Each risk factor that makes URI more common also increases the risk of AOM (Hoffman et al. 2013). Children aged 6-12 months suffer an average of 6 to 8 URIs per year and after the age of 2 to 3 years URIs become less prevalent (Pukander et al. 1982a, Teele et al. 1989). During the first years of life, boys appear to have more URIs than girls (Alho et al. 1990, Hoffman et al. 2013, Pukander et al. 1982a, Sipilä et al. 1987, Teele et al. 1989). After the age of 4-5 years the difference in AOM morbidity is equal between the genders (Pukander et al. 1982a). The incidences of URIs and AOMs showed a similar seasonal pattern with an increase in the autumn and in spring and decreases in midwinter and even more in the summer in Finland (Alho et al. 1991, Pukander et al. 1982a, Vesa et al. 2001); this same variation was also found in the UK and the US (Williamson et al. 1991). Conversely, seasonal variation was not found in children with RAOM younger than 1 year of age and in children 5 years old and over (Williamson et al. 1991).

The number of children together, at home or in day-care, seems to be a risk factor for URI and AOM (Alho et al. 1990, Aniansson et al. 1994, Paradise et al. 1997).
The risk for AOM is higher among children attending a day-care center than children in family day-care (Alho et al. 1990). This is mostly due to the increased transmission of viruses from other children and the increased nasopharyngeal colonization by bacterial pathogens (Aniansson et al. 1994). The adverse effect of day-care is most evident in children under 2 years old (Wald et al. 1991).

Although the mechanism of tobacco smoke as a risk factor to AOM is unclear, it has been shown that tobacco smoke contains substances that prompt dysfunction of ciliated cells, epithelial damage, and facilitation of the adhesion and colonization of pathogenic microbes (Wanner 1985, Willems et al. 2005). Eliminating exposure to passive tobacco smoke has also been postulated to reduce the incidence of AOM in infancy (Paradise 1997).

Breastfeeding for at least 4 to 6 months reduces AOM and RAOM (Daly & Giebink 2000, Paradise 1997). Also partial breastfeeding for 6 months or longer is associated with reduced risk of RAOM (Hatakka et al. 2010). There are many possible explanations for the protective effect of breastfeeding. Human milk contains large amounts immunoglobulin with antibodies, which can offer protection via passive mucosal defenses, as well as factors of innate immune system (Hanson 1998). Also, higher serum IgG might facilitate protection against AOM and nasopharyngeal colonization in breastfed children (Hoffman et al. 2013). The aspiration of fluids into the middle ear may be easier in bottle-fed infants because of the different intraoral pressure and more horizontal position during feeding (Teel et al. 1989).

Pacifier use may modify the colonization of the mucous membranes of the mouth and nasopharynx. Sucking on a pacifier could also be harmful for the functioning of the ET. In a study of 482 children, parents of children younger than 18 months old were instructed to limit pacifier use during their prescheduled visits to the clinic (Niemelä et al. 2000). After the intervention, a 21% decrease in continuous pacifier use at the age of 7 to 18 months was achieved, and the occurrence of AOM per person-months at risk was 29% lower among children at intervention clinics than in control clinics. Children who did not use a pacifier continuously had 33% fewer AOM episodes than children who did. (Niemelä et al. 2000). The use of a pacifier was found not to increase the risk of URI (Niemelä et al. 1995).

AOM heritability has been reported to be around 40%–70% (Rye et al. 2011a). Parental history of AOM does not appear to be as important as a history of AOM in siblings (Teel et al. 1989). However, one third of all children without
RAOM have an otitis prone family history (Harsten et al. 1989). Twin and triplet studies have provided powerful evidence for a genetic predisposition towards OM (Kvaerner et al. 1997). The genetic factors resulting in predisposition towards OM are not well understood (Rye et al. 2011a), but recently specific gene polymorphisms in TLR4 (MacArthur et al. 2014) and FBXO11 (Rye et al. 2011b) have been implicated as risk factors for OM.

AOM is more common in white populations than in black populations (Hoffman et al. 2013). Certain populations are known to have a higher incidence of OM, for example Australian aborigines, New Zealand Maoris, American Indians, Alaskan Eskimos and children from Greenland (Coates et al. 2002, Giles & Asher 1991, Kaplan et al. 1973, Koch et al. 2011, Wiet et al. 1980). A study of Apache-Indians showed that even when children from higher risk populations are adopted into non-risk families, the risk of OM remains (Spivey & Hirschhorn 1977).

Table 1. Risk factors for acute otitis media and recurrent acute otitis media.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Design</th>
<th>N</th>
<th>Age, Outcome groups</th>
<th>RR or OR (95% CI)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Population based cohort</td>
<td>146822</td>
<td>AOM 0-1 vs. 10-15 years of age</td>
<td>RR 18.3</td>
<td>Pukander et al. 1982b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-2 vs. 10-15 years of age</td>
<td>RR 20.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-3 vs. 10-15 years of age</td>
<td>RR 14.3</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Cohort</td>
<td>877</td>
<td>AOM Boys vs. girls OR 1.7 (1.21-2.38)</td>
<td></td>
<td>Teele et al. 1989</td>
</tr>
<tr>
<td></td>
<td></td>
<td>698</td>
<td>AOM 0-3              OR 2.10 (1.31-3.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heritability</td>
<td>Meta-analytic review of 3 studies</td>
<td>1240</td>
<td>AOM Positive vs. negative family history RR 2.63 (1.86-3.72)</td>
<td></td>
<td>Uhari et al. 1996b</td>
</tr>
<tr>
<td>Cow’s milk allergy</td>
<td>Case-control</td>
<td>260</td>
<td>RAOM Yes vs. no RR 2.14 (1.21-3.78)</td>
<td></td>
<td>Juntti et al. 1999</td>
</tr>
<tr>
<td>Risk factor</td>
<td>Design</td>
<td>N</td>
<td>Age, years</td>
<td>Outcome</td>
<td>Comparison groups</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>----</td>
<td>------------</td>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>Environmental factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URI</td>
<td>Cohort</td>
<td>221</td>
<td>1-3</td>
<td>RAOM</td>
<td>Recurrent URI during 12 moths yes vs. no</td>
</tr>
<tr>
<td>Season</td>
<td>Cohort</td>
<td>2512</td>
<td>0-2</td>
<td>AOM</td>
<td>Spring and autumn vs. summer</td>
</tr>
<tr>
<td>Siblings</td>
<td>Meta-analytic review of 2 studies</td>
<td>1344</td>
<td>AOM</td>
<td>At least 1 sibling vs. no siblings</td>
<td>RR 1.92 (1.29-2.85)</td>
</tr>
<tr>
<td>Day-care outside home</td>
<td>Meta-analytic review of 6 studies</td>
<td>1972</td>
<td>AOM</td>
<td>Day-care outside home vs. home care</td>
<td>RR 2.45 (1.51-3.98)</td>
</tr>
<tr>
<td></td>
<td>Meta-analytic review of 3 studies</td>
<td>1111</td>
<td>RAOM</td>
<td>Day-care outside home vs. home care</td>
<td>RR 1.82 (1.21-2.73)</td>
</tr>
<tr>
<td>Cohort</td>
<td>221</td>
<td>0-2</td>
<td>RAOM</td>
<td>13-23 months vs. 12 months or less day-care attendance</td>
<td>OR 3.34 (1.03-10.78)</td>
</tr>
<tr>
<td>Use of pacifier</td>
<td>Cohort</td>
<td>129</td>
<td>0-2</td>
<td>RAOM</td>
<td>Use of pacifier vs. no use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>138</td>
<td>2-3</td>
<td>RAOM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meta-analytic review of 2 studies</td>
<td>4110</td>
<td>RAOM</td>
<td>Use of pacifier vs. no use</td>
<td>RR 1.24 (1.06-1.46)</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>Meta-analytic review of 6 studies</td>
<td>2548</td>
<td>AOM</td>
<td>Over 3 months vs. 0 months</td>
<td>RR 0.87 (0.79-0.95)</td>
</tr>
<tr>
<td>Parental smoking</td>
<td>Meta-analytic review of 3 studies</td>
<td>1784</td>
<td>AOM</td>
<td>Yes vs. no</td>
<td>RR 1.66 (1.33-2.06)</td>
</tr>
<tr>
<td>Cohort</td>
<td>217</td>
<td>1-4</td>
<td>RAOM</td>
<td>Maternal smoking after tympanostomy yes vs. no</td>
<td>OR 4.15 (1.45-11.9)</td>
</tr>
</tbody>
</table>

Abbreviations: (R)AOM, (Recurrent) Acute otitis media. RR, Risk ratio. OR, Odds ratio.
2.5 Symptoms, duration and natural history

2.5.1 Symptoms

Several signs and symptoms that are traditionally associated with AOM, for example fever, purulent rhinitis, coughing, poor appetite, vomiting, diarrhea, and tiredness, have been shown to be unspecific to AOM but to be caused by the concurrent viral infection (Heikkinen & Ruuskanen 1995, Kontiokari et al. 1998, Laine et al. 2010, Niemelä et al. 1994, Uhari et al. 1995). In a study of 857 healthy day-care children (mean age 3.7 years) who had their symptoms compared during URIs with and without AOM over a three month time period, 138 children had URI with and without AOM (Kontiokari et al. 1998). The symptom with the strongest association with AOM was earache, [Risk ratio (RR) 21.3, 95% confidence interval (CI) 7.0 to 106, P<0.0001], but sore throat (RR 3.2, 95% CI 1.1 to 11, P=0.027), night restlessness (RR 2.6, 95% CI 1.1 to 6.9, P=0.024) and fever (RR 1.8, 95% CI 1.1 to 3.2, P=0.025) also had significant associations (Kontiokari et al. 1998). Logistic regression analysis showed that 71% of the cases were correctly diagnosed based on the symptoms of earache and night restlessness (Kontiokari et al. 1998). However, in young preverbal children, ear pain (as suggested by tugging/rubbing/holding of the ear), excessive crying, fever, or changes in the child’s sleep or behavior pattern as noted by the parent are relatively nonspecific symptoms (Lieberthal et al. 2013). In another study of symptoms of AOM among children 6 to 35 months of age, a total of 469 children had URI with or without AOM (Laine et al. 2010). In that study the most common reason for parental suspicion of AOM, restless sleep, was not predictive of AOM. Neither ear rubbing, the occurrence of fever nor the highest mean temperature within 24 hours predicted AOM. The duration and severity of symptoms were not predictive for AOM and symptom-based scores cannot differentiate AOM from respiratory tract infection in young children. (Laine et al. 2010).

2.5.2 Duration of symptoms

The risk for prolonged symptoms was 2 times higher for children younger than 2 years old with bilateral AOM than for children 2 years of age and older with unilateral AOM (Rovers et al. 2007). In a meta-analysis of 6 randomized controlled trials (RCTs) for AOM, 37% of children between 6 months to 12 years
of age had pain and/or fever at 3 to 7 days in the observation groups (Rovers et al. 2007). There are 2 RCTs (Hoberman et al. 2011a, Tähtinen et al. 2011), both of which used stringent diagnostic criteria consistent with those in the recent guideline (Lieberthal et al. 2013) for diagnosing AOM. Among children younger than 2 years who received placebo, 14% had a sustained resolution of symptoms by day 2, 36% by day 4, and 53% by day 7 (Hoberman et al. 2011a). In the second study, among children younger than 3 years old who had received a placebo, 78% had some improvement in their overall condition by day 3, and, by day 8, 84% had some improvement but less than 13% were healthy with respect to their overall condition (Tähtinen et al. 2011).

2.5.3 Duration of middle ear effusion

MEE following an episode of AOM can often take weeks or even months to resolve. Twelve percent of children were free from MEE by otoscopy by day 8 in the placebo group in the RCT with stringent diagnostic criteria (Tähtinen et al. 2011). In an RCT of 563 children with non-severe AOM cases given a placebo, 37% of children were free from MEE after 2 weeks (43% of children less than 2 years old at 6 weeks and 54% of children over 2 years old at 6 weeks) (Kaleida et al. 1991). OME after untreated AOM had a 59% resolution by 1 month and a 74% resolution by 3 months in the meta-analysis of 63 RCTs or cohort studies (Rosenfeld & Kay 2003). In the Boston cohort study, the total time spent with MEE during the first year of life was estimated to be 75 days and 61 days in the second year of life (Paradise et al. 1997, Teele et al. 1989). Independent predictors of a prolonged duration of MEE after AOM were the age less than 2 years old (Iino et al. 1993, Rothman et al. 2003, Shurin et al. 1979), bilateral AOM (Rothman et al. 2003), male gender, sibling history of ear infection, and not being breast-fed (Teele et al. 1989).

RAOM has been found to spontaneously heal in the review (Rosenfeld & Kay 2003) of 14 RCTs of antibiotic prophylaxis for RAOM in children 2 months to 15 years of age, excluding children with OME or persistent MEE from participation. Children with RAOM entered these trials with a mean baseline rate of 5.5 or more annual episodes but averaged only 2.8 annual episodes while taking a placebo (Rosenfeld & Kay 2003). Furthermore, 41% of children had no additional episodes of AOM while on a placebo for a median duration of 6 months, and 83% had only 2 or fewer episodes. Seventeen percent of the children
remained otitis prone with 3 or more total AOM episodes. (Rosenfeld & Kay 2003).

2.6 Diagnosis

Criteria to diagnose AOM vary both in the literature and in clinical practice. AOM was previously defined as being present when the child had a sudden and short-term inflammation of the middle ear with the presence of MEE or a purulent discharge through the TM (Berman 1997, Karma et al. 1987, Klein et al. 1989). In 2004, the American Academy of Family Physicians and American Academy of Pediatrics (AAP) published the “Clinical Practice Guideline: Diagnosis and Management of Acute Otitis Media” with definitions for the acute onset of symptoms, presence of MEE and signs of acute middle ear inflammation for AOM with children from 6 months to 12 years of age. (American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media 2004). In 2009, the AAP convened a new subcommittee to review and revise the previous guideline (Lieberthal et al. 2013). The current guideline endorses stringent otoscopic diagnostic criteria as a basis for management decisions to discriminate AOM from OME (Table 2). Diagnosing between AOM and OME is important given that antibiotic treatment is unnecessary for OME.

2.6.1 Pneumatic otoscopy

Pneumatic otoscopy and tympanometry is the standard tool used in diagnosing OM (Lieberthal et al. 2013). Examination of the TM is a subjective method and active training improves the accuracy of diagnosis of AOM. Sufficient lighting and cerumen removal are necessary. In one study, when pneumatic otoscopy was performed and the findings were compared to those obtained via myringotomy, sensitivity to AOM was 93% and specificity was 58% (Finitzo et al. 1992). TM changes in AOM can be observed as early as the first day of symptomatic viral URI and changes may be present at various stages even in the same child with bilateral disease (Kalu et al. 2011).
Table 2. Guidelines for acute otitis media: diagnosis, treatment and prevention.

<table>
<thead>
<tr>
<th>Acute otitis media Clinical practice guideline from AAP 2013</th>
<th>Finnish nationwide guideline 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Diagnosis</strong> A. Moderate to severe bulging of the TM or new onset of otorrhea not due to acute otitis externa</td>
<td>A. Acute URI with impaired or absent mobility of TM or MEE with</td>
</tr>
<tr>
<td>B. Mild bulging of the TM and recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM</td>
<td>C. red, yellowish or light, cloudy, flat or bulging of TM, light reflex diminished or absent from TM</td>
</tr>
<tr>
<td>C. Do not diagnose AOM in children who do not have MEE (based on pneumatic otoscopy and/or tympanometry)</td>
<td></td>
</tr>
<tr>
<td><strong>2. Pain</strong></td>
<td></td>
</tr>
<tr>
<td>If pain is present, the clinician should recommend treatment to reduce pain (ibuprofen and paracetamol)</td>
<td></td>
</tr>
<tr>
<td><strong>3. Antibiotic therapy</strong></td>
<td>A. If the diagnosis is sufficiently certain, it is recommended as a rule that AOM be treated with antibiotics.</td>
</tr>
<tr>
<td>A. In severe AOM (i.e., moderate or severe otalgia or otalgia for at least 48 hours or a temperature of 39°C or higher) in children 6 months and older</td>
<td>B. Particularly in children under two years of age, bilateral AOM and otorrhea act in favour of starting antibiotic treatment.</td>
</tr>
<tr>
<td>B. In non-severe bilateral AOM (i.e., mild otalgia for less than 48 hours and a temperature less than 39°C) in children from 6 months through 23 months of age</td>
<td>C. If the co-operation with the parents leads to the conclusion that in non-severe AOM antibiotic treatment is not started, the child’s condition should be monitored closely; the child should be re-examined after 2-3 days if his condition has not notably improved.</td>
</tr>
<tr>
<td>C. In non-severe unilateral AOM in children from 6 months to 23 months of age: either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent</td>
<td></td>
</tr>
<tr>
<td>D. In non-severe in 24 months or older children: either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent</td>
<td></td>
</tr>
<tr>
<td>Acute otitis media</td>
<td>Clinical practice guideline from AAP 2013</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>A. 80 mg/kg/day, up to the daily dose divided by two when the child has not received amoxicillin in the past 30 days or the child does not have concurrent purulent conjunctivitis or the child is not allergic to penicillin.</td>
</tr>
<tr>
<td></td>
<td>B. Prescribe amoxicillin-clavulanate (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate, in 2 divided doses), when the child has received amoxicillin in the last 30 days or has concurrent purulent conjunctivitis, or has a history of RAOM unresponsive to amoxicillin.</td>
</tr>
<tr>
<td></td>
<td>C. For children younger than 2 years and children with severe symptoms, a standard 10-day course is recommended. A 7-day course of oral antibiotic appears to be equally effective in children from 2 to 5 years of age with mild or moderate AOM. For children 6 years old and older with mild to moderate symptoms, a 5- to 7-day course is adequate treatment.</td>
</tr>
<tr>
<td></td>
<td>D. Reassess the patient if the caregiver reports that the child’s symptoms have worsened or failed to respond to the initial antibiotic treatment within 48 to 72 hours and determine whether a change in therapy is needed.</td>
</tr>
<tr>
<td></td>
<td>E. If the child’s condition does not become better despite antibiotic treatment, a reassessment should be made.</td>
</tr>
<tr>
<td></td>
<td>F. Reassessment after 3-4 weeks of treatment initiation is recommended even if a child is symptom free.</td>
</tr>
</tbody>
</table>

4. Prevention

Antibiotic: Do not prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with RAOM.

The efficacy of long-term antibiotic prophylaxis for AOM prevention is statistically significant but small. Because of potential for increasing bacterial resistance long-term antibiotic therapy should be considered critically.
Acute otitis media Clinical practice guideline from AAP 2013
Vaccines Recommend pneumococcal conjugate vaccine to all children according to the schedule of the Advisory Committee on Immunization Practice, AAP and AAFP.

Finnish nationwide guideline 2010
10-valent pneumococcal conjugate vaccine started to be used in the national vaccination program for young children in September 2010 in Finland.

Recommend annual influenza vaccine to all children according to the schedule of the Advisory Committee on Immunization Practices, AAP and AAFP.

Recommend annual influenza vaccine for all children 6 to 35 months of age. Both inactivated and live attenuated influenza vaccine has been shown to reduce AOM during a flu epidemic.

Abbreviations: AAFP, American Academy of Family Physicians. AAP, American Academy of Pediatrics. AOM, Acute otitis media. MEE, Middle ear effusion. RAOM, Recurrent acute otitis media. TM, Tympanic membrane. URI, Upper respiratory tract infection.
1 Lieberthal et al. 2013
2 Acute otitis media. Current Care Guidelines 2010
3 When observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms

### 2.6.2 Tympanometry

Tympanometry is a measurement of acoustic admittance as a function of ear canal pressure, and it is useful with a co-operative child. The sensitivity of tympanometry for the detection of MEE has been reported as 79%-90% and the specificity as 86%-93% (Finitzo et al. 1992, Helenius et al. 2012, Koivunen et al. 1997). In a study that combined tympanometry and pneumatic otoscopy, the sensitivity was 90% and the specificity 90% (Finitzo et al. 1992). In other words, a tympanogram with an A curve almost eliminates the possibility of abundant MEE (Figure 1). A tympanogram with a B curve is associated with MEE but can also be due to other reasons such as stiffness of the TM or obstruction of the ear canal (Figure 1). A tympanogram with a C curve can result from low middle ear pressure or the presence of MEE (Figure 1). Among children with MEE, flat tympanograms reportedly correspond to hearing losses ranging from 20 to 50 dB (MRC Multi-centre Otitis Media Study Group 2009), whereas a peaked tympanogram rules out the risk for conductive hearing impairment (Dempster & MacKenzie 1991). Tympanometry cannot distinguish between AOM and OME. Thus, tympanometry can be used as an adjunctive tool, but accurate diagnosis requires careful pneumatic otoscopy.
Fig. 1. Tympanograms; A curve, B curve and C curve. The classification of tympanograms is based on studies by Margolis et al. and Jerger (Jerger 1970, Margolis & Heller 1987). An A curve, with a static admittance (SA) of ≥0.2 mmho and tympanic peak pressure (TPP) of >-139 daPa, is classified as normal. When the SA is <0.2 mmho, the tympanogram is called a B curve. In C curve the SA is ≥0.2 mmho and the TPP is <-139 daPa.

2.7 Complications and sequelae

Infection of the middle ear can spread to surrounding structures and have serious consequences. As with most infectious diseases, the burden of AOM varies substantially across countries, the main differences residing in the frequency of suppurative complications such as mastoiditis and meningitis and of hearing loss (Vergison et al. 2010)

2.7.1 Hearing impairment

The most frequent complication of OM is hearing loss. OME is the most common cause of hearing impairment among children in the developed world (Monasta et al. 2012). Hearing impairment in OM affects as many as 80% of all children at some stage (Kubba et al. 2000, van Zon et al. 2012). Medical care of children with AOM has improved such that only a few will suffer permanent hearing loss (Rosenfeld & Kay 2003, van Zon et al. 2012). A worldwide systematic review
estimated that OM related hearing impairment was present in 30.82 per 10,000 of the population (Monasta et al. 2012).

Conductive hearing loss in OME is usually between 15 and 40 dB, with an average loss of 27 dB (Bluestone 2003). Overall, hearing levels vary based on the volume of MEE (Koivunen et al. 2000). Thirty-one percent of children aged 2 to 12 years showed conductive hearing losses of more than 20 dB one month after the diagnosis of AOM (Kaleida et al. 1991, van Buchem et al. 1981), and after 2 months the figure was still 19% (Kaleida et al. 1991).

2.7.2 Language development and education

Conductive hearing loss due to fluctuating or prolonged MEE, particularly if bilateral in early childhood, may have harmful consequences later in school age. A nation-wide, population-based study of 1708 children in 119 school classes carried out in Finland evaluated the association between early RAOM and later school achievement (Luotonen et al. 1998). RAOM episodes before the age of 3 years were associated with lower performance in mathematical skills (RR 1.2 to 1.4, 95% CI 1.0 to 1.7, P=0.05) among girls, and in reading (RR 1.3, 95% CI 1.0 to 1.6, P=0.05) and oral performance (RR 1.2, 95% CI 1.1 to 1.4, P=0.01) among boys (Luotonen et al. 1998). The authors concluded that even though the RRs were low, the finding is still important because RAOM is a common problem during infancy and school achievement has many practical influences on a child's future (Luotonen et al. 1998). Possible linguistic delays in children with RAOM are suggested to be consequences of an immature central auditory system with auditory deprivation being a result of repeated fluctuant periods of hearing loss (Whitton & Polley 2011). Recently, in a study among 44 2-year-old Finnish children, it was found that children with RAOM had an elevated responsiveness for frequency and intensity changes and an immature pattern of discriminating small speech sound contrasts, such as consonants (Haapala et al. 2014).

In an RCT of 187 children aged 1 to 2 years old with persistent OME it was found that there were delays in expressive language compared with their age expected values (Rovers et al. 2000). In a meta-analysis that included 14 prospective studies or RCTs, both receptive and expressive languages were impaired in children who had previously suffered from OM, when compared with controls (Roberts et al. 2004). Time spent with MEE during the first 3 years of life was associated with significantly lower scores in mathematics and reading at age 7 in prospective cohort studies of 207 children (Teele et al. 1990).
Also studies with only small or questionable developmental delays have been published. In a meta-analysis that included 14 studies, small impairments in both receptive and expressive languages were found in children who had previously suffered from OM when compared with controls (Roberts et al. 2004). OME caused either small, circumscribed impairments of receptive language and verbal aspects of cognition in certain groups of children, or unidentified, confounding factors predisposed children both to early-life OM and to certain types of developmental impairment (Paradise et al. 2000). In randomized trials, prompt VT placement did not markedly improve the later cognitive outcome of children with chronic MEE over that of children who underwent surgery later (Maw et al. 1999, Paradise et al. 2005, Paradise et al. 2007, Rovers et al. 2000).

2.7.3 Mastoiditis

Mastoiditis occurs when AOM spreads from the middle ear into the mastoid air cells and their covering peristium, with symptoms of AOM plus post-auricular swelling and mastoid tenderness present. The condition typically requires hospital admission, intravenous antibiotics, and surgery if an abscess has formed or the mastoiditis has not responded to antibiotics. Mastoiditis usually occurs in children under 2 years of age (Chesney et al. 2014). Bacterial distribution in mastoiditis differs from that of AOM. In Finland between 2003 and 2012, the most common pathogens were S. pneumoniae (38%), S. pyogenes (11%) and Pseudomonas aeruginosa (11%) (Laulajainen-Hongisto et al. 2014).

The incidence of mastoiditis in the Western world is about 1-4/100000/ year (Van Zuijlen et al. 2001). The incidence of acute mastoiditis in the Netherlands (with a low antibiotic prescription rate of 31%) and in Norway and Denmark (with prescription rates of about 70%) is about the same 4/100000/ year (Van Zuijlen et al. 2001). In the US, the UK and Australia (all with very high prescription rates of about 96%), the incidence rates were considerably lower, ranging from 1.2 to 2.0/100000/ year (Van Zuijlen et al. 2001). Between 2003 and 2012, the incidence of mastoiditis was 1.88/100000/year in Finland (Laulajainen-Hongisto et al. 2014). In the Netherlands the incidence has increased by treating AOM more conservatively (Van Zuijlen et al. 2001). It has been found that antibiotics cut the risk of mastoiditis in half (Thompson et al. 2009). The use of pneumococcal vaccine has not been shown to affect the incidence and clinical picture of mastoiditis, and S. pneumoniae remains the most common pathogen (Van Zuijlen et al. 2001).
2.7.4 Others

Approximately 5% of AOM in children leads to perforation of the TM (Kalu et al. 2011). Most perforations of the TM heal itself. Persistent perforation has high success rates for surgical closure with a single outpatient procedure (Kalu et al. 2011).

The incidence of intratemporal and intracranial complications of AOM has decreased, and the need for operative treatment has declined in developed countries during the antibiotic era. In Southern Finland, from 1990-2000, the incidence of intratemporal and intracranial complications of AOM was 1.1/100000/year (Leskinen & Jero 2004). Intratemporal complications of OM include facial nerve paralysis, cholesteatoma, adhesive OM, tympanosclerosis and ossicular discontinuity, and resorption or fixation. Rare but serious intracranial complications, mainly as sequelae of untreated mastoiditis, include meningitis, brain abscess, sigmoid sinus thrombosis, extradural abscess, and subdural empyema. A worldwide systematic review estimated that 21,000 deaths were attributable to OM related complications (Monasta et al. 2012).

2.8 Treatment

2.8.1 Pain medication

Analgesics relieve pain associated with AOM within 24 hours (Bertin et al. 1996) and should be used for as long as necessary, regardless of whether antibiotic therapy is prescribed (Table 2) (Lieberthal et al. 2013). Eardrops with analgesic components provided additional but brief benefit with AOM (Adam et al. 2009).

2.8.2 Antibiotics or observation

AOM is the most frequent reason for antimicrobial treatment in children (McCaig et al. 2002, Schappert 1992). A beneficial effect of antibiotics on AOM was first demonstrated in 1968 (Halsted et al. 1968). The rationale for antibiotic therapy in children with AOM is based on the high prevalence of bacteria in the MEE (Heikkinen & Chonmaitree 2003). Observation without antibiotics is also an option. This is based on systematic reviews of AOM, in which the majority of uncomplicated cases of AOM resolved spontaneously without suppurative complications (Takata et al. 2001).
Benefits of antibiotic treatment

Antibiotics reduce pain and/or fever in children with AOM. Several RCTs have revealed a 6-12% increase in clinical improvement of symptoms and signs with antibiotics compared to placebo or no treatment (Coker et al. 2010, Rovers et al. 2006, Sanders et al. 2009). In a Cochrane review (Table 3A), 60% of children were painless at 2 days post-treatment regardless of whether they had placebo or antibiotics, and 82% of children had spontaneously recovered from pain by day 7 (Venekamp et al. 2013). According to the 2 RCTs that used stringent diagnostic criteria for diagnosing AOM, antimicrobial treatment was more beneficial than in previous studies, showing a 26% to 35% increase in clinical improvement (Table 3B) (Hoberman et al. 2011a, Tähtinen et al. 2011).

Treatment with amoxicillin–clavulanate significantly accelerated the resolution of fever, poor appetite, decreased activity, and irritability (Tähtinen et al. 2011). Antibiotic therapy also decreased school or day-care absence and parent days missed from work (Le Saux et al. 2005, Little et al. 2001, McCormick et al. 2005, Neumark et al. 2007, Tähtinen et al. 2011). In most studies, antibiotics were most beneficial in children younger than 2 years of age with bilateral AOM or with otorrhea (Hoberman et al. 2011a, Rovers et al. 2006, Sanders et al. 2009, Tähtinen et al. 2011, Venekamp et al. 2013).

Several randomized studies and meta-analyses concluded that antimicrobial treatment has no impact on the duration of MEE as assessed by tympanometry or otoscopy (Rovers et al. 2006, Sanders et al. 2009, van Buchem et al. 1981, Venekamp et al. 2013). However, in studies that used stringent diagnostic criteria for AOM, the duration of MEE was shorter among children who received antimicrobial treatment as compared to placebo (Hoberman et al. 2011a, Tähtinen et al. 2011). In the study by Tähtinen et al., 66% of the children in the amoxicillin-clavulanate group and 81% of the children in the placebo group had MEE 1 week after the onset of AOM (Tähtinen et al. 2011). In the study by Hoberman et al., 50% of children in the amoxicillin-clavulanate group and 63% in the placebo group had MEE 3 weeks after the onset of AOM (P=0.05) (Hoberman et al. 2011a).

In addition, tube otorrhea was resolved in 82% of children receiving amoxicillin-clavulanate compared with 41% of children taking a placebo (NNT=2) at the end of the 7-day medication period among young children with VTs (Ruohola et al. 2003). The median duration of bacterial growth in the middle-ear
fluid was shorter in the antibiotic than in the placebo group (1 vs. 8 days) (Ruohola et al. 2003).

Table 3. a) Antibiotics versus placebo for acute otitis media. Summary of findings for the main comparison of Cochrane review (Venekamp et al. 2013).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of patients (RCTs)</th>
<th>RR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at 24 hours</td>
<td>1394 (6)</td>
<td>0.89 (0.78 to 1.01)</td>
<td>NA</td>
</tr>
<tr>
<td>Pain at 2 to 3 days</td>
<td>2320 (7)</td>
<td>0.70 (0.57 to 0.86)</td>
<td>20 (14 to 50)</td>
</tr>
<tr>
<td>Pain at 4 to 7 days</td>
<td>2320 (7)</td>
<td>0.79 (0.66 to 0.95)</td>
<td>20 (11 to 100)</td>
</tr>
<tr>
<td>Abnormal tympanometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 to 6 weeks</td>
<td>2144 (7)</td>
<td>0.92 (0.83 to 1.01)</td>
<td>NA</td>
</tr>
<tr>
<td>3 months</td>
<td>809 (3)</td>
<td>0.97 (0.76 to 1.24)</td>
<td>NA</td>
</tr>
<tr>
<td>Vomiting, diarrhea or rash</td>
<td>2023 (7)</td>
<td>1.34 (1.16 to 1.55)</td>
<td>14 (10 to 25)</td>
</tr>
<tr>
<td>Tympanic membrane perforation</td>
<td>991 (4)</td>
<td>0.37 (0.18 to 0.76)</td>
<td>33 (17 to 100)</td>
</tr>
</tbody>
</table>

Table 3. b) Antibiotics versus placebo for acute otitis media. Summary of findings for the main comparison of Hoberman et al. (2011a), Tähtinen et al. (2011).

<table>
<thead>
<tr>
<th>RCT</th>
<th>N</th>
<th>Age, months</th>
<th>Treatment failure</th>
<th>Difference antibiotic/placebo % (95% CI)</th>
<th>P value</th>
<th>NNT (95% CI)</th>
<th>Adverse events antibiotic/placebo % (95% CI)</th>
<th>Rate difference P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tähtinen</td>
<td>319</td>
<td>6-35</td>
<td>19/45, at 7 d</td>
<td>HR 0.38 (0.25 to 0.59)</td>
<td>&lt;0.001</td>
<td>4 (3 to 6)</td>
<td>16.7 (5.8 to 27.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hoberman</td>
<td>291</td>
<td>6-23</td>
<td>4/23, at 4-5 d</td>
<td>RR 19% (12 to 27)</td>
<td>&lt;0.001</td>
<td>Diarrhea</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16/51, at 10-12 d</td>
<td>RR 35% (25 to 45)</td>
<td>&lt;0.001</td>
<td>Dermatitis</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

1 symptoms and persistence of signs of acute infection on otoscopic examination

Abbreviations: HR, hazard ratio. NA, not applicable. NNT, number needed to treat. RCT, randomized controlled trial. RR, relative risk.

**Disadvantages of antibiotic treatment**

Antibiotic treatment causes side effects, mostly diarrhea and rash or dermatitis, in children (Table 3). Other disadvantages of antibiotic use include cost of therapy, allergic reactions, toxicity and interaction with other drugs. Recently it has been suggested that 2-year-old children exposed to antibiotics were heavier than unexposed children (in boys P<0.001 and in girls P<0.05) (Saari et al. 2015).
Antibiotic resistance of bacteria is a serious threat related to the use of antibiotics. Antibiotic-resistant bacteria develop as a result of natural adaptations, spontaneous changes in DNA, or when different bacteria exchange genes with each other. Antibiotics also affect the normal flora and interfere with the human bacterial balance, the effects of which could last for at least a year. Since the normal flora provides guidance to the development of the infant's immune system, any changes can have a lasting impact on a child's life.

**Wait-and-see approach and delayed prescription**

In RCT comparing initial antibiotic treatment with a wait-and-see prescription, a significant part of parents in the wait-and-see group did not use the antibiotic prescription (62% vs. 13%, P<0.001) (Spiro et al. 2006). Recent evidence from Norway indicates that delayed prescription may lead to a reduction in antibiotic use, mainly for sinusitis and OM (Llor & Bjerrum 2014). National guidelines for initial observation of AOM in selected children were first implemented in the Netherlands and subsequently in Sweden, Scotland, the US, the UK, Italy and also in Finland (Table 2). Only about approximately one-third of children initially observed received a rescue antibiotic for persistent or worsening AOM (Little et al. 2001, McCormick et al. 2005, Tähtinen et al. 2011), and about half of all patients who received a placebo did not experience treatment failure (Hoberman et al. 2011a, Tähtinen et al. 2011).

**Recommendations**

A recent US guideline (American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media 2004, Lieberthal et al. 2013) and a Finnish nationwide guideline give recommendations for antibiotic treatment (Table 2). The authors of 2 independent clinical trials with stringent diagnostic criteria for diagnosing AOM (Hoberman et al. 2011a, Tähtinen et al. 2011) suggest that the AAP guideline’s recommendation of prompt antimicrobial treatment for children younger than 2 years old with AOM should be extended to include children whose disease is unilateral and apparently non-severe (Hoberman et al. 2013).
2.9 Prevention of recurrent acute otitis media

2.9.1 Tympanostomy

Insertion of VTs and circumcision are the most common cause for surgery in children in the developed world. Approximately 700,000 VT treatments and more than 100,000 adenoidectomies are performed annually in the US among children under 15 years of age (Cullen et al. 2009). VT insertion rates decreased in the last years of a study between 2001 and 2011 in the US (Marom et al. 2014). Haapkylä et al. (2008) found that from 1999 to 2005, VT insertions increased by 52% in Finland but remained stable in Norway in children between 0 and 7 years of age. In Finland, 1.5% of children less than 8 years of age underwent VT insertion in 2005. The increase in tube insertions might be explained by the decrease in adenoidectomies. (Haapkylä et al. 2008).

Benefits of tympanostomy

Objective benefits of surgery for OM include improved hearing, reduced MEE prevalence, reduced AOM incidence, and reduced need for reoperation (Casselbrant et al. 1992, Gebhart 1981, Gonzalez et al. 1986, Mandel et al. 1989, Mandel et al. 1992, Paradise et al. 1990). Several systematic reviews have attempted to assess the efficacy of VT for RAOM, but there has been widespread disagreement regarding trial selection and inclusion criteria, with most reviews excluding studies where children were allowed to have MEE or OME at baseline. Systematic reviews reported the efficacy of VT in preventing RAOM with insufficient evidence (Hellstrom et al. 2011), small short-term benefits (Damoiseaux & Rovers 2011, McDonald et al. 2008, Rosenfeld 2000) or no additional benefit when compared to antibiotic use (Casselbrant et al. 1992, Lous et al. 2011) (Table 4).

VT insertions have not been found to significantly impact speech, language, or cognitive outcomes in RCTs (Browning et al. 2010, Hellstrom et al. 2011); trials have typically included only healthy children without developmental delays at entry. A non-randomized study, however, did show improved caregiver perception of speech and language after VT placement, especially for children with developmental delays (Rosenfeld et al. 2011).

Although the primary rationale for offering VTs to children with RAOM is to reduce the incidence of future middle ear infections, there are additional benefits,
including decreased pain, allowed drainage of infected secretions and bacterial culture, as well as the ability to manage such infections with topical antibiotic eardrops (Rosenfeld et al. 2013). Eardrops alone are highly effective for AOM with tubes (Hellstrom et al. 2011) avoiding the adverse effects of systemic therapy.

Table 4. Tympanostomy for recurrent acute otitis media.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study features</th>
<th>No. of patients (studies)</th>
<th>Age</th>
<th>Follow-up time, months</th>
<th>Findings of tympanostomy</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonald et al. 2008</td>
<td>Cochrane review RAOM without OME</td>
<td>148 (2)</td>
<td>&lt;3y</td>
<td>6</td>
<td>Reduce AOM by 1.5 episodes/ 6 m. and has a significant role in maintaining a “disease-free” state.</td>
<td>3</td>
</tr>
<tr>
<td>Lous et al. 2008</td>
<td>Meta-analysis</td>
<td>519 (5)</td>
<td>6-12</td>
<td>2-5</td>
<td>Reduce AOM by about one attack/ 6 m.</td>
<td></td>
</tr>
<tr>
<td>Casselbrant et al. 1992</td>
<td>Excluded children with baseline MEE</td>
<td>264 (1)</td>
<td>7-35m</td>
<td>24</td>
<td>An average rate of new episodes per child year 1.08 in the placebo group and 1.02 in the tympanostomy tube group, P= 0.25. No benefit for reducing the subsequent incidence of AOM</td>
<td></td>
</tr>
<tr>
<td>Rosenfeld 2000</td>
<td>Meta-analysis</td>
<td>(5)</td>
<td>6-12y</td>
<td>6-36</td>
<td>A mean absolute decrease in AOM incidence of 1.0 episode per child-year (95% CI 0.4–1.6), with a relative decrease of 56%. Reduced MEE prevalence by 115 days per child-year.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AOM, acute otitis media. NNT, number needed to treat. RAOM, recurrent acute otitis media. OME, otitis media with effusion. MEE, middle ear effusion.

Disadvantages of tympanostomy

Risks for VT insertion include general anesthesia and direct tube-related sequelae. A review of animal studies suggested that neurodegeneration, with possible
cognitive sequelae, is a potential long-term risk of anesthetics in neonatal and young pediatric patients (Mellon et al. 2007). These observations have raised concerns regarding the use of these drugs in pediatric patients. In the fourth symposium of The Pediatric Anesthesia NeuroDevelopment Assessment team pediatric surgeons and anesthesiologists concluded that length, dosing, and repetition of anesthetic events remain unclear in terms of neurotoxic and neurodevelopmental effects (Byrne et al. 2014). In the perioperative period, children are more prone to laryngospasm and bronchospasm than adults, which may increase the risk of anesthetic complications. A recent review looking at protocols for minimizing operative risks reported no major complications (such as sensorineural hearing loss, vascular injury, or ossicular chain disruption), in 10,000 tube insertions, although minor complications such as TM tears or displaced tubes in the middle ear were seen in 0.016% of ears (Isaacson 2008).

The most common harmful effect of VTs is otorrhea, seen in approximately 16% of children within 4 weeks of surgery and 26% of children at any time the VT remains in place (Kay et al. 2001). In a review (Syed et al. 2013) of 15 RCTs it was concluded that either saline irrigation or antibiotic eardrops at the time of surgery would significantly reduce the rate of postoperative otorrhea in children with tympanostomy. In a meta-analysis, tympanosclerosis was observed in 32% of patients after placement of VTs (Kay et al. 2001). TM perforations were found in 2.2% of patients who had short-term tubes and in 16.6% of patients with long-term tubes (Kay et al. 2001). Usually TM perforations, atrophy, atelectasis, and retraction pockets appear to resolve over time in many children, rarely requiring medical or surgical treatment (Rosenfeld et al. 2013). Other complications include blockage of the VT lumen in 7% of intubated ears, granulation tissue in 4%, premature extrusion of the VT in 4%, and VT displacement into the middle ear in 0.5% (Kay et al. 2001). VTs are only effective for the duration of VT stay time; most VTs extrude 6–9 months after placement. If they stay in place for over 2 years, the practice is to remove the tube.

**Recommendations**

When making clinical decisions, the risks of VT insertion must be weighed against the risks of prolonged AOM or RAOM. The natural history of persistent MEE is favorable, but when MEE persists, it is thought to be an indicator of underlying ET dysfunction that may predispose an individual to AOM recurrence. The absence of MEE at the time of assessment for tube candidacy, even if
recently documented by another clinician, suggests favorable ET function and a good prognosis (Rosenfeld et al. 2013). Recent guidelines give different recommendations for children with RAOM of VTs (Table 5), but whether to proceed with surgery is largely dependent on shared decisions with the child’s caregiver.

Table 5. Guidelines for acute otitis media: ventilation tubes.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Insertion of ventilation tubes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical practice guideline from AAP 2013¹</td>
<td>For at least 3 episodes in 6 months or 4 episodes in 1 year with 1 episode in the preceding 6 months</td>
</tr>
<tr>
<td>Finnish nationwide guideline 2010²</td>
<td>For over 3 episodes in 6 months or over 4 episodes in 1 year</td>
</tr>
</tbody>
</table>
| Clinical practice guideline 2013³ | A. Do not perform tubes in children with RAOM who do not have MEE in either ear at the time of assessment for tube candidacy, but the child should be reassessed if he continues to have RAOM.  
B. Bilateral VT insertion for children with RAOM who have unilateral or bilateral MEE at the time of assessment for tube candidacy.  
C. For a child with RAOM who is at increased risk of suffering from speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors.  
D. Topical antibiotic eardrops only, without oral antibiotics, for children with uncomplicated acute VT otorrhea.  
E. Not encourage routine, prophylactic water precautions (use of earplugs or headbands; avoidance of swimming or water sports) for children with VTs. |

Abbreviations: AAP, American Academy of Pediatrics. MEE, Middle ear effusion. RAOM, Recurrent acute otitis media. VT, Ventilation tube

¹ Lieberthal et al. 2013  
² Acute otitis media. Current Care Guidelines 2010  
³ Rosenfeld et al. 2013

2.9.2 Adenoidectomy with tympanostomy

The rate of adenoidectomy decreased in Finland from 1999 to 2005 (Haapikylä et al. 2008) because of studies that showed little or no benefit of adenoidectomy for AOM. A Cochrane review concluded that the absence of significant benefit of adenoidectomy on AOM suggests that routine surgery for this indication is not warranted (van den Aardweg et al. 2010). In RAOM, adenoidectomy alone was ineffective to prevent further AOM in 180 children younger than 2 years (Koivunen et al. 2004). In 3 randomized studies, adenoidectomy showed no

The effect of adenoidectomy with or without VT was evaluated in a large meta-analysis of 10 RCTs of 1761 children up to 12 years of age with RAOM and/or persistent OME (Boonacker et al. 2014). In that study it was found that 16% (44/281) of children younger than 2 years of age with RAOM who failed at 12 months had an adenoidectomy, whereas 27% (120/438) of those who failed did not have an adenoidectomy (RD 12%, 95% CI 6% to 18%, NNT= 9, RR 0.63, 95% CI 0.47 to 0.85) (Boonacker et al. 2014).

2.9.3 Immunization

The pneumococcal conjugate vaccine was primarily developed to address invasive pneumococcal disease. The heptavalent pneumococcal conjugate vaccine (PCV-7) became available for routine administration in infants in the US in 2000. The overall reduction in AOM incidence due to PCV-7 has been suggested to range from 6-13% (Jansen et al. 2009, Wals et al. 2009). PCV-7 has only modest beneficial effects in healthy infants but may still have public health relevance (Jansen et al. 2009). Serotype replacement, as happened in nasopharyngeal colonization and in MEE (Hoberman et al. 2011b), may reduce the long-term efficacy of pneumococcal conjugate vaccines against AOM. The 13-valent pneumococcal conjugate vaccine has been approved in the US since 2010 (Centers for Disease Control and Prevention 2010). The 10-valent pneumococcal conjugate vaccine has potential benefits of protection against 10 serotypes of S. pneumoniae and nontypeable H. influenzae (Jansen et al. 2009), giving a significant reduction (33.6%) in the overall incidence of AOM (Prymula et al. 2006) (Table 2).

Influenza virus is the only respiratory virus for which effective vaccines and antiviral drugs are currently available (Table 2). Many studies have demonstrated 30-55% efficacy of influenza vaccine in prevention of AOM (Belshe & Gruber 2000, Heikkinen et al. 1991). In a pooled analysis (Block et al. 2011) of 6 studies, live-attenuated intranasal influenza vaccine efficacy against influenza-associated AOM was 85% compared with placebo, and 54% compared with trivalent inactivated influenza vaccine, and efficacy against all-cause AOM was 8% compared with placebo (Heikkinen et al. 2013).
2.9.4 Xylitol

A Cochrane review (Azarpazhooh et al. 2011) summed up 4 RCTs (Hautalahti et al. 2007, Tapiainen et al. 2002, Uhari et al. 1996a, Uhari et al. 1998) and found that xylitol seems to have a preventive effect against AOM. A statistically significant 25% reduction in the risk of occurrence of AOM among healthy children at childcare centers was seen in the xylitol group compared with the control group. Using xylitol 5 times per day daily reduced AOM episodes, while sporadic use was not effective. (Azarpazhooh et al. 2011).

2.9.5 Chemoprophylaxis

A 2006 Cochrane review analyzed 16 RCTs of antibiotic use for AOM over 6 weeks and found that antibiotics reduce the number of episodes of AOM per year from around 3 to around 1.5. Approximately 5 children would need to be treated long-term to prevent 1 child from experiencing AOM. Long-term antibiotics were not found to cause a significant increase in adverse events. The authors believe that larger absolute benefits are likely in high-risk children. (Leach & Morris 2006).

In an RCT of children for whom antiviral treatment by oral oseltamivir was started within 12 hours of the onset of symptoms, the incidence of AOM decreased by 85% during influenza illness (Heinonen et al. 2010).

2.10 Quality of life

2.10.1 Quality of life assessment and instrument evaluation

The World Health Organization defines QoL as individuals’ perceptions of their position in life in the context of the culture and value system (The WHOQOL Group 1998). Functional health status is a combination of health status reflecting the signs and symptoms of disease and functional status reflecting the adequacy of an individual’s daily functioning across various life-domains (Brouwer et al. 2005a, Brouwer et al. 2007). The health related QoL instruments (Wilson & Cleary 1995) measure the level of satisfaction of a person with those aspects of his or her life that are affected by the effects of an illness and its treatment (Brouwer et al. 2005a, Brouwer et al. 2007). Assessing QoL is done via structured
questionnaires that measure an individual’s perception of his/her physical, mental, emotional and social ability to function.

Disease-specific instruments may identify problem areas typical for this particular patient group. Disease-specific QoL questionnaires on the other hand, assess health related issues specific to particular conditions and may be able to detect small changes that are often small but clinically important; these provide a more detailed assessment of QoL, but cannot be used for comparisons across health conditions (Brouwer et al. 2007). Generic QoL instruments have the advantage of broad applicability across specialties or populations, and they are useful in burden of disease studies. They have the capacity to compare healthy with ill populations or 2 groups with different health problems (Stewart et al. 2000). However, generic QoL instruments are usually less sensitive to disease-specific functional or emotional issues. The use of generic and disease-specific QoL instruments together can provide perspective on the overall effect on a child’s condition, allow comparison of the scores between healthy and ill populations, and measure the QoL of both the child and his/her caregivers. Because it is impossible to directly assess the feelings of young children, parental reports are used as a surrogate measure of their child’s QoL (Brouwer et al. 2007).

To assess QoL, instruments need to be reliable and valid. One aspect of reliability is internal consistency, i.e. the homogeneity and coherence of the items of an instrument. Some studies assessed another aspect of reliability: reproducibility, i.e. the ability to reproduce the same results when nothing has changed. Construct validity, i.e. the degree to which an instrument measures the concept it is supposed to measure, is assessed by comparing mean scores of the questionnaire with physician-rated clinical severity, functional severity or other clinical symptoms, or by comparing instrument results between two groups on the extreme, i.e. one with the condition and one without. Finally, to evaluate treatment effects, QoL instruments need to be responsive, i.e. they should be able to detect clinically important change(s) over time. (Brouwer et al. 2005a)

Otolaryngologists treat many childhood problems that affect a child’s health and function; thus, assessing QoL should be considered an important outcome to measure in intervention studies. Since the introduction of QoL instruments in the 1990s, their use has gradually increased. In the review of RCTs included in the Cochrane database of systematic reviews of the most common ear, throat and nose operations it was found that only 10% used a validated QoL instrument and 49% collected some sort of patient-reported outcome measures of QoL (Alakärppä & Alho 2012). Most studies on OM have focused on the acute
symptoms of OM and on its effects on hearing, language, cognition and psychosocial development and recurrence frequency. Less attention has been paid to the effects of OM on QoL. However, during the last few years there has been an increasing focus on how QoL is affected in children with OM. The focus has primarily been on the short-term effects of the disease and the effects of treatment such as surgical intervention or insertion of VTs on QoL. QoL is an important aspect when treatment effect is considered. Research into both child and caregiver QoL is important for understanding the full burden of diseases in pre-school children and in assessing treatment outcomes and planning future treatment strategies.

2.10.2 Quality of life instruments used in otitis media research

The disease-specific QoL questionnaire, Otitis Media-6 (OM-6) (Figure 2), is recognized as a valid, reliable and responsive disease-specific measure of QoL for children with OM (Brouwer et al. 2007, Heidemann et al. 2013, Kubba et al. 2004, Rosenfeld et al. 1997, Timmerman et al. 2007, Witsell et al. 2005). This questionnaire is the most widely used measurement instrument in the studies of OM (Brouwer et al. 2005a, Brouwer et al. 2005b, Heidemann 2014, Heidemann et al. 2015, Kubba et al. 2004, Lee et al. 2006, Rosenfeld et al. 2000). It can be completed within a matter of minutes (Rosenfeld et al. 1997). OM-6 has the best qualities for evaluation of clinical change (Brouwer et al. 2005a, Brouwer et al. 2007, Timmerman et al. 2007). OM-6 scores have found to correlate well with global QoL measures and are free from many potential biases (Kubba et al. 2004). However, it has been suggested not to adequately reflect the disease severity (Kubba et al. 2004). In a review from 2005, the authors recommended that OM-6 should be regarded as the best available instrument for assessing functional health status among children with OM, keeping in mind that the OM-6 was originally designed to evaluate change and not to discriminate between populations (Brouwer et al. 2005a). The OM-22 is an extended version of the OM-6 and has been used in one study investigating basic psychometric properties (Richards & Giannoni 2002).

The Child Health Questionnaire (CHQ) is a generic objective measure of QoL for children aged 5 to 18 years that has been shown to have good internal consistency and validity with diverse patient groups (Landgraft et al. 1999). The questionnaire allows the measurement of child-reported and caregiver-reported QoL. It requires adaptation rather than the exclusion of questions when applied to
age groups younger than 4 years (Raat et al. 2002). The CHQ was developed in the USA, and has since been cross culturally validated in 21 languages (32 countries) (Ruperto et al. 2001). It has also been translated into Finnish according to international guidelines (Pelkonen et al. 2001, Ruperto et al. 2001). The parental version of the CHQ (CHQ-PF50) can be completed in approximately 10-15 minutes (Table 6). The number of response options of questions varies from 4-6. Some scales survey domains from the past 4 weeks, the global health items survey about health “in general” and the global change items surveys as compared to 1 year ago. All the domain scores are standardized from 0 to 100, with higher scores indicating better functioning and greater wellbeing. (Landgraft et al. 1999)

In a study of 1001 children with OM, CHQ-28 was used in children over 5 years of age (Lee et al. 2006).
Instructions: Please help us understand the impact of ear infections or fluid on your child’s quality of life by checking one box [X] for each question below. Thank you.

**Physical Suffering:** Ear pain, ear discomfort, ear discharge, ruptured eardrum, high fever, or poor balance. How much of a problem for your child during the past 4 weeks?

<table>
<thead>
<tr>
<th>Not present/no problem</th>
<th>Hardly a problem at all</th>
<th>Quite a bit of a problem</th>
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**Hearing Loss:** Difficulty hearing, questions must be repeated, frequently says “what,” or television is excessively loud. How much of a problem for your child during the past 4 weeks?

<table>
<thead>
<tr>
<th>Not present/no problem</th>
<th>Hardly a problem at all</th>
<th>Quite a bit of a problem</th>
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**Speech Impairment:** Delayed speech, poor pronunciation, difficult to understand, or unable to repeat words clearly. How much of a problem for your child during the past 4 weeks?

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<th>Not present/no problem</th>
<th>Hardly a problem at all</th>
<th>Quite a bit of a problem</th>
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<tr>
<td>(or not applicable)</td>
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</table>

**Emotional Distress:** Irritable, frustrated, sad, restless, or poor appetite. How much of a problem for your child during the past 4 weeks as a result of ear infections or fluid?

<table>
<thead>
<tr>
<th>Not present/no problem</th>
<th>Hardly a problem at all</th>
<th>Quite a bit of a problem</th>
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**Activity Limitations:** Playing, sleeping, doing things with friends/family, attending school or day care. How limited have your child’s activities been during the past 4 weeks because of ear infections or fluid?

<table>
<thead>
<tr>
<th>Not limited at all</th>
<th>Hardly limited at all</th>
<th>Moderately limited</th>
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<tbody>
<tr>
<td></td>
<td>Very slightly limited</td>
<td>Very limited</td>
</tr>
<tr>
<td></td>
<td>Slightly limited</td>
<td>Severely limited</td>
</tr>
</tbody>
</table>

**Caregiver Concerns:** How often have you, as a caregiver, been worried, concerned, or inconvenienced because of your child’s ear infections or fluid over the past 4 weeks?

<table>
<thead>
<tr>
<th>None of the time</th>
<th>Hardly any time at all</th>
<th>A good part of the time</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A small part of the time</td>
<td>Most of the time</td>
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<tr>
<td></td>
<td>Some of the time</td>
<td>All of the time</td>
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Overall, how would you rate your child’s quality of life as a result of ear infections or fluid? (Circle one number)

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</thead>
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<tr>
<td>Worse Possible</td>
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<tr>
<td>Quality-of-Life</td>
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<td>Half-way Between</td>
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<tr>
<td>Worst and Best</td>
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<tr>
<td>Best Possible</td>
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<tr>
<td>Quality-of-Life</td>
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Fig. 2. Otitis Media-6 questionnaire.

54
Table 6. The Child Health Questionnaire-50 (CHQ-50).

<table>
<thead>
<tr>
<th>CHQ-50</th>
<th>Child’s physical quality of life</th>
<th>Child’s psychosocial quality of life</th>
<th>Parents’ quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health (GGH)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning (PF)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role/social limitations due to physical health (RP)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily pain /discomfort (BP)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General health (GH)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role/social limitations attributable to emotional or behavioral difficulties (REB)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior (BE)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global behavior (GBE)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health (MH)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-esteem (SE)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional impact on the parents (PE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time impact on the parents (PT)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family activities (FA)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family cohesion (FC)</td>
<td>X</td>
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</table>

2.10.3 Impact of otitis media on quality of life

There are only a few studies in which the QoL of children with OM are correlated with the general/healthy or other disease population. In a study of 384 children those aged 1-7 years with RAOM scored lower on the generic health questionnaire than healthy children of similar age, and lower than children with mild-to-moderately severe chronic illness, and similarly to children with asthma (Brouwer et al. 2005b). Additionally, in a large cross-sectional study, children with OM had a poorer QoL than healthy children of similar age, when using generic CHQ-PF28 (Lee et al. 2006).

OM was reported to have a substantial and negative effect on various domains of QoL for children in a review of 13 studies (Brouwer et al. 2005a). In prospective cohort studies of 248 children (median age 1.4 years) and of 186 children (median age 3.4 years), with RAOM and chronic OME, it was found that, as measured by OM-6, Physical suffering was at least somewhat of a problem for 85% of children, while Emotional distress was a problem for two thirds and
Activity limitations affected over half, especially in those admitted for VT insertion (Rosenfeld et al. 1997, Rosenfeld et al. 2000). QoL for children with 4 or more episodes of AOM in a year was poorer than for children with 2 to 3 episodes in the OM-6 questionnaire (Brouwer et al. 2005b). Physical suffering and Caregiver concerns were associated with frequent OM or effusion duration in the cross-sectional study (Lee et al. 2006). Furthermore in the study of subgroups of OM, children with RAOM scored significantly worse on Physical suffering, Activity limitations and Emotional distress than children with OME without acute infection when using OM-6 (Heidemann et al. 2015). Nearly 80% of children with RAOM experienced important improvements at 1-month follow-up. In contrast, only about 60% of children with OME improved (Heidemann 2014). In a telephone questionnaire based on OM-6 domains, a moderate to high correlation was seen between the severity and duration of AOM episodes and poorer QoL scores (Dube et al. 2010). Children with OM have been reported to be hyperactive and have behavioral problems (Brouwer et al. 2005a, Brouwer et al. 2005b).

AOM significantly reduced QoL among children and parents, caused substantial use of medical services and significant loss of workdays in an interview study (Greenberg et al. 2003). In the OM-6 studies on children with RAOM and chronic OM, 88% of caregivers were worried or concerned about their child’s ear infections at least some of the time and 19% spent all their time preoccupied with their child’s condition (Rosenfeld et al. 1997, Rosenfeld et al. 2000). In another study, 52% of caregivers were nervous or agitated because of their child’s ear problems, 29% lost sleep and 56% had to change their daily activities (Boruk et al. 2007). The authors of this study concluded that caregiver ratings of QoL for children with OM are highly influenced by the caregiver’s own QoL (Boruk et al. 2007). In the study of subgroups of OM, the poorest QoL was found for caregivers of children with RAOM (Heidemann et al. 2014).

2.10.4 Impact of surgery in otitis media on quality of life

Only one RCT (Rovers et al. 2001) has examined QoL in children with OM. Rovers used a generic TNO-AZL Infant Quality of Life questionnaire, in children aged 1-2 years with OME, and found that there was an improvement in QoL, but the VT group did not improve significantly more than the watchful waiting group (Rovers et al. 2001). In a randomized study using the OM-6 questionnaire, a significant improvement in QoL after 6 months, but not after 12 months, was seen.
by using VT, compared with myringotomy, both with concurrent adenoidectomy (Vlastos et al. 2011).

QoL improvements after VTs have been observed in many prospective cohort studies, which included children with RAOM and/or OME using disease-specific OM-6 (Chow et al. 2007, Richards & Giannoni 2002, Rosenfeld 2000, Ryborg et al. 2014, Witsell et al. 2005) or OM-22 (Richards & Giannoni 2002) questionnaire. In a study of 272 children with medically or surgically treated OM, large overall improvement was seen in QoL after 9 months, but it was 2.6 times larger in the VT groups (Witsell et al. 2005). QoL improvements were also noted at 13 months in a study of 397 children with OM, regardless of whether treatment was with or without VT (Ryborg et al. 2014). The improvement in QoL was significantly lower in children with sleep problems and in children whose parents had been absent from work due to the child’s OM (Ryborg et al. 2014). QoL improved significantly after VT insertion for OM with the greatest improvements in the subsets of Caregiver concern, Physical suffering and Emotional distress (Chow et al. 2007, Richards & Giannoni 2002, Rosenfeld et al. 2000).

There are also 3 retrospective cohort studies of QoL in children with OM (Facione 1991, Mui et al. 2005, Rosenfeld et al. 2011). In 1991, a study specifically aimed at assessing QoL in relation to OM used generic The Parent’s Questionnaire (Facione 1991). In this study, improvements in QoL were supported by decreased health care visits and decreased oral antibiotic after VT. In a telephone survey, improvements were found in QoL after VTs in 90% of children and 91% of their parents (Mui et al. 2005). In a study of VTs in children at-risk and not at-risk of developmental delay, it was found that caregivers reported favorable outcomes regardless of their child's risk status after treatment, but much more in children at-risk of delays in speech, language, learning, and school performance (Rosenfeld et al. 2011).

Caregivers’ QoL and daily functioning improved after VT treatment among children with OM at 1 to 18 months’ follow-up (Heidemann et al. 2014). The poorest baseline QoL was found for caregivers of children with RAOM (Heidemann et al. 2014). Many studies found that Caregiver concern, included in the OM-6 and OM-22 questionnaire is the domain showing the greatest improvements after VT in children with OM (Chow et al. 2007, Richards & Giannoni 2002, Rosenfeld et al. 2000).
3 Aims of the study

To evaluate

1. the effect of antibiotic treatment on symptoms of AOM and on the duration of MEE in AOM (I).
2. the benefit of VT with and without an adenoidectomy on the prevention of AOM in children (II).
3. the QoL in children with AOM and their parents, with disease-specific and generic QoL instruments (III, IV).
4. the effect of VT with or without an adenoidectomy on the QoL in children with AOM and their parents (III, IV).
Fig. 3. Enrollment, randomization, follow-up, and middle ear status at the end of follow-up (60 days) among children with acute otitis media (I). ©American Medical Association and Copyright Clearance Center.
4 Patients, materials and methods

4.1 Improvement of acute otitis media with antibiotic treatment (I)

The study was a randomized, double blind, placebo-controlled trial in Oulu, Finland in children aged between 6 months and 15 years with an AOM. Children with acute symptoms of URI and ear-related symptoms and signs of TM inflammation together with MEE detected by pneumatic otoscopy performed by a study physician were eligible for the trial (American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media 2004, Klein et al. 1989). Exclusion criteria included a history of AOM diagnosis within the previous month, VT, AOM complication (mastoiditis or TM perforation), amoxicillin allergy, Down’s syndrome, congenital craniofacial abnormality and immunodeficiency.

The families of 120 children with AOM were invited (Figure 3). Altogether 84 patients were recruited. The recruitment of the patients occurred between September 1999 and January 2000 (31 children) from among day care children attending an OM prevention trial (Tapiainen et al. 2002) at the Department of Pediatrics at Oulu University Hospital, and from October 2005 to December 2005 (12 children) from children visiting public health care services in the City of Oulu Health care Center and from September 2009 to June 2012 (41 children) from children visiting the Mehiläinen Private Medical Practice in Oulu, Finland. After written informed consent, the children were randomized to receive either an oral mixture of amoxicillin-clavulanate (40 mg/kg of amoxicillin per day divided into two daily doses) or a placebo mixture for seven days. The placebo mixture was flavored and sweetened to resemble the taste of the amoxicillin-clavulanate mixture, and the volume of the mixture and the dosing schedule were similar to those in the amoxicillin-clavulanate group. The product bottles were indistinguishable. A computerized randomization list was created in blocks of 4 prior to the study and was kept in the pharmacy (Oulu University Hospital Pharmacy and Oulun Vanha Apteeikki Pharmacy), which delivered the study drugs to the families according to the consecutive study number. The children, their families, and all participants of the study group were blinded to the treatment group until the data entry and checking were completed for all children.

The study physician examined the children by pneumatic otoscopy or otosmicroscopy and tympanometry at study entry, after 3 and 7 days, and then weekly until both ears were healthy according to pneumatic otoscopy or
otoscopy. In addition families were encouraged to contact the study physician during office hours or the Department of Pediatrics, Oulu University Hospital, at any time if the study participant experienced severe symptoms. In these cases the rescue treatment with amoxicillin-clavulanate in a non-blinded manner was started. If the child still had MEE after 60 days, the follow-up at the study clinic was stopped, and the children were referred to the Department of Otolaryngology, Oulu University Hospital for clinical examination after 1 month. Parents kept a symptom sheet diary to collect daily data on other symptoms (fever > 38.0°C, ear ache, cough, rhinitis, throat ache, vomiting, diarrhea, conjunctivitis, sleeping difficulties, and eating difficulties), as well as the number of study drug doses and other medications administered.

Each family received a hand-held tympanometer (Welch Allyn®) for daily follow-up at home for up to 14 days or until the study physician declared both ears healthy according to pneumatic otoscopy or otomicroscopy. The study physician trained the parents to carry out the daily tympanometric examination. Families were instructed to repeat the measurement if they obtained a flat curve, to save and print the results, and to return them to the study clinic during visits. Based on our validation and our previous studies (Koivunen et al. 1996, Koivunen et al. 1997, Koivunen et al. 2000, Renko et al. 2006) the tympanograms were classified as an A curve (static admittance (SA) ≥0.2 mmho, tympanic peak pressure (TPP) −200 to +100 daPa), a B curve (SA <0.2 mmho), a C curve (SA ≥0.2 mmho, TPP <−200 daPa), a positive pressure curve (SA ≥0.2 mmho, TPP >+100 daPa), and an undefined curve (noisy measurement or other technical problem). The curves were interpreted separately by 2 authors, and in cases of disagreement, a consensus was reached through a group conference.

The primary outcome measure was the time till the disappearance of the MEE as defined by a normal tympanogram finding (A curve) from both ears on 2 consecutive measurement days, either at home or at the study clinic. Secondary outcome measures were: the time taken to reach improved tympanogram findings (i.e., A or C curves) from both ears, the time until normal pneumatic otoscopy or otomicroscopy findings from both ears were observed and the time taken until reduced ear pain was observed. Analysis was performed per child. The proportions of children with persistent MEE on days 7, 14, and 60 were compared between the groups. The disappearance of pain and fever, the use of pain medication, and data on possible adverse effects of antimicrobial treatment were recorded and compared between the groups.
The calculations of sample size were based on the median duration of MEE (7.5 days) evaluated with daily tympanometry in our previous study (Renko et al. 2006). We regarded longer median duration of MEE in the placebo group as clinically significant if the difference in median survival times was 7 days. Each group required 38 children for a type I error of 0.05 and a power of 80%. To ensure that this number was achieved in the analyses, we recruited 84 participants. We used the Kaplan-Meier survival analysis to analyze the durations of MEE and ear pain and a log-rank test to test the differences between the groups. We used a standardized normal deviation test to compare the proportions of the children with resolved MEE between the amoxicillin-clavulanate group and the placebo group, and we calculated the NNT based on the absolute differences in the proportions between the study groups as well as 95% CIs for the differences. All analyses were performed in the intention-to-treat population. The analyses were carried out with IBM SPSS 20 and StatsDirect software 2.7.8.
Fig. 4. Trial profile and participant flow of 413 children (II) with recurrent acute otitis media. 300 eligible children were randomized into groups for tympanostomy, tympanostomy with adenoidectomy and control (no surgery) at entry. Analysis was carried out according to the original randomized groups, despite possible protocol violations, until intervention failure (2 episodes of acute otitis media within 2 months, 3 within 6 months or persistent effusion lasting for 2 months) or loss of child to follow-up. ©Wolters Kluwer Health Lippincott Williams & Wilkins
4.2 Benefit of ventilation tubes with and without adenoidectomy on prevention of acute otitis media in children (II)

The study was a randomized and controlled trial in children between 10 months and 2 years of age with RAOM who were referred to the Department of Otorhinolaryngology at Oulu University Hospital, Finland. The inclusion criteria consisted of having at least 3 AOM episodes during the past 6 months and residence within 40 kilometers of the hospital. The exclusion criteria consisted of chronic OME, a prior adenoidectomy or VT, cranial anomalies, documented immunological disorders, or ongoing antimicrobial prophylaxis for a disease other than AOM. Participation was offered to 413 children who met the inclusion criteria between March 2002 and June 2004. Three hundred children were randomly allocated using permutated blocks with a size of 3 to receive 1) VT 2) VT with an adenoidectomy or 3) neither as indicated in consecutively numbered sealed opaque envelopes, which were opened sequentially only after written informed consent had been received (Figure 4).

To include only children with RAOM without chronic effusion, the follow-up began only after the middle ear was found to be free of effusion. If effusion was found, the AOM was usually treated with antibiotics and weekly control visits were arranged until both ears were free of effusion. In the surgery groups the study started at the day of surgery if the ears were healthy at the operation and if not, the study started once the ears were healthy after operation. The tympanostomy and adenoidectomy operations were performed under general anesthesia as daycare surgery at Oulu University Hospital by one of the otolaryngologists attached to this project. Donaldson silicone tubes (TympoVent®, Atos) were inserted into both ears after anteroinferior radial myringotomy and aspiration of the effusion. An adenoidectomy was performed under visual control using a Beckmann ring curette and smaller curettes to remove residual tissue.

Follow-up visits were scheduled at every 4 months for assessment of the clinical ear status and collection of the symptom diaries. If the child had acute respiratory symptoms or the parents suspected AOM they were advised to visit one of the team’s otolaryngologists within 3 days. If respiratory symptoms continued, weekly control visits were scheduled until the child was found to be symptom free. If the child had AOM diagnosed by a doctor who did not belong to the research team, the parents were advised to visit one of the team’s otolaryngologists as soon as possible.
The criteria for AOM consisted of the presence of acute URI symptoms together with middle ear inflammation and effusion (bulging and/or decreased mobility of the ear drum, air-fluid level) detected by pneumatic otoscopy, tympanometry or otomicroscopy, or acute URI symptoms together with otorrhea (American Academy of Pediatrics Subcommitte on Management of Acute Otitis Media 2004, Klein et al. 1989). Only AOM diagnoses confirmed by the team’s otolaryngologists were accepted in the analyses. Control visits were scheduled weekly until the middle ear was found to be free of effusion. A new episode of AOM was recorded whenever the middle ear had previously been found to be free of effusion, or if the child had been without any respiratory symptoms for 3 days. AOM was treated according to the Finnish guidelines. The primary choice of antimicrobial was amoxicillin (40 mg/kg per day) for 5 days and in the case of a prolonged episode another antibiotic was prescribed, usually amoxicillin-clavulanate (45 mg/kg of amoxicillin per day).

The primary outcomes in each group were intervention failure and the time to the intervention failure. The intervention was deemed to have failed if the child experienced 2 AOM episodes in 2 months or 3 in 6 months, or had MEE for at least 2 months as assessed by one of the team’s otolaryngologists. The secondary outcomes were the incidence density of AOM episodes and time to the first recurrence of AOM.

On the basis of previous experience a 40% intervention failure rate was expected in the control group (Koivunen et al. 2004). A difference of 20 percentage points between the operated and non-surgery groups was considered clinically important. Each group required 82 children for a type I error of 0.05 and a power of 80%. To allow comparison between the 3 groups and to ensure that this number was achieved in the analyses, we recruited 100 children for each group. The times to intervention failure and to the first AOM episode were analyzed by using the Kaplan-Meier method and the statistical significances of the differences between the 3 groups were tested with the Log Rank test. Differences in the proportions of failures were tested using the Binomial standardized normal deviation test. The incidence rate of AOM episodes was calculated by dividing the number of AOM episodes by the follow-up time. The Poisson distribution based Chi-Square test was used to test the difference in incidence rates between the 3 groups. Adjusted logistic regression analysis was used to evaluate the occurrence of failures between the treatment groups when adjusted for the differences on familial propensity to RAOM or form of day care. The results were analyzed according to the original randomized groups despite
possible protocol violations, until such time as the intervention failed or the child was lost from the follow-up. The data were analyzed using IBM SPSS 19.0 for Windows and StatsDirect software 2.5.6.

4.3 Quality of life for children with acute otitis media and their parents, and the benefit of ventilation tubes with and without adenoidectomy on the quality of life (III, IV)

The last 159 consecutive children of the study (II), recruited between June 2003 and June 2004, were evaluated to measure QoL according to questionnaires OM-6 and CHQ-50 (Figure 5, 6). These questionnaires were filled at the entry of study before the surgery, and at the 4- and 12-month follow-up appointments. If the child did not come for the scheduled follow-up examination, the questionnaires with a stamped return envelope were sent to the home address. Since there was no Finnish version of OM-6, we validated the questionnaire in Finnish by forward translation, reconciliation and back translation. The Finnish parental CHQ-50 questionnaire requires a certain amount of adaptation, and we modified some of the questions for use with the children in the study aged 10-36 months.

Three control children for each participant with RAOM were selected randomly from the general population of children born in the Northern Ostrobothnia Hospital District on the same days as the study children. CHQ-50 questionnaires were sent with a stamped return envelope to the control children at the time when the child with RAOM entered the study.

Outcome measures in the study (III) consisted of the comparison of disease-specific QoL scores at entry and at 4 and at 12 months after randomization. In the study (IV), the QoL of the children with RAOM was compared to that of the control children who were not affected by RAOM, and the QoL of the children with RAOM was compared at entry to 1-year of follow-up. The effects of surgery on the QoL were also evaluated after 4 and 12 months in the 3 randomized groups with RAOM.

The CHQ responses were scored for each of the 14 concepts according to the CHQ-PF50 manual (Landgraft et al. 1999). The baseline differences in QoL between the children with RAOM and the control children (IV) and also the differences in QoL between the surgery and non-surgery groups at entry, at 4 months and at 1 year (III, IV) were tested using a variance analysis (ANOVA) with Tukey’s post hoc correction for multiple comparison tests (IV). The differences in the QoL of the children with RAOM between the questionnaires
administered at entry and after 1 year of follow-up were tested using a paired t-test (IV), and those between the children with RAOM after 1 year and the healthy control children at entry were tested using Student’s t-test (IV). A general linear model (GLM) analysis with simple and repeated contrast for repeated measurements was used to evaluate how the QoL scores changed over time within the randomized groups of children with RAOM (IV). Repeated measures analysis of variance (RANOVA) was used to evaluate how the disease specific QoL scores changed over time, and to test differences in disease specific QOL scores among the randomization groups and the times of measurement (III). Spearman’s rank correlation was used to evaluate the statistical dependence of disease specific QoL on the incidence of AOM (III). All the results were analyzed according to the original randomization groups (III, IV). Analyses were carried out with IBM SPSS 20.0 (III) and IBM SPSS 21.0 (IV).

4.4 Ethical aspects

The Ethical Committee of the Northern Ostrobothnia Hospital District, Finland, found the study protocols ethically acceptable in all four studies. The parents of all children who participated in the trials provided written informed consent.
Fig. 5. Trial profile and participant flow (123 children with recurrent acute otitis media).

The parents answered the Otitis Media-6 at entry, 4 months and 1 year of follow-up (III).
Fig. 6. The parents of children with recurrent acute otitis media (RAOM) answered the Child Health Questionnaire (CHQ) at entry, 4 months and 1 year of follow-up. 456 control children were divided into 2 groups: controls without episodes of acute otitis media (AOM) and controls with a history of 1 to 4 AOM episodes.
5 Results

5.1 Improvement of acute otitis media with antibiotic treatment (I)

5.1.1 Study population

A total of 84 children were randomized (Figure 3). The baseline characteristics of the participants were similar across the study groups (Table 7). One child in the amoxicillin-clavulanate group and 3 children in the placebo group prematurely discontinued the follow-up (Figure 3). In total 15 children in the amoxicillin-clavulanate group and 11 children in the placebo group developed new URI symptoms before the MEE was resolved. According to the symptom sheet diaries, the proportion of the study drug doses administered as planned was 96% in the amoxicillin-clavulanate group and 95% in the placebo group. The mean number of tympanograms was 18.3 (SD 6.4) per child for each ear in the amoxicillin-clavulanate group and 20.7 (SD 7.3) in the placebo group. Tympanometry proved successful in 95.8% of all examinations at the study clinic and in 86.5% of examinations at home. The child’s anxiety or crying was the main cause of failure of an examination at the study clinic.
Table 7. Baseline characteristics of the participants and symptoms and findings at study entry (I).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amoxicillin-clavulanate group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=42</td>
<td>N=42</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Age, mean (SD) y</td>
<td>4.5 (3.1)</td>
<td>4.3 (2.8)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>7 (17)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>2-&lt;4</td>
<td>16 (38)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>4-6</td>
<td>10 (24)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>9 (21)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>No. of boys</td>
<td>19 (45)</td>
<td>17 (44)</td>
</tr>
<tr>
<td>Attending day care</td>
<td>31 (74)</td>
<td>31 (74)</td>
</tr>
<tr>
<td>Attending school</td>
<td>4 (10)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Maternal level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>14 (33)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Polytechnic</td>
<td>19 (45)</td>
<td>18 (43)</td>
</tr>
<tr>
<td>Senior high school</td>
<td>5 (12)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Vocational school</td>
<td>4 (10)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Parental smoking</td>
<td>11 (26)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>No. of previous AOM episodes, mean (SD)</td>
<td>5.7 (4.7)</td>
<td>5.0 (5.5)</td>
</tr>
<tr>
<td>Previous adenoidectomy</td>
<td>9 (21)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Previous ventilation tubes</td>
<td>11 (26)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>3 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Symptoms at study entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear ache</td>
<td>23 (55)</td>
<td>18 (43)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (2)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Sleeping difficulties</td>
<td>10 (24)</td>
<td>16 (38)</td>
</tr>
<tr>
<td>Eating difficulties</td>
<td>13 (31)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Amoxicillin-clavulanate group</td>
<td>Placebo group</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>No. (%)</td>
<td>N=42</td>
<td>N=42</td>
</tr>
<tr>
<td>Tympanometry result curves$^3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B/B$^4$</td>
<td>8 (19)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>B/C or C/B</td>
<td>6 (14)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>B/A or A/B</td>
<td>19 (45)</td>
<td>20 (48)</td>
</tr>
<tr>
<td>C/C</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>C/A or C/A</td>
<td>5 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>A/A$^5$</td>
<td>2 (5)</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>

Abbreviation: AOM, acute otitis media

1 Children who had received three doses of pneumococcal conjugate vaccine. Pneumococcal conjugate vaccine was included in the national immunization program in Finland for children born on or after 1 June 2010.

2 Reported by parents and/or by children on day 1

3 All children presented with acute symptoms of respiratory infection and/or ear-related symptoms. Only children with signs of tympanic membrane inflammation, together with middle ear effusion detected in pneumatic otoscopy performed by a study physician, were eligible for the trial.

4 Six tympanograms with a positive pressure finding were included.

5 In 5 of 6 children with A/A tympanograms in the first examination, the next tympanograms obtained during the follow up were abnormal (3 A/B or B/A, 1 C/C and 1 A/C). One child had normal tympanometry results throughout the study and had air-fluid interface in the middle ear detected in pneumatic otoscopy.

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### 5.1.2 Duration of MEE and symptoms

The duration of MEE was shorter in the amoxicillin-clavulanate group than in the placebo group. MEE disappeared 2.0 weeks (13.7 days) earlier ($P=0.02$) in the antimicrobial group (mean 18.9 days; 95% CI 12.1 to 25.8) than in the placebo group (mean 32.6 days; 95% CI 25.0 to 40.2) (Table 8, Figure 7A). The mean duration of MEE per AOM episode decreased by 8 days among children younger than 2 years of age, by 20 days among children 2 to 6 years of age, and by 1 day among older children (Table 8). The median time to MEE disappearance was 8.0 days (95% CI 5.3 to 10.7) in the amoxicillin-clavulanate group and 29.0 days (95% CI 3.3 to 54.7) in the placebo group.

The mean time to improvement of tympanometry findings was 2 weeks shorter in the antibiotic than in the placebo group, $P=0.001$ (Table 8, Figure 7B). Normal otoscopy or otoscopy findings appeared 9.7 days sooner ($P=0.02$) in children in the amoxicillin-clavulanate (mean 24.7 days; 95% CI 19.2 to 30.1) than in the placebo group (mean 34.4; 95% CI 28.0 to 40.7) (Table 8, Figure 7C).
When combined tympanometry and otoscopy findings were used in the analysis, MEE resolved 11.5 days (P=0.002) sooner in the antimicrobial group than in the placebo group (Table 8).

Table 8. Effect of antimicrobial treatment on the duration of middle ear effusion (I).

<table>
<thead>
<tr>
<th>Outcome value</th>
<th>Amoxicillin-clavulanate group</th>
<th>Placebo group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 42</td>
<td>N = 42</td>
<td></td>
</tr>
<tr>
<td>Time to outcome, Mean (95% CI), day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal tympanometry findings²</td>
<td>18.9 (12.1 to 25.8)</td>
<td>32.6 (25.0 to 40.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>31.5 (13.1 to 49.9)</td>
<td>39.7 (21.3 to 58.1)</td>
<td>NA³</td>
</tr>
<tr>
<td>2-&lt;4</td>
<td>19.9 (7.4 to 32.5)</td>
<td>40.1 (28.3 to 52.0)</td>
<td>NA³</td>
</tr>
<tr>
<td>4-&lt;6</td>
<td>12.9 (3.5 to 22.2)</td>
<td>32.6 (18.0 to 47.1)</td>
<td>NA³</td>
</tr>
<tr>
<td>≥6</td>
<td>14.4 (1.9 to 27.0)</td>
<td>15.6 (4.7 to 26.4)</td>
<td>NA³</td>
</tr>
<tr>
<td>Normal otoscopy findings</td>
<td>24.7 (19.2 to 30.1)</td>
<td>34.4 (28.0 to 40.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Improved tympanometry finding⁴</td>
<td>13.7 (8.2 to 19.3)</td>
<td>28.2 (20.4 to 36.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Left ear</td>
<td>7.3 (2.9 to 11.6)</td>
<td>18.2 (10.8 to 25.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Right ear</td>
<td>10.8 (5.7 to 16.0)</td>
<td>19.0 (11.7 to 26.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Improved tympanometry or normal otoscopy findings³</td>
<td>11.4 (7.1 to 15.7)</td>
<td>22.9 (16.2 to 29.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable
1 Log Rank (Mantel-Cox) test was used for the comparisons.
2 Two A-curves on at least two consecutive measurement days from both ears.
3 Statistical testing in subgroups not performed since the sample size (power) was calculated only for the whole study group.
4 Two non-B curves were required on at least two consecutive measurement days. The non-B curve group includes both A curve tympanograms and C curve tympanograms (tympanic peak pressure < -200 daPa).
5 Shortest time used for analysis.

On days 7 and 14, the proportion of children with resolved MEE was greater among children who received amoxicillin-clavulanate than among those who received placebo (Table 9, Figure 7A). After one week, 47.6 % of children in the antibiotic group were free from MEE and correspondingly 26.2% of children in the placebo group P= 0.05. The absolute difference in the percentage of children with resolved MEE between the study groups was 31% on day 14; 3.2 children (95% CI 2.0 to 10.5) required treatment with amoxicillin-clavulanate to prevent 1 child from exhibiting abnormal tympanometry findings (Table 9, Figure 7A). Two children (5%) treated with amoxicillin-clavulanate had persistent MEE (≥60 days),
and 10 children (23%) in the placebo group had persistent MEE at the end of the trial (95% CI 4.5 to 34.7, P=0.01) (Figure 3) when combined tympanometry and otoscopy findings were used in the analysis. To prevent persistent MEE at 2 months in 1 child, 5.3 children required treatment with amoxicillin-clavulanate (95% CI NNT 2.9 to 22.2).

Table 9. Effect of antimicrobial treatment on the proportion of children without middle ear effusion (I).

<table>
<thead>
<tr>
<th>Outcome difference</th>
<th>Amoxicillin-clavulanate group</th>
<th>Placebo group</th>
<th>Difference (95% CI)</th>
<th>P value¹ (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved tympanometry²</td>
<td>N 42</td>
<td>N 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 7 d</td>
<td>25 (59.5)</td>
<td>14 (33.3)</td>
<td>26.2 (4.7 to 45.3)</td>
<td>0.02</td>
<td>3.8 (2.2 to 21.3)</td>
</tr>
<tr>
<td>At 14 days</td>
<td>32 (76.2)</td>
<td>22 (52.4)</td>
<td>23.8 (3.2 to 42.6)</td>
<td>0.03</td>
<td>4.2 (2.4 to 31.2)</td>
</tr>
<tr>
<td>Normal tympanometry³</td>
<td>N 42</td>
<td>N 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 7 d</td>
<td>20 (47.6)</td>
<td>11 (26.2)</td>
<td>21.4 (0.6 to 40.5)</td>
<td>0.05</td>
<td>4.7 (2.5 to 166.0)</td>
</tr>
<tr>
<td>At 14 days</td>
<td>29 (69.0)</td>
<td>16 (38.1)</td>
<td>30.9 (9.6 to 49.6)</td>
<td>0.005</td>
<td>3.2 (2.0 to 10.5)</td>
</tr>
<tr>
<td>Normal otoscopy</td>
<td>N 42</td>
<td>N 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 7 d</td>
<td>9 (21.4)</td>
<td>3 (7.1)</td>
<td>14.3 (-0.8 to 30.1)</td>
<td>0.07</td>
<td>NA</td>
</tr>
<tr>
<td>At 14 days</td>
<td>19 (45.2)</td>
<td>8 (19.1)</td>
<td>26.1 (6.2 to 44.4)</td>
<td>0.01</td>
<td>3.8 (2.3 to 16.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, Confidence interval. NA, not applicable. NNT, number needed to treat.
1 Standardized normal deviate test was used for the comparisons.
2 Two non-B curves form both ears were required on at least two consecutive measurement days. The non-B curve group includes both A curve tympanograms and C curve tympanograms (tympanic peak pressure < -200 daPa).
3 Two A curves from both ears were required on at least two consecutive days.

The mean (SD) times until disappearance of the earache were 2.2 (2.2) days in the amoxicillin-clavulanate group and 3.2 (2.3) days in the placebo group (95% CI -2.0 to 0.13 days, P=0.08). The proportion of the children with earache differed 5 days after administration of the study drug; at that time, none of the children in the amoxicillin-clavulanate group experienced ear pain, whereas 17% in the placebo group did (95% CI 7.4 to 33, P=0.004), NNT= 5.8 (95% CI 3.05 to 13.5). Differences in the dosage or duration of the pain medication between the groups were not statistically significant nor were differences in the disappearance of fever.
Amoxicillin-clavulanate was administered as a rescue treatment for 1 child in the placebo group owing to severe symptoms (Figure 3). None of the children developed mastoiditis or TM perforation. Five children (12%) in the amoxicillin-clavulanate group and none in the placebo group had diarrhea that resolved within 3 days without treatment. Four children (9.5%) in the amoxicillin-clavulanate group and 2 children (4.8%) in the placebo group experienced vomiting within 10 days of study entry. None of the children had a rash or oral thrush during treatment.
Fig. 7. Probability of persistent middle ear effusion in children with acute otitis media who received amoxicillin-clavulanate or placebo (I). The log-rank test was used for comparisons. A, Time to normal middle ear status was defined as having normal tympanometry findings (A curve) from both ears on 2 consecutive days (primary outcome) (P=0.02). B, Time to improved middle ear status was defined as receiving a peaked tympanogram finding (A or C curve) from both ears on 2 consecutive days (P=0.001). C, Time to normal pneumatic otoscopy finding (P= 0.002). ©American Medical Association and Copyright Clearance Center.
5.2 Benefit of ventilation tubes with and without adenoidectomy for recurrent acute otitis media (II)

5.2.1 Study population

Seventy-eight out of the 100 children in the VT group, 94/100 in the VT with adenoidectomy group and 80/100 in the non-surgery group received the allocated interventions and completed the entire follow-up (Figure 4). No serious complications were recorded in any of the children who participated in the trial. The groups appeared to be comparable in their background and demographic data on enrolment (Table 10).

Table 10. Baseline characteristics of 300 children with recurrent acute otitis media randomized into groups undergoing tympanostomy, tympanostomy with adenoidectomy and no surgery (II).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tympanostomy N=100</th>
<th>Tympanostomy with adenoidectomy N=100</th>
<th>No surgery N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in months (SD)</td>
<td>16.1 (4.0)</td>
<td>17.7 (4.3)</td>
<td>15.9 (3.8)</td>
</tr>
<tr>
<td>Boys/girls</td>
<td>57/43</td>
<td>58/42</td>
<td>53/47</td>
</tr>
<tr>
<td>Breast feeding &lt;3 months (%)</td>
<td>21</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Father / mother (either) smoking (%)</td>
<td>36/21 (40)</td>
<td>33/27 (42)</td>
<td>36/24 (43)</td>
</tr>
<tr>
<td>Attending day care (%)</td>
<td>36</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>At least one sibling (%)</td>
<td>81</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Children with a sibling operated on for AOM</td>
<td>39</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Dummy sucking while awake (%)</td>
<td>69</td>
<td>72</td>
<td>69</td>
</tr>
<tr>
<td>Atopic dermatitis diagnosed by a doctor (%)</td>
<td>14</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean age at the first AOM, in months (SD)</td>
<td>6.0 (3.4)</td>
<td>7.4 (4.0)</td>
<td>6.8 (3.7)</td>
</tr>
<tr>
<td>Mean AOM episodes in the last half year (SD)</td>
<td>5.3 (1.4)</td>
<td>5.1 (1.2)</td>
<td>5.0 (1.2)</td>
</tr>
<tr>
<td>Mean total AOM episodes (SD)</td>
<td>6.7 (1.9)</td>
<td>6.3 (1.7)</td>
<td>6.4 (1.9)</td>
</tr>
</tbody>
</table>

Abbreviation: AOM, acute otitis media

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5.2.2 Acute otitis media episodes

Insertion of VT alone or with adenoidectomy was effective in preventing RAOM episodes in children younger than 2 years of age. Intervention failed (2 AOM episodes in 2 months, 3 in 6 months or persistent effusion lasting for 2 months) during the 1-year follow-up in 21% of cases (21/100) in the VT group, 16% (16/100) in the VT with adenoidectomy group and 34% (34/100) in the non-surgery group (Figure 8, Table 11). The absolute differences were -13% (95% CI -25 to -1%, P=0.04) between the VT and non-surgery groups and -18% (CI -30 to -6%, P=0.004) between the VT with adenoidectomy and non-surgery groups (Table 11). Insertion of VT and VT with adenoidectomy reduced the risk of failure by 38% and 53%, respectively, as compared with the group of children who received no surgery. To avoid 1 failure, it was necessary to perform VT on 8 children or VT with adenoidectomy on 6 children (95% CI 4 to 168 and 4 to 17, respectively). Controlling for the differences in familial propensity to RAOM or form of day care in adjusted logistic regression analysis did not eliminate the effects of interventions. The differences in the time to failure between the VT and non-surgery groups (P=0.03) and the VT with adenoidectomy and non-surgery groups (P=0.001) were significant as well (Figure 8B). Only 1 child experienced otorrhea lasting longer than 2 months, all the other intervention failures being due to RAOM episodes.

The children in both surgical groups had fewer episodes of AOM than the controls (Table 11). Altogether 48% of the children in the VT group, 49% in the VT with adenoidectomy group and 34% in the non-surgery group had no episodes of AOM during the follow-up. VT and VT with adenoidectomy reduced the cumulative number of AOM episodes by 23% and 34%, respectively, compared with children who received no surgery. There were 32% and 46% fewer AOM episodes per person-year at risk in the VT and VT and adenoidectomy groups than in the non-surgery group, and there were also significant differences in the time to the first AOM episode between the VT and non-surgery groups (P=0.01) and the VT with adenoidectomy and non-surgery groups (P=0.002) (Figure 8A).

There was no significant difference between the VT with adenoidectomy and VT groups in the number of failures (absolute difference -5%, 95% CI -16 to 6, P=0.37), in the time to failure (P=0.29) or to the first AOM (P=0.6), or in the proportion of children with no AOM episodes (absolute difference 1%, 95% CI -13 to 15, P=1.0).
Fig. 8. Cumulative occurrences of (A) the first acute otitis media episode and (B) intervention failures (two episodes of acute otitis media within two months, three within six months or persistent effusion lasting for two months) during the one-year follow-up in 300 children by treatment groups. Analyzed according to the original randomized groups, despite possible protocol violations, until intervention failure or loss of the child to follow-up. (A) Significant differences in the time to the first acute otitis media episode between the tympanostomy and non-surgery groups (P=0.01) and between the tympanostomy with adenoidectomy and non-surgery groups (P=0.002), Log Rank test. (B) Significant differences in the time to failure between the tympanostomy and non-surgery groups (P=0.03) and between the tympanostomy with adenoidectomy and non-surgery groups (P=0.001), Log Rank test (II). ©Wolters Kluwer Health Lippincott Williams & Wilkins.
Table 11. Outcome measures after one year of follow-up in 300 children with recurrent acute otitis media randomized into groups undergoing tympanostomy, tympanostomy with adenoidectomy or no surgery (II).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tympanostomy N=100</th>
<th>Tympanostomy with adenoidectomy N=100</th>
<th>No surgery N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failures¹ %</td>
<td>21</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Difference² (95% CI)</td>
<td>-13 (-25 to -1)</td>
<td>-18 (-30 to -6)</td>
<td></td>
</tr>
<tr>
<td>AOM episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children with no AOM %</td>
<td>48</td>
<td>49</td>
<td>34</td>
</tr>
<tr>
<td>Difference² (95% CI)</td>
<td>14 (0.3 to 27)</td>
<td>15 (1.3-28)</td>
<td></td>
</tr>
<tr>
<td>Cumulative number of AOM episodes</td>
<td>92</td>
<td>79</td>
<td>119</td>
</tr>
<tr>
<td>One-year AOM incidence rate</td>
<td>1.15</td>
<td>0.91</td>
<td>1.70</td>
</tr>
<tr>
<td>Difference² (95% CI)</td>
<td>-0.55 (-0.93 to -0.17)</td>
<td>0.79 (-1.14 to -0.43)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AOM, acute otitis media
¹ Defined as having two episodes of acute otitis media in two months, three in six months or persistent effusion lasting for two months
² Compared with controls

5.3 Quality of life in children with acute otitis media and in their parents (III, IV)

5.3.1 Study population

The last 159 consecutive children from the study II were participants of the studies III (Figure 5) and IV (Figure 6). Seven of the first CHQ-50 questionnaires were incorrect and were excluded. The parents of 149 children returned the filled out CHQ-50 questionnaire at study entry, and these children were compared with control children without RAOM (IV, Figure 6). From these, 125 children whose parents completed the CHQ-50 also at the 1-year follow-up were included in the analyses to evaluate the effect of surgery on the QoL (IV, Figure 6, Table 12A). The 123 children whose parents completed the OM-6 questionnaire, at entry and at the 1-year follow-up, were also included in the analyses to evaluate the effect of surgery on the QoL (III, Figure 5, Table 13). The control children whose parents had returned completed questionnaires were divided into 2 groups, 104
without any AOM episodes and 120 with a history of 1 to 4 AOM episodes (IV, Figure 6, Table 12B).

AOM episodes were treated in surgery groups less often than in non-surgery groups during the follow-up (III, Table 13) (IV, Table 12A). Ten of the children in the non-surgery group who experienced a failure of treatment underwent VT treatment with (7) or without an adenoidectomy (3). One child in each surgery group (2%) did not have any operation because of the parents’ refusal. Eight children (7%) experienced re-operation during the 1-year follow-up, mostly because of new episodes of AOM after tube extrusion. No serious surgical complications were recorded.

5.3.2 Effect of acute otitis media on quality of life

The QoL of the children with RAOM was statistically significantly poorer on almost all scales related to CHQ-50 as compared to the controls without AOM or with 1 to 4 episodes of AOM, the greatest differences being in Global health, Role/social limitations due to physical health, Bodily pain, General health and in Emotional impact on the parents, Time impact on the parents and Family activities among the parameters describing the QoL of the parents (Figure 9). Only the scores on Role/social limitations due to emotional or behavioral difficulties and on Family cohesion did not differ statistically significantly between children with and without RAOM. The scores on Global health and General health indicated that the QoL was statistically significantly poorer in the children with 1 to 4 episodes of AOM than in those without any episodes among the children from general population (Figure 9). At the baseline of the study, Emotional distress and Physical suffering were the poorest scored subsets of OM-6 (Figure 10). The number of AOM episodes did not show any correlation with the QoL in any of the OM-6 subsets at entry to the study among children with RAOM.
Table 12. Baseline characteristic (IV). A. Children with recurrent acute otitis media, N=125, randomized into groups undergoing tympanostomy, tympanostomy with adenoidectomy or no surgery and the Child Health Questionnaire completed at entry, 4 months and 1-year follow-up. B. Children with recurrent acute otitis media, control children without acute otitis media episodes, and control children with a history of 1 to 4 acute otitis media episodes, and the Child Health Questionnaire completed at entry to the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A.</th>
<th>B.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tympanostomy with adenoidectomy</td>
<td>Tympanostomy with adenoidectomy</td>
</tr>
<tr>
<td>Number of patients</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>Mean age in months (SD)</td>
<td>16.3 (3.6)</td>
<td>17.6 (4.5)</td>
</tr>
<tr>
<td>Number of boys/girls N (%)</td>
<td>20/22</td>
<td>29/18</td>
</tr>
<tr>
<td>(48/52)</td>
<td>(62/38)</td>
<td>(47/53)</td>
</tr>
<tr>
<td>Number of previous AOM episodes, mean (SD)</td>
<td>7.2 (2.2)</td>
<td>7.0 (2.6)</td>
</tr>
<tr>
<td>Mean age at the first AOM, months (SD)</td>
<td>6.6 (3.3)</td>
<td>7.9 (4.1)</td>
</tr>
<tr>
<td>Mean duration of breast feeding, months (SD)</td>
<td>7.1 (4.0)</td>
<td>6.9 (5.0)</td>
</tr>
<tr>
<td>Attending day care N (%)</td>
<td>15 (36)</td>
<td>23 (49)</td>
</tr>
<tr>
<td>Mean number of siblings (SD)</td>
<td>2.1 (2.2)</td>
<td>1.9 (2.0)</td>
</tr>
<tr>
<td>Parental smoking N (%)</td>
<td>12 (29)</td>
<td>21 (45)</td>
</tr>
<tr>
<td>Maternal level of education</td>
<td>28 (67)</td>
<td>30 (64)</td>
</tr>
<tr>
<td>University/ polytechnic/ senior high school N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>4 (10)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>At 4 months follow-up N (%)</td>
<td>9 (21)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>At 1-year follow-up N (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RAOM, recurrent acute otitis media; AOM, acute otitis media

1 Two AOM episodes in 2 months or 3 in 6 months, as assessed by a doctor attached to the project
Table 13. Baseline characteristics of 123 children with recurrent acute otitis media randomized into groups undergoing tympanostomy, tympanostomy with adenoidectomy and no surgery (III).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tympanostomy</th>
<th>Tympanostomy with adenoidectomy</th>
<th>No surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>42</td>
<td>46</td>
<td>35</td>
</tr>
<tr>
<td>Mean age in months (SD)</td>
<td>15.6 (3.6)</td>
<td>18.0 (4.8)</td>
<td>16.8 (3.6)</td>
</tr>
<tr>
<td>Number of boys/girls N (%)</td>
<td>20/22 (48/52)</td>
<td>29/17 (63/37)</td>
<td>16/19 (46/54)</td>
</tr>
<tr>
<td>Number of previous AOM episodes, mean (SD)</td>
<td>7.2 (2.2)</td>
<td>7.1 (2.6)</td>
<td>6.2 (1.7)</td>
</tr>
<tr>
<td>Mean age at the first AOM, in months (SD)</td>
<td>6.6 (3.3)</td>
<td>7.9 (4.2)</td>
<td>7.3 (2.8)</td>
</tr>
<tr>
<td>Mean breast feeding, in months (SD)</td>
<td>7.1 (4.0)</td>
<td>7.7 (5.4)</td>
<td>7.3 (2.8)</td>
</tr>
<tr>
<td>Attending day care N (%)</td>
<td>15 (36)</td>
<td>23 (50)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Mean number of siblings (SD)</td>
<td>2.1 (2.2)</td>
<td>1.9 (2.1)</td>
<td>1.6 (1.6)</td>
</tr>
<tr>
<td>Parental smoking N (%)</td>
<td>12 (29)</td>
<td>20 (43)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Maternal level of education N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University/ polytechnic/ senior high school</td>
<td>26 (62)</td>
<td>27 (59)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Vocational school/ comprehensive school</td>
<td>11 (26)</td>
<td>13 (28)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Treatment failure¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1-year follow-up N (%)</td>
<td>9 (21)</td>
<td>8 (17)</td>
<td>12 (34)</td>
</tr>
</tbody>
</table>

Abbreviation AOM, acute otitis media

¹ Two AOM episodes in 2 months or 3 in 6 months, as assessed by a doctor attached to the project
Fig. 9. Quality of life (IV) of 149 children with recurrent acute otitis media (RAOM), 104 children with no acute otitis media (AOM) episodes and 120 children with a history of 1 to 4 AOM episodes. Child Health Questionnaire: Global health (GGH), Physical functioning (PF), Role/social limitations due to emotional or behavioral difficulties (REB), Role/social limitations due to physical health (RP), Bodily pain /discomfort (BP), Behavior (BE), Global behavior (GBE), Mental health (MH), Self-esteem (SE), General health (GH), Emotional impact on the parents (PE), Time impact on the parents (PT), Family activities (FA), Family cohesion (FC). Statistically significant differences (ANOVA, Tukey’s post hoc P< 0.05) in comparisons * of the RAOM children with the control children without AOM and with 1-4 AOM, and § between the control children without AOM and with 1-4 AOM episodes.
Fig. 10. Quality of life (QoL) (III) (in 123 children with recurrent acute otitis media randomized to undergo tympanostomy, tympanostomy with adenoidectomy or no surgery at entry and after 4 and 12 months of follow-up measured by Otitis Media-6 questionnaire. Global ear-related QoL on a visual analogue scale running from 0 (the worst possible) to 10 (the best possible). Outcome measures of QoL with a scale running from 1 (no problem/not present) to 7 (severe problems). Significant differences were found between entry and 1 year in RANOVA, (P=0.000, in all 3 groups), however there were no clinically significant differences between the treatment groups during the follow-up.
5.4 Impact of surgery on the quality of life for children with recurrent acute otitis media and for their parents (III, IV)

A significant improvement in the ear-related QoL (OM-6), between entry and the 12-month follow-up was seen on the 10-point visual analogue scale in all 3 randomized groups, with no difference among them (Figure 10). Statistically significant improvements during the 12-month follow-up period were detected in the subsets of Emotional distress, Physical suffering and Caregiver concern in children with RAOM (Figure 10), with Caregiver concern being the greatest improvement subset. Having VT (with or without an adenoidectomy) did not have any effect on the QoL during the 12-month follow-up compared with the non-surgery group in any of the 6 subsets (Figure 10).

The QoL of the children with RAOM improved on all scales of the generic CHQ-50 aspects during the 1-year follow-up (Figure 11 and 12). The change was statistically significant in physical Global health, Role/social limitations due to physical health, Bodily pain/discomfort and General health, and psychosocial Behavior, Mental health, Self-esteem, Emotional impact on the parents, Time impact on the parents and Family activities. The biggest improvements were seen in the parents’ Emotional impact, Time impact and Family activity scores, and the physical Bodily pain score. The QoL of the children with RAOM after the 1-year follow-up was still poorer according to CHQ-50 than that of the healthy control children without any AOM episodes at entry, and it was only in the Self esteem, Role/social limitations due to emotional or behavioral difficulties and Family cohesion scores that the difference was not statistically significant (Table 14).

There were no clinically significant differences between the randomized VT, VT with adenoidectomy and non-surgery groups (Figure 12) on any of the QoL scores after 4 months and 1 year of follow-up according to the CHQ-50 questionnaire. On the other hand, the only difference at entry was that the parents of the children in the VT with adenoidectomy group reported their children to have a marginally better QoL in terms of Global health than did those of the VT group (P=0.048).

The QoL of the children with RAOM according to the CHQ-50 questionnaire improved within the first 4 months in all 3 randomized groups (Figure 12). The largest proportions of statistically significant improvements between the scores on individual scales at entry and after 4 months of follow-up were in the QoL scores of the parents in the control and VT with adenoidectomy groups, and in the physical scores among those of the VT group.
Between entry and the 1-year follow-up assessment, the QoL had improved significantly according to the CHQ-50 questionnaire in the case of 7 scores in the non-surgery group and 8 in each of the surgery groups (Figure 12). Statistically significant improvements were observed in all 3 randomized groups in the physical scores for Bodily pain and General health and the psychosocial scores for Mental health, Self-esteem, Time impact on the parents and Family activities, but the QoL had improved statistically significantly between the 4 and 12-month questionnaires only in the case of the General health and Family cohesion scores for the VT group.

Table 14. Quality of life (IV) of the children with recurrent acute otitis media (RAOM) at 1-year follow-up and the children without AOM (acute otitis media) episodes.

<table>
<thead>
<tr>
<th>Child health questionnaire</th>
<th>RAOM at 1-year follow-up</th>
<th>Controls with no AOM</th>
<th>Difference1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>N=125</td>
<td>Mean (SD)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Global health (GGH)</td>
<td>81.5 (17.1)</td>
<td>94.9 (8.4)</td>
<td>-17.2 to -9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical functioning (PF)</td>
<td>87.4 (21.4)</td>
<td>95.0 (14.0)</td>
<td>-12.1 to -2.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Role/social limitations due to emotional/behavior difficulties (REB)</td>
<td>88.2 (20.3)</td>
<td>92.9 (16.7)</td>
<td>-9.7 to 0.0</td>
<td>0.052</td>
</tr>
<tr>
<td>Role/social limitations due to physical health (RP)</td>
<td>82.3 (25.6)</td>
<td>94.5 (14.9)</td>
<td>-17.6 to -7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bodily pain /discomfort (BP)</td>
<td>77.1 (21.6)</td>
<td>82.5 (18.3)</td>
<td>-10.9 to -0.5</td>
<td>0.031</td>
</tr>
<tr>
<td>Behavior (BE)</td>
<td>81.6 (15.6)</td>
<td>85.5 (13.2)</td>
<td>-7.8 to -0.2</td>
<td>0.041</td>
</tr>
<tr>
<td>Global behavior (GBE)</td>
<td>82.9 (17.2)</td>
<td>87.3 (14.0)</td>
<td>-8.5 to -0.2</td>
<td>0.038</td>
</tr>
<tr>
<td>Mental health (MH)</td>
<td>69.8 (14.4)</td>
<td>54.9 (9.2)</td>
<td>11.8 to 18.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Self-esteem (SE)</td>
<td>82.9 (18.0)</td>
<td>86.2 (13.9)</td>
<td>-7.8 to 0.8</td>
<td>0.109</td>
</tr>
<tr>
<td>General health (GH)</td>
<td>70.9 (14.7)</td>
<td>83.0 (9.6)</td>
<td>-15.3 to -9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional impact on parents (PE)</td>
<td>82.0 (21.1)</td>
<td>88.1 (10.3)</td>
<td>-10.9 to -3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time impact on parents (PT)</td>
<td>85.6 (15.8)</td>
<td>92.5 (11.7)</td>
<td>-12.1 to -4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family activities (FA)</td>
<td>76.5 (19.0)</td>
<td>83.1 (13.9)</td>
<td>-11.5 to -2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Family cohesion (FC)</td>
<td>78.9 (16.7)</td>
<td>79.2 (19.6)</td>
<td>-5.1 to 4.0</td>
<td>0.816</td>
</tr>
</tbody>
</table>

1 Standardized normal deviate test was used for the comparisons.
Fig. 11. Changes in the quality of life in 125 children with recurrent acute otitis media (RAOM) at the 1-year follow-up (IV). Child health questionnaire: Global health (GGH), Physical functioning (PF), Role/social limitations due to emotional or behavioral difficulties (REB), Role/social limitations due to physical health (RP), Bodily pain /discomfort (BP), Behavior (BE), Global behavior (GBE), Mental health (MH), Self-esteem (SE), General health (GH), Emotional impact on the parents (PE), Time impact on the parents (PT), Family activities (FA), and Family cohesion (FC). Statistically significant differences (paired t-test P< 0.05)*.
Fig. 12. Quality of life for 125 children with recurrent acute otitis media and results covering 4 and 12 months of follow-up, in the 3 randomized groups: tympanostomy with adenoidectomy (N=42), tympanostomy (N=47) and non-surgery (N=36) (IV). Child health questionnaire: Global health (GGH), Physical functioning (PF), Role/social limitations due to emotional or behavioral difficulties (REB), Role/social limitations due to physical health (RP), Bodily pain/discomfort (BP), Behavior (BE), Global behavior (GBE), Mental health (MH), Self-esteem (SE), General health (GH), Emotional impact on the parents (PE), Time impact on the parents (PT), Family activities (FA), and Family cohesion (FC). Statistically significant differences (General linear model with repeated contrast P< 0.05) between scores * at entry and after 4 months of follow-up and between scores § at entry and after 12 months of follow-up. Differences between the randomized groups were tested (ANOVA, Tukey’s post hoc P< 0.05) at entry and after 4 months and 1 year of follow-up. Only the GGH score at entry was marginally better (P=0.048) in the tympanostomy with adenoidectomy group than in the tympanostomy group.
6 Discussion

6.1 Duration of middle ear effusion of acute otitis media with antibiotic treatment (I)

In this study, MEE disappeared significantly earlier among children who received amoxicillin-clavulanate than in children who received placebo. In children receiving antimicrobial treatment, the mean duration of MEE was reduced by 2 weeks and the median duration of MEE by 3 weeks per AOM episode. To prevent 1 child from exhibiting abnormal tympanometry at 2 weeks, 3 children required antimicrobial treatment. Thus, antimicrobial treatment effectively reduced the duration of MEE and possible concomitant hearing impairment among children with AOM.

The main aim of the treatment of AOM is to eradicate bacteria from the middle ear and to normalize hearing. Thus, the duration of MEE is an ideal outcome measure if it can be assessed reliably and accurately. In most studies, the duration of MEE, if considered at all, has been monitored only during control visits made weekly or at even longer intervals. Although the accuracy of tympanometry in detecting MEE is good (Helenius et al. 2012, Koivunen et al. 1997), few studies have used hand-held tympanometry for daily surveillance at home (Renko et al. 2006). The approach that was used for this study was feasible, as the majority of home measurements were successful. Our results are important, since MEE impairs hearing, which may cause long-term damage to future linguistic or other cognitive skills. A child begins to engage in the long-term storage of words as early as 8 months old (Jusczyk & Hohne 1997), which also happens to be the time period when the incidence of AOM episodes is highest. Moreover, children under 3 years of age have a much higher risk of persistent effusion after AOM (Alho et al. 1991, Henderson FW et al. 1982, Shurin et al. 1979, Sipilä et al. 1987), and persistent MEE was significantly related to the development of RAOM (Monobe et al. 2003). In this trial, antibiotics protected children from experiencing longer bouts of MEE. Five percent of children treated with amoxicillin-clavulanate and 23% of children in the placebo group had persistent MEE (≥60 days).

Our findings are consistent with 2 other RCTs that used strict criteria for AOM (Hoberman et al. 2011a, Tähtinen et al. 2011) in young children and infants with AOM. These studies found that antimicrobials appear to have a modest effect
on the proportion of abnormal otoscopy findings at 1 week (Tähtinen et al. 2011) and on the rate of the remaining MEE at 3 weeks (Hoberman et al. 2011a). In our study, however, the magnitude of the effect was greater, which may be due to the older age of participants in our study and/or methodological differences in the follow-up. Daily evaluation of the resolution of otorrhea has been performed in patients with VT (Ruohola et al. 2003). The study showed 82% resolution of MEE with antibiotic treatment and 41% resolution of MEE with placebo after 1-week follow-up (Ruohola et al. 2003), which is in line with our results despite samples that are not fully comparable. Our findings contradict those of several RCTs and those of two meta-analyses which conclude that antimicrobial treatment has no impact on the duration of MEE evaluated either by tympanometry or otoscopy (Burke et al. 1991, Damoiseaux et al. 2000, Kaleida et al. 1991, Mygind et al. 1981, Rovers et al. 2006, van Buchem et al. 1981, Venekamp et al. 2013). In these other studies the existence of MEE was checked at an interval of several weeks, and thus at least some of the noted MEEs could have been due to re-infection. The most likely explanation for this discrepancy between our study and others is that we obtained daily information on the middle ear status. In this way, an accurate measure of the duration of MEE was obtained, and including new respiratory tract infections and the subsequent development of new MEE in the study population was avoided.

The current study has an issue with generalizability because only about 20% of the enrolled patients were in the peak AOM age group of 6 to 24 months, which is the typical age range for AOM. Pneumococcal resistance to penicillin is rather low in Finland (Siira et al. 2009). Consequently, the appropriate antimicrobial dosing for our setting may be insufficient in other countries.

The recommended treatment of OME after an acute infection episode is a watchful waiting period of three months with interval visits to a physician in order to document any persistent effusion (Acute otitis media. Current Care Guidelines 2010, American Academy of Family Physicians et al. 2004). In unresolved cases, hearing should then be examined and surgery should be considered (Acute otitis media. Current Care Guidelines 2010, American Academy of Family Physicians et al. 2004). This study was not designed to estimate the difference in follow-up visits and subsequent surgery due to chronic OME between the study groups. However, we are concerned that restricting the antimicrobial treatment of AOM may increase the need for subsequent follow-up visits and possible surgery, since this study showed that the risk for persistent
MEE at two months among children in the placebo group was 5-fold higher than in the antimicrobial group.

Findings from the literature and from this study may be summarized as guidance for AOM as follows: Accurate and stringent diagnosis is very important in children with AOM. Physicians should enlighten parents about the natural history of AOM and only children with a confirmed AOM diagnosis should be offered antibiotic treatment. Antibiotic treatment reduces pain compared to placebo treatment and may, therefore, accelerate the return to normal life. In addition, antibiotic treatment precipitates the resolution of MEE and ensures hearing. In reference to our study and the 2 other studies that had stringent diagnostic criteria (Hoberman *et al.* 2011a, Tähtinen *et al.* 2011), Pichichero (*Pichichero* 2015) concluded that:

“*These findings supported a recent US Food and Drug Administration panel’s decision that the evidence in favor of the beneficial effects of antibiotics on AOM is clear and that further trials are not needed.*”

6.2 The quality of life (III, IV)

6.2.1 Children with acute otitis media

We found that children with RAOM had a significantly poorer QoL in terms of generic measurements than children without AOM episodes. Correspondingly, QoL among children with only a few (1 to 4) episodes of AOM in their history was better than that of children with RAOM, but poorer than children without AOM episodes.

QoL measurements can be important for assessing the burden caused by a disease and in part for evaluating the efficacy of treatment. To achieve a realistic picture of QoL, it is useful to obtain both disease-specific and generic measurements. Sometimes disease-specific instruments may be too sensitive, and in particular, the burden imposed by RAOM cannot be compared with that arising from other diseases and health populations when using only disease-specific QoL instruments. We combined both questionnaires in order to benefit from the merits of both types.

Using data obtained from the generic questionnaire, QoL showed a rapid improvement within 4 months. In the data derived from the disease-specific questionnaire, improvements were found to be more linear during the follow-up
time. Although QoL among children with RAOM improved considerably once AOM became less frequent during the 1-year follow-up, it did not reach the level achieved by the healthy control children with no history of AOM. Our results are in line with 2 previous studies that used other generic measurements, where children over 5 years of age affected by various forms of OM (AOM, RAOM and OME) (Lee et al. 2006) and children 1 to 7 years of age with RAOM (Brouwer et al. 2005b) had a lower global QoL than healthy children of a similar age. However, those studies did not include a follow-up. Our findings were the same as in the previous studies, in that the OM-6 subsets of Physical suffering, Emotional distress and Activity limitations gained the highest scores, indicating poorer QoL in children with RAOM (Rosenfeld et al. 2000).

The use of a generic QoL instrument in the case of children with a heavy otitis burden enables the impact of RAOM to be compared with those of other illnesses known to have a detrimental effect on a child’s everyday life. It was found, for example, that the QoL among children with RAOM in this study was poorer than that of Finnish children 11 to 15 years of age with asthma (Merikallio et al. 2005), as has been reported earlier (Brouwer et al. 2005b). RAOM in young children in this study seemed to detract from QoL in a similar manner to chronic juvenile arthritis in Finnish children in about 10 years of age (Pelkonen et al. 2001). Similarly, QoL for children with RAOM is poorer than that of children with mild-to-moderate diseases, for instance, allergies, chronic bronchitis or intestinal problems (Brouwer et al. 2005b). Thus RAOM has a fairly significant effect on the QoL.

We found that the number of AOM episodes correlates with QoL according to the data obtained from the generic questionnaire in general populations and RAOM children. Moderate correlations have been reported between the frequency of OM and the physical suffering of children (Lee et al. 2006). Children with 4 or more episodes of AOM within 1 year have been found to have a poorer QoL than children with 2 or 3 episodes (Brouwer et al. 2005b). It seems that a few episodes of AOM in early childhood have an effect on well-being. This highlights the importance of the exact diagnosis of AOM and early prevention of RAOM.

6.2.2 Parents of children with acute otitis media

Our results showed that OM impaired the QoL of parents and all QoL domains for the parents improved markedly in the course of the follow-up with a rapid
improvement exhibited within the first 4 months. This result is supported by other disease-specific studies (Chow et al. 2007, Heidemann et al. 2014, Richards & Giannoni 2002, Rosenfeld et al. 2000). The parents’ QoL has been reported to deteriorate when facing illnesses in their children (Aitken et al. 2002, Pelkonen et al. 2001) as was the case among the parents in the present study as well.

In addition to the fact that AOM gives rise to health care costs in the form of physician’s visits, the prescription of antibiotics, surgery and loss of working days for parents, (Alsarraf et al. 1999, Niemelä et al. 1999) we found that RAOM detracts from the QoL of both the children and their parents to an extent comparable to that seen in asthma and juvenile arthritis. Parents play an important role in the cooperation between children and healthcare professionals, and the QoL among parents may have the potential to influence the treatment strategy for the child. Consequently, research on QoL of both child and caregiver is important for understanding the full burden of diseases among young children and in assessing treatment outcomes and planning future treatment strategies.

6.2.3 Methods

The validity of the questionnaires and their results may be limited for this study, because the instruments have not been assessed in the language (OM-6) the questionnaire was used, or among the younger age group with modified questionnaires (CHQ-50). We aimed to minimize these deficiencies. Although the CHQ was developed and tested for children aged 5 to 18 years, it has been used for younger age groups as well (Aitken et al. 2002). In this study the validated Finnish version was used, although it had to be adapted for younger children. However, the scores on the CHQ questionnaires of children with no AOM episodes in this study were comparable to those reported in older healthy Finnish children in previous studies (Merikallio et al. 2005, Pelkonen et al. 2001). In the present case the existence of an age-matched control group without AOM episodes excludes errors due to age. Similarly the inevitable impact of the aging of children in the surgical treatment groups with RAOM was allowed for by having a group of RAOM children who did not undergo surgery. Thus, we believe that this modified questionnaire for children less than 2 years of age was not biased.

One reason for the rapid improvement in QoL could be the follow-up and the parents’ opportunities to contact the doctor engaged in this project at any time during the follow up period if their child showed URI symptoms or there was a
suspicion of AOM in their child. In the present setting, children were treated by otolaryngologists at regularly scheduled appointments. Frequent follow-ups were particularly reassuring for the parents despite continuing infections, and may have led to a positive impact on QoL among children. The proxy problem of studies among younger children, who are not able to answer questionnaires themselves, is that reports may vary substantially depending on who completes the questionnaire. Caregiver concern may be a domain of pediatric QoL, although those concerns may be more indicative of caregiver QoL than of child QoL. Caregivers’ own personal situations in life may influence their ratings of their child’s QoL (Boruk et al. 2007).

We selected children who had been referred for assessment with regard to surgical treatment for RAOM, and compared QoL among these children at entry to that of age-matched controls who were further classified into 2 groups according to their history of AOM. Although the health care system in Finland guarantees equal treatment for all children with no financial burden on parents, there are some possible confounding factors. Parents seeking referral to a specialist because of RAOM in their children were perhaps more concerned than those who did not seek referral, and it is certainly the case that not all children who have experienced RAOM episodes are referred for further treatment (Alho et al. 1994). Another flaw may be the fact that the evaluation of the number of AOM episodes in the CHQ questionnaire was based on information received from parents. It has been shown that parents seeking surgical treatment for their child’s RAOM tend to exaggerate the number of AOM episodes (Alho et al. 1994). Even so, we found that among the controls selected from the general child population, 1-4 AOM episodes may already detract from QoL, such that there was a significant difference relative to the control group without any AOM. Therefore we believe that even though the RAOM group may have been somewhat selective, the results are generalizable and our protocol reflects the manner in which RAOM children are treated in actual everyday clinical practice. However, in other countries with other cultural backgrounds or a more diverse genetic/racial/ethnic background, the impacts may not be the same.
6.3 Prevention of recurrent acute otitis media with ventilation tubes and adenoidectomy (II, III, IV)

6.3.1 AOM episodes (II)

We found that the insertion of VTs significantly reduced the risk of RAOM among children younger than 2 years as compared to children for whom no preventive measures were taken. Concurrent adenoidectomy did not significantly increase this effect.

The incidence of AOM is highest for children under the age of 2 years and about 30% of children suffer from RAOM, yet thus far there have been few RCTs addressing prevention with VTs and adenoidectomy in this age group (Mattila et al. 2003). This study focused on the prevention of RAOM among children younger than 2 years of age and included only children with RAOM. Children with chronic MEE were excluded and the study started when the middle ear had been confirmed to be free from effusion. Since the diagnosis of AOM is crucial, only AOM diagnosed by our team of otolaryngologists was accepted and analyzed, using tympanometry as an independent measure of effusion in the middle ear (Koivunen et al. 1997) and requiring pathological findings in pneumatic otoscopy as well. If there was uncertainty in making the diagnosis, otomicroscopy was also employed. The children are representative of the population of patients in Finland, since our hospital serves as the primary hospital for children with RAOM. The compliance shown by parents was good. The analyses were performed on an intention-to-treat basis in order to avoid overestimation of the efficacy of surgical procedures.

Although the insertion of VTs is common, a recent Cochrane review of the efficacy of VT contained only 2 controlled studies on children younger than 3 years of age with a history of RAOM (McDonald et al. 2008). It was found that VTs have a significant role in maintaining time without OM in the first 6 months after insertion, but further research would be required to investigate the effect beyond 6 months (McDonald et al. 2008). Among older children, a meta-analysis of 5 randomized trials comparing no surgery with VT for RAOM with or without MEE showed that the tubes reduced the overall AOM incidence by 1 episode per child-year, so that the risk of developing AOM declined by 56% relative to controls (Rosenfeld 2000). These results are in line with 2 earlier studies that indicate that the insertion of VTs is effective, but that adenoidectomy together with VT insertion does not have a major advantage over tubes alone in preventing
AOM in children younger than 2 years (Hammaren-Malmi et al. 2005) or younger than 4 years of age (Mattila et al. 2003). Our research supports this finding.

The fact that we assessed AOM episodes on a weekly basis and not more frequently may have caused some inaccuracy in controlling the resolution of effusion, especially among the control group. Furthermore, irregular attendance or missing of some of the follow-up visits might have been a source of some potential errors when estimating the length of AOM episodes. However, compliance with the follow-up schedule did not differ between the groups, and adherence to the study protocol on the whole was very good. In addition, the resolution of effusion was not the main outcome of the study. When comparing children with VTs to children without surgery, the investigator and parents cannot be blinded, which may lead to positive placebo effects of the surgery.

AOM episodes cause many problems for children and their families. The risk factors for AOM are well known, but only a few of them can be influenced by any form of intervention (Block et al. 2011, Niemelä et al. 2000, Uhari et al. 1998, Uhari & Möttönen 1999, Wals et al. 2009). The Clinical Practice Guideline (Rosenfeld et al. 2013) proposes that bilateral VTs should be considered if RAOM is associated with a persistent MEE between AOM attacks, and should not be inserted in children with RAOM without MEE in either ear at the time of assessment for tube candidacy (Rosenfeld et al. 2013). Recommendations are based on studies which highlight the situation of children’s ears at the point of study recruitment. This is confusing in part because MEE associated with AOM can take anywhere from 1 week to 3 months to clear in practice.

VTs are usually inserted under general anesthesia. The procedure is simple but performing an adenoidectomy at the same time makes it more invasive, with additional surgical and anesthetic risks. Even though complications were not detected in our surgical groups, clinicians should keep in mind the possibilities of such complications occurring and weigh them up against the rather modest additional benefit offered by adenoidectomy. We conclude that VT insertion is efficient in preventing AOM episodes in children younger than 2 years, which is the group at highest risk of developing RAOM.

6.3.2 Quality of life (III, IV)

Our study provides evidence regarding the impact of VTs with and without adenoidectomy on QoL for a child with RAOM and their parents. Because we
concentrated our analyses on comparing QoL scores among 2 operation groups and 1 non-surgery group in a randomized and controlled trial, the impact of the child growing up is taken into account.

We found that even though these surgical procedures were effective in preventing RAOM, QoL of children with RAOM and of children’s parents was not affected by whether they were treated surgically or merely followed up. There were significant improvements in both generic and disease-specific QoL questionnaires but without any differences among the 3 groups. The same has been found earlier among 1 to 2-year-old children with persistent bilateral OM, for whom generic measurements of QoL improved, but the VT group did not show a significantly greater improvement than the non-surgery group (Rovers et al. 2001). QoL showed rapid improvement within the first 4 months among all 3 randomized groups in this study in the generic measurements of QoL. In previous otitis-specific measurement studies, VTs induced significant improvements in QoL within 1 to 6 months of placement (Chow et al. 2007, Richards & Giannoni 2002, Rosenfeld et al. 2000), but those studies did not include a non-surgery group. Follow-up, along with parents having opportunity to contact the doctors engaged in this project at any time if they suspected AOM in their child may have reduced the differences in QoL between the surgery and non-surgery groups.

Assessment of the treatment options and measurements of treatment’s efficacy should include perspectives from both children and their parents. QoL should also be considered together with objective parameters. The parents should also be informed of the natural course of RAOM.
7 Conclusion

1. Antimicrobial treatment effectively reduced ear pain and the duration of MEE, as well as the risk for persistent MEE and possible concomitant hearing impairment among children with AOM. Antimicrobial treatment is useful in AOM after careful diagnosis.

2. VT insertion is efficient in preventing AOM episodes among children younger than 2 years of age, the group that is at highest risk of developing RAOM.

3. Even a few AOM episodes lead to a poorer QoL. RAOM detracts from the QoL of children and their families even when assessed with generic QoL measures. However, QoL improves when children are closely monitored but it does not reach the same level as observed in children without AOM.

4. VT insertion with or without adenoidectomy does not provide any additional QoL benefit for children with RAOM, even though these operations are effective in preventing further AOM episodes. Thus, the indications for surgery in cases of RAOM should be carefully considered and watchful observation could be regarded as one option if a child’s QoL is the main concern. It seems that only primary prevention of AOM episodes can ensure good OM-related QoL during early childhood.
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