ACUTE
SEVERE COMPLICATIONS
OF OTITIS MEDIA
IN CHILDREN AND ADULTS

ANU LAULAJAINEN-HONGISTO
ACUTE SEVERE COMPLICATIONS OF OTITIS MEDIA IN CHILDREN AND ADULTS

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Academic dissertation

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Helsinki 2016
To Jonatan, Emil and Oskar

*Education is not the learning of facts but the training of the mind to think*

*Albert Einstein*
ABSTRACT

Acute otitis media (AOM) is an infection that is particularly common in children. The bacterial etiology of AOM, in both children and adults, affects its clinical picture. While in some cases the infection can simply be carefully monitored without treatment, antimicrobials are often prescribed. Caution is required, however, when prescribing antimicrobials as their excessive use has led to antimicrobial resistance; this resistance has been seen among some of the causative pathogens for these infections.

Before the development of antimicrobial treatment, complications due to middle ear infections were common, potentially causing severe symptoms or even death. Some middle ear infections spread into surrounding structures, leading to intratemporal or extratemporal (extracranial or intracranial) complications. This thesis focuses on complicated otitis media and the causative factors of its complications.

In the first two studies, we evaluated the medical records of all (n=100) children (0-16 years old) hospitalized at the Department of Otorhinolaryngology in the Helsinki University Hospital from 2003 to 2012 for acute mastoiditis (AM) or AOM, as well as the infection's bacteriology in relation to the patient's clinical findings and treatment. Using this information, we analyzed the differences in the etiologies and clinical pictures of those children hospitalized due to AOM compared to AM.

In our third study, we examined the medical records of all (n=166) patients hospitalized at our institution from 1970 to 2012 due to intracranial abscesses (IA), including those of otogenic background (oIA).

In the fourth study, we evaluated the bacteriology in relation to the patients' clinical findings and treatment in all (n=160) adult patients treated at our institution from 2003 to 2012 for AOM or acute mastoid infection. In adults, acute mastoid infection was subclassified into AM, latent mastoiditis (LM), and AM following chronic middle ear infection (AMc).

The clinical picture of AM in children differed according to the causative pathogen. *Streptococcus pneumoniae* (*Pnc*), especially its resistant strains, caused severe symptoms and often led to mastoidectomies. *Pseudomonas aeruginosa* (*Ps*) typically affected older children with prior tympanostomy tubes and generally caused milder symptoms. Furthermore, the bacteriological etiology of hospitalized AOM and AM patients was different compared to outpatient AOM. Two of the typical AOM pathogens, *Haemophilus influenzae* (*Hi*) and *Moraxella catarrhalis* (*Mc*), were uncommon among the hospitalized patients. *Pnc*, especially its resistant strains, was less common in children hospitalized for AOM compared to AM, and less common in adults than children. *Streptococcus pyogenes* (*StrA*) and *Ps* were both linked to otorrhea and were found only in older children.

Over our 42 year study period, oIAs became less common and typically developed following chronic middle ear infections, often in connection with cholesteatoma.
In adults, the bacteriological etiology and clinical picture of AMc differed from AOM as well as the other acute mastoid infection types (AM, LM). AOM and AM led to less surgical procedures than the more prolonged forms of acute mastoid infection (LM, AMc).

In children, the hospitalized cases of AOM and AM differed from outpatient AOM. In adults, severe AOM, AM, and LM seem to compose a continuum that may lead to chronic otitis media and its acute complications, including oIAs. Otogenic IAs are quite rare, however, and became less common over our study period.
TIIVISTELMÄ

Äkillinen välikorvatulehdus on yksi lasten tavallisimmista taudeista; aikuisilla se on lapsia harvinaisempi. Vaikka pelkkä seuranta voi riittää äkillisen välikorvatulehdoksen hoidoksi, usein hoitona käytetään antibioottia. Välikorvatulehdus voi levitä välikorvaa ympäröiviin rakenteisiin aiheuttaen vakaviakin komplikaatioita (esim. kartiolisäketulehdus, aivopaise). Ennen antibioottien kehittämistä välikorvatulehdoksen komplikaatioita esiintyi nykyistä enemmän. Turhaa antibioottien käyttöä on vältettävä, mutta komplisoitunutta tautia sairastavat potilait on tunnistettava varhain ja hoidettava tehokkaasti. Tässä tutkimuksessa selvitetiin komplisoituneen välikorvatulehdoksen taustatekijöitä.


*Streptococcus pneumoniae* on tavallinen välikorvatulehdoksen taudinaiheuttaja, myös tässä tutkimuksessa. Merkittävemmin vaikuttavat aikuisia lapsia ja aikuisia kuvioo epätavallisesti kardioekstremistiin, joiden aiheuttamia *Streptococcus pneumoniae*-kantoja. Erityisesti kartiolisäketulehdusta sairastavia aikuisia ja lapsia muilla korvaperäisten aivopaiseiden kehityksen ja kehityksen säännönmukaisuudenkin huomioillessa. M. kardiolisäketulehdussa on esiintynyt *Haemophilus influenzae* ja *Moraxella catarrhalis* aineistossa harvoin, mutta harvoin on tutkimusaineistossa esiintynyt *Streptococcus pneumoniae*

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to by their roman numerals:


IV Laulajainen-Hongisto A, Jero J, Markkola A, Saat R, Aarnisalo AA. Severe acute otitis media and acute mastoiditis in adults. (Submitted)

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<td>AM</td>
<td>acute mastoiditis</td>
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<td>AMc</td>
<td>acute mastoiditis in a patient with CSOM</td>
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<tr>
<td>AOM</td>
<td>acute otitis media</td>
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<td>CSOM</td>
<td>chronic suppurative otitis media</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein (mg/l)</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>EAC</td>
<td>external auditory canal</td>
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<td>ENT</td>
<td>ear, nose, and throat</td>
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<td>ET</td>
<td>Eustachian tube</td>
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<tr>
<td>Hi</td>
<td><em>Haemophilus influenzae</em> (non-encapsulated)</td>
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<td>IA</td>
<td>intracranial abscess</td>
</tr>
<tr>
<td>ICD-9</td>
<td>international classification of diseases, version 9</td>
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<td>ICD-10</td>
<td>international classification of diseases, version 10</td>
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<td>LM</td>
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<td>Mc</td>
<td><em>Moraxella catarrhalis</em></td>
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<td>MEE</td>
<td>middle ear effusion</td>
</tr>
<tr>
<td>MIC</td>
<td>minimal inhibitory concentration (mg/l)</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>oIA</td>
<td>otogenic intracranial abscess</td>
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<tr>
<td>OM</td>
<td>otitis media</td>
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<tr>
<td>OME</td>
<td>otitis media with effusion</td>
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<tr>
<td>PCV</td>
<td>pneumococcal conjugate vaccine</td>
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<tr>
<td>Pnc</td>
<td><em>Streptococcus pneumoniae</em></td>
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<tr>
<td>Ps</td>
<td><em>Pseudomonas aeruginosa</em></td>
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<tr>
<td>Sa</td>
<td><em>Staphylococcus aureus</em></td>
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<tr>
<td>StrA</td>
<td><em>Streptococcus pyogenes</em></td>
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<tr>
<td>TM</td>
<td>tympanic membrane</td>
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<tr>
<td>URTI</td>
<td>upper respiratory tract infections</td>
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<tr>
<td>WBC</td>
<td>leukocyte count (E9/l)</td>
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Acute otitis media (AOM), infection of the middle ear, is one of the most common infections in children, though it affects adults as well. Middle ear infections, and the problems caused by them, however, differ between children and adults. Children are prone to developing AOM due to anatomical and immunological immaturity, whereas adult ear infections are typically chronic in nature (Bluestone 2008). AOM is treated with antimicrobials, or in some cases by expectant observation.

Viral upper respiratory tract infections (URTI) often precede bacterial AOM, especially in children. The AOM-causing bacteria typically originate from the nasopharynx via the Eustachian tube (ET). AOM caused by Streptococcus pneumoniae (Pnc) has been associated with a severe form of the infection, with fever and earache, while AOM caused by non-encapsulated Haemophilus influenzae (Hi) has been associated with conjunctivitis (Palmu et al. 2004). Hi and Moraxella catarrhalis (Mc) rarely cause complications, whereas Streptococcus pyogenes (StrA) has been associated with complicated AOM (Segal 2005). In prolonged middle ear infections, middle ear mucosa swells, resulting in hypoxemia and metabolic changes which leads to the selection of pathogens that survive in these conditions.

Tympanic membrane (TM) perforations and bone erosions may allow for the spreading of infection to and from the middle ear, allowing for complications to arise. Complications of otitis media (OM) can be classified into intratemporal and extratemporal (either intracranial or extracranial). Anatomical or immunological conditions may predispose patients to these complications. The thinner bony structures of children may more easily be resorbed by infection, allowing for easier development of AOM complications (Stenfeldt et al. 2014).

Before the development of antimicrobial treatment, complications of OM were common and caused severe morbidity, and even death (Valentine 1924, Palva et al. 1959). Complications due to OM have since become uncommon, but have not completely disappeared. Furthermore, the clinical picture of complications has changed with antimicrobial treatment potentially masking symptoms and leading to a prolonged, mild form of disease (Faye-Lund 1989).

Complications of OM can develop following untreated or incompletely treated infections as well as cases with adequate antimicrobial treatment, and are also seen with infections caused by bacteria that are resistant to antibiotics (Zapalak et al. 2002). Antimicrobial resistance of pathogens has developed due to the excessive use of antibiotics. While patients with severe infections, or those at risk of developing complications, should be effectively treated, antimicrobial treatment may be unnecessary in patients with only mild infection.

We need to better understand which patients require antimicrobial treatment to achieve a successful recovery, and which patient's infections will resolve themselves - to be able to do this, we must study complicated cases of OM; this study aims to do that.
2 REVIEW OF THE LITERATURE

2.1 Historical aspects

“Acute pain of the ear, with continual and strong fever, is to be dreaded; for there is danger that the man may become delirious and die. Since, then, this is a hazardous spot, one ought to pay particular attention to all these symptoms from the commencement. Younger persons die of this disease on the seventh day, or still earlier, but old persons much later; for the fevers and delirium less frequently supervene upon them, and on that account the ears previously come to a suppuration, but at these periods of life, relapses of the disease coming on generally prove fatal. Younger persons die before the ear suppurates; only if white matter run from the ear, there may be hope that a younger person will recover, provided any other favorable symptom be combined” (Hippocrates, 400 BC).

Despite the immense advancements in medicine since Hippocrates’ time, his description of complicated OM does not sound outdated to a modern otorhinolaryngologist. Not only have the knowledge of anatomy and the understanding of the disease’s underlying conditions advanced since his time, but fairly recent great developments have been made in the diagnostics, and treatment of diseases. While living in the age of antimicrobials means we are often able to prevent the most severe complications that Hippocrates saw, we still see patients, young and old, presenting with OM and its complications.

Before the late 1800s, intracranial abscesses (IA) almost always led to death (Mathisen et al. 1997). Then antimicrobials arrived, with sulfonamides being introduced in the 1930s and penicillin, streptomycin, chloramphenicol, and tetracyclins all being introduced in the 1940s (Simpson 2013). Before antibiotics, complications due to OM were difficult to treat, with StrA being the most common pathogen that led to AOM complications (Valentine 1924, Palva et al. 1959, Vergison 2008).

In less than 100 years since their introduction, however, the effectiveness of antimicrobials has been reduced. Currently, bacterial resistance to antimicrobials is a growing global problem due, in large part, to the often excessive use of antibiotics in the human medical field as well as in agriculture and aquaculture (Silbergeld et al. 2008, Heuer et al. 2009).

Thankfully, tools to aid in the diagnostics and treatment of OM and its complications have been developed. Computed tomography (CT) imaging was introduced in the 1970s (Simpson 2013), and magnetic resonance imaging (MRI) was utilized in clinical practice starting in the early 1980s (Ai et al. 2012).
2.1 **Anatomy**

*The ear and temporal bone*

The outer ear consists of the pinna (auricula) and the external auditory canal (EAC). At the end of the EAC lies the TM, which forms the lateral border of the middle ear (Figure 1).

The middle ear is an air-filled cavity lined by mucous membrane; situated inside the temporal bone it consists of the squamous, petrous, mastoid, tympanic, and styloid bones (Figure 2). The uppermost part of the middle ear, the epitympanum or atticus, is superior to the TM. The structure of the TM's superior portion (pars flaccida, Schrapnell's membrane) is less robust than that of the main part (pars tensa). Negative pressure in the middle ear may lead to retractions and perforations of the pars flaccida.

The middle ear connects to the nasopharynx by the ET, which helps in pressurizing the middle ear and in removing middle ear secretion. The ET is shorter, softer, and has a more horizontal course in children than adults. Running medially to the ET is the internal carotid artery.

The auditory ossicles - malleus, incus, and stapes - form a chain with the malleus attaching to the TM in the umbo, while the stapes footplate is situated over the oval window. The whole chain is attached to the roof of the middle ear via ligaments connected to the malleus and incus. Blood supply to the middle ear mainly comes from branches of the internal maxillary artery. Infections may cause bone resorption of the auditory ossicles, which may cause hearing problems. The middle ear is inferiorly separated from the bulbus of the internal jugular vein by only a thin layer of bone; if this bone is resorbed, an infectious thrombus may result.

The bony labyrinth consists of the cochlea, the vestibule, and the semicircular canals (Figure 1). The membranous labyrinth, filled with endolymph, floats inside the bony labyrinth surrounded by perilymph. These structures are involved in the sense of balance and hearing. The vestibule connects to the saccus endolymphaticus situated within the dura mater. The vestibule connects to the middle ear via the oval and round windows, while the cochlea connects to the subarachnoid space via a cochlear aqueduct. The sensory organ of hearing, the organ of Corti, is situated within the cochlea. Intracranial spreading of a middle ear infection may occur through the middle cranial fossa bone at the roof of the middle ear (tegmen tympani), as well as through the saccus endolymphaticus or the cochlear aqueduct.

The facial nerve travels through the internal acoustic meatus, along with the cochlear and vestibular nerves. The facial nerve can be divided into sections: the meatal segment, the labyrinthine segment, the tympanic segment, the mastoid segment, and the extratemporal segment. The facial nerve may become infected if the bone covering it becomes dehiscent or resorbed.
Figure 1. Anatomy of the ear (images by, and modified by, Helena Schmidt; from Laulajainen-Hongisto et al. 2012, with permission of Duodecim)
The inner and middle ear structures develop before birth. The mastoid process, however, is close to nonexistent in neonates and the position of the entire temporal bone is inferolateral compared to adults. Due to the neonatal absence of the mastoid process, the facial nerve exits the stylomastoid foramen on the lateral aspect of the skull, and, thus, is prone to injury during operative treatment in young children. While the antrum is already present in infants, and connects to the upper part of the middle ear through the aditus ad antrum, mastoid pneumatization is not completed at birth. Air-filled cells, covered by mucous membrane, develop as the bony structures are pneumatized, with the degree of pneumatization being affected by middle ear ventilation, hereditary, environmental, nutritional, and infectious factors (Palva 1991, Glasscock & Shambaugh 1990, Cinamon 2009).

Figure 2. The temporal bone and its surrounding structures (by Helena Schmidt)
The brain and intracranial space in relation to the ear

The roof of the middle ear, the tegmen tympani, is situated under the brain. The middle ear and the brain are separated by mucous membrane, periosteum, bone, and the meninges. Three layers of meninges surround the brain: the dura mater, the pia mater, and the arachnoid mater. The resulting epidural, subdural, and subarachnoid spaces are seen in Figure 3.

The cerebrum is situated above the tentorium cerebelli and it can be divided into temporal, occipital, parietal, and frontal lobes. The cerebellum is located under the tentorium cerebelli. The pons and the brain stem are located anterior to the cerebellum. The brain's ventricular system comprises four interconnected ventricles: two lateral ventricles and the third and fourth ventricles. The fourth ventricle continues into the spinal cord.

The brain receives arterial blood from the internal carotid artery and the vertebral arteries. The choroid plexuses of the lateral ventricles produce cerebrospinal fluid from arterial blood; this fluid flows in the ventricular system and is gradually absorbed by the arachnoid villi of the subarachnoid space (Purves et al. 2001). Dural venous sinuses (two sigmoid sinuses on either side of the head, the transverse sinus connecting these two, and the superior sagittal sinus extending superiorly) receive this absorbed cerebrospinal fluid, as well as blood from the veins of the brain. The dural venous sinuses empty into the internal jugular veins. Additionally, venous blood from extracranial structures may pass through the skull bone via emissary veins into the dural venous sinuses.

Figure 3. The brain and meninges in relation to the mastoid air cells (image by Helena Schmidt; from Laulajainen-Hongisto et al. 2012, with permission of Duodecim)
2.3 Otitis media

**Definition, epidemiology and risk factors**

Otitis media is an inflammation of the middle ear with AOM being an acute inflammation of the middle ear. The diagnosis of AOM should be based on acute symptoms, presence of middle ear effusion (MEE), and signs of acute middle ear inflammation with a bulging of the TM (Lieberthal et al. 2013). AOM is a common infection in children; by the age of three, 83% have had at least one episode of AOM (Teele et al. 1989). On average, children experience five URTI episodes and two AOM episodes per child-year during their first three years of life (Chonmantree et al. 2008). Some children suffer from glue ear (otitis media with effusion, OME) or recurrent AOM. OME has been defined as inflammation of the middle ear with MEE, but without signs and symptoms of infection; while recurrent AOM is defined as three or more documented, separate episodes of AOM in the preceding six months, or four or more episodes in the preceding 12 months, with at least one episode within the last six months (Lieberthal et al. 2013). OME and recurrent AOM may lead to surgical interventions. A prolonged middle ear infection may lead to the development of chronic suppurative otitis media (CSOM), which is defined as purulent otorrhea persisting for more than 6 weeks in a patient with a chronic TM perforation (Gould et al. 2010). Although problems caused by AOM predominate in the pediatric population, middle ear infections also affect adults. The problems in children, however, are not the same in adults. Adults have more prolonged ear problems, CSOM, and cholesteatoma than children. CSOM and cholesteatoma have become less common over time in Finland, probably due to the more efficient treatment of AOM (Alho et al. 1997). The annual incidence of cholesteatoma in Finland was 9/100,000 in 1982-1991 (Kemppainen et al. 1999).

In Finland, 500,000 episodes of AOM occur annually (Niemelä et al. 1999). Globally, 709 million cases of AOM occur annually, 51% of these in children under the age of five (Monasta et al. 2012). Additionally, 31 million cases of CSOM occur annually, of which 23% are children under the age of five (Monasta et al. 2012). CSOM is uncommon in developed countries compared to developing ones. The prevalence and severity of both acute and chronic OM in developing countries is higher, along with deafness and severe suppurative complications (Bluestone 1998, Vergison et al. 2010, Monasta et al. 2012).

AOM reduces the quality of life for children and their parents, and recurrent AOM may even delay a child’s language development. AOM also burdens society through the cost of the medical treatment for AOM, the use of medical care facilities, as well as loss of productivity due to parental absence from work (Greenberg et al. 2003, Brouwer et al. 2005, Arguedas et al. 2010, Haapala et al. 2014).

Children are prone to develop AOM due to anatomical factors (position of ET) and their underdeveloped immune system (Bluestone 2008). Innate immunity is already functioning at birth, whereas adaptive immunity develops as pathogens are encountered (Mittal et al. 2014a).

OM is a multifactorial disease; environmental, bacteriological, host, immunological, and genetic factors affect its development (Rye et al. 2012). From twin and family studies, we know that genetic factors play a major part in susceptibility to OM with heritability being approximately 40-70% (Hafrén et al. 2012, Mittal et al. 2014a). A family history of AOM is a risk factor for
development of AOM in a child (McCormick et al. 2011). Ciliary dysfunction, cleft palate, craniofacial anomalies, and Down syndrome are additional known risk factors for AOM (Gould et al. 2010).

As with AOM, CSOM is also a multifactorial disease (Bluestone 1998, Mittal et al. 2015). Susceptibility to OM may, in adults, be affected by how well an individual’s (innate) immunity functions (Mittal et al. 2014b). Since CSOM is preceded by AOM or OME, prevention of the earlier infections can reduce the cases of CSOM (Bluestone 1998).

Children who experience their first AOM before the age of six months are more prone to additional AOM infections later in childhood (Gould et al. 2010). The amount of contacts with other children (leading to increased exposure to viruses and bacteria) is a risk factor for the development of AOM. Children with siblings and those in day-care have more AOM than others (OR=1.8 for children in day care to become otitis-prone with ≥3 episodes of AOM) (Alho et al. 1990, Uhari et al. 1996). Passive smoking and the use of a pacifier are additional risk factors for AOM (Etzel et al. 1992, Uhari et al. 1996, Warren et al. 2001). Passive smoking is also a risk factor for recurrent AOM after tympanostomy tube insertion (Hammarén-Malmi et al. 2007). The presence of these risk factors, such as passive smoking and family history of AOM, are also associated with a more severe clinical picture (McCormick et al. 2011). Breast-feeding for at least three months, on the other hand, reduces the risk of AOM (Uhari et al. 1996).

**Etiopathogenesis**

AOM often develops as a complication of viral URTI. Many viruses can cause URTI: rhino-, corona-, adeno-, entero-, and influenza viruses. The respiratory syncytial virus in particular has been associated with AOM (Heikkinen et al. 1999). Viruses alone can cause acute middle ear infection, but the interplay of viruses with bacteria is important in the development of AOM, with the resulting AOM being a combination of a viral and bacterial infection (Chonmaitree et al. 2008, Marom et al. 2012, Nokso-Koivisto et al. 2015).

Viral URTI results in inflammatory responses of the nasopharynx and ET, as well as an increased bacterial colonization of the nasopharynx. ET dysfunction leads to negative pressure in the middle ear, allowing bacteria and viruses to enter, which causes inflammatory changes in the middle ear mucosa resulting in accumulation of MEE. Additionally, the mucous membrane lining the mastoid air cells may become inflamed, swollen, and produce mucous secretion.

In some cases, a middle ear infection may continue despite antimicrobial treatment. Prolonged inflammation results in inflammatory changes in the middle ear and its surrounding structures (Palva et al. 1985). In OME, prolonged AOM leads to negative pressure in the middle ear, trapping sterile MEE (Bluestone 1998). Middle ear infections may become chronic, and result in CSOM or chronic mastoiditis. ET dysfunction and TM perforation are common mechanisms for developing CSOM. Chronic infection and ET dysfunction may result in negative pressure in the middle ear, creating conditions for the weaker part of the TM, the pars flaccida, to become retracted and perforated.
Keratinizing stratified squamous epithelium may start to grow into the middle ear through a TM perforation and accumulate in the middle ear or temporal bone, forming a cholesteatoma. Most cholesteatomas are situated in the atticus and are acquired. Only 2% are congenital and are thought to develop from epithelial rests of the middle ear. Cholesteatoma may erode bone, become infected, and cause serious complications (Juliano et al. 2013, Prasad et al. 2013). Additionally, a TM perforation may allow a bacterial infection to spread into the middle ear from the EAC or from the nasopharynx through the ET, and lead to otorrhea.

In patients with CSOM, hearing loss may result from chronic MEE, as well as from bone erosion leading to disruptions in the auditory ossicles.

**Bacteriology**

The most common bacterial pathogens of AOM in children are *Pnc* (23%-26%), *Mc* (18%-23%), and *Hi* (16%-23%) (Virolainen et al. 1994, Kilpi et al. 2001, Palmu et al. 2004), while the most common pathogens of AOM in adults are *Hi* (26%), *Pnc* (21%), and *StrA* (4%) (Celin et al. 1991, Bluestone et al. 1992) (Figure 4). The bacteriological etiology of AOM changes over time and is affected by environmental factors, vaccinations, and development of antimicrobial resistance; these changes must be monitored, especially since the introduction of PCV vaccinations (Vergison 2008, Jalava 2014).

The bacterial etiology of AOM affects its clinical picture. For example, *Pnc* causes severe symptoms with fever, earache, and clear signs of infection of the TM (Rodriguez et al. 1999, Palmu et al. 2004). It is reported to be the major pathogen present in 70% of infants with AM (Stenfeldt et al. 2014), and is a common pathogen involved in complicated AOM. There is an increasing trend of multi-drug resistant *Pnc* strains among complicated cases of AOM, which may result in an overall rise in the number of AOM complications (Antonelli et al. 1999, Zapalac et al. 2002, Mattos et al. 2014). Additionally, seasonal variation in penicillin susceptibility of *Pnc* isolates has been reported, with more nonsusceptible strains seen as the winter months progress, resulting in potential seasonal variation in the number of OM complications (Hoberman et al. 2005). In Finland, in 2014, *Pnc* resistance to penicillin was detected in the pus samples of 12% of ≥ 5-year-olds and in 9% of < 5-year-olds, whereas in 2010-2011, 20% of *Pnc* were resistant to penicillin. In 2014, *Pnc* resistance to trimethoprim-sulfonamide was 10%, whereas in 2009, up to 30% of *Pnc* were resistant to trimethoprim-sulfonamide. *Pnc* resistance to macrolides is reported to be 14-27% (Jalava 2014).

Non-encapsulated *Hi* is a major pathogen of AOM and is associated with older age, recurrent AOM, and bilateral AOM, but not with severe complications (Leibovitz et al. 2004, Segal 2005, McCormick et al. 2007, Pichichero et al. 2008, Casey et al. 2010). Due to its relatively low virulence, *Mc* is not common in complications of AOM and seldom causes AM (Leskinen & Jero 2003, Segal 2005). Some *Hi*, and almost all *Mc*, produce beta-lactamase, and thus have natural resistance to penicillin and amoxicillin. This resistance can, however, be compensated for by the
addition of a beta-lactamase-inhibitor, clavulanic acid for example (Jalava 2014). *H. influenzae* are resistant to trimethoprim-sulfonamide in 30% of cases, and almost all *H. influenzae* are intrinsically resistant to macrolides (Leibovitz et al. 2004, Jalava 2014).

*StrA* is more common in older than younger children, and has been associated with complicated infections, TM perforations, and mastoiditis (Katz et al. 2003, Segal 2005, Shulman et al. 2005).

As in other chronic infections, bacteria involved in CSOM infection may form biofilms that are resistant to treatment (Lampikoski et al. 2012). *Pseudomonas aeruginosa* (*Ps*) and *Staphylococcus aureus* (*Sa*) are common pathogens involved in CSOM, though *Proteus vulgaris*, *Klebsiella pneumoniae*, *Enterobacteriaceae*, and anaerobes are also found in this group of patients (Brook 2005, Yeo et al. 2007, Mittal et al. 2015). Especially in children with prior recurrent AOM, *Ps* may cause AM (Butbul-Aviel et al. 2003). *Fusobacterium necrophorum* is a rare pathogen of complicated AOM, that may lead to Lemierre’s syndrome with internal jugular vein thrombosis and septic emboli (Gorphe et al. 2011, Wright et al. 2015).

**Vaccinations**

Vaccinations are hoped to reduce the burden caused by AOM, especially in developing countries with less advanced health care facilities (Vergison et al. 2010). Influenza vaccinations have been shown to prevent seasonal influenza and associated AOM (Block et al. 2011, Heikkinen et al. 2013). While AOM is sometimes caused by *H. influenzae*, the *H. influenzae* type b vaccinations do not protect against it because AOM-causing strains are non-encapsulated (nontypable) (Leibovitz et al. 2004).
Pneumococcal conjugate vaccines (PCVs) reduce AOM episodes by 6% and the risk of tympanostomy tube insertion in children (between ages 2 to 5) by 34% (Eskola et al. 2001, Poehling et al. 2007, Sarasoja et al. 2013). PCVs are also effective against invasive pneumococcal disease (Whitney et al. 2003, Palmu et al. 2013). Replacement of Pnc with other pathogens or non-vaccination serotype Pnc, however, must be monitored (Hicks et al. 2007). Certain Pnc serotypes may cause severe infections due to their virulence (e.g. 19A, not included in the 7 valent PCV), and some have a tendency to develop antimicrobial resistance (e.g. 19A and 35B, which is included in the 13 valent PCV) (Hoberman et al. 2011b, Martin et al. 2014). Increased antimicrobial resistance of Pnc has been reported after onset of pneumococcal vaccinations (Farrell et al. 2007). Replacement of Pnc by these non-vaccination Pnc serotypes, may cause more acute mastoiditis (Halgrimson et al. 2013, Koutouzis et al. 2016).

A large US insurance claims database study suggests that the incidence of AM has decreased following the introduction of PCVs (Marom et al. 2014), however, several other studies found no decrease in AM incidence after PCV introduction (Roddy et al. 2007, Leibovitz 2008, Choi et al. 2011, Daniel et al. 2013, Kordeluk et al. 2015).

![Figure 5.](image)

**Figure 5.** The tympanic membranes of a healthy patient (A) and of a patient with acute otitis media (B). © David P. McCormick, M.D., UTMB, with permission.

**Diagnostics and treatment**

Patients with AOM often present with symptoms of URTI, earache, and fever. The diagnosis of AOM cannot, however, rely solely on symptoms.

In the current Finnish guideline for treatment of AOM, the diagnosis of AOM is based on acute symptoms of URTI, MEE, and impaired or absent mobility of the TM, or otorrhea (Heikkinen et al. 2010). The fact that MEE can be a sign of OME, for which no antimicrobial treatment is needed, or of AOM, is a diagnostic challenge. Pneumatic otoscopy and tympanometry are important tools for detecting MEE. A healthy TM is translucent and pearl gray in color (Figure 5A). Changes in the translucency (from translucent to semiopaque or opaque) or color (from gray to yellow, white, or red) of the TM are used to evaluate patients with AOM, however, a bulging of the TM, in particular, has been found to be an important sign of AOM (Lieberthal et al. 2013) (Figure 5B). The current clinical practice guideline from the American Academy of...
Pediatrics advises that the diagnosis of AOM should be based on acute symptoms, the presence of MEE, and signs of acute middle ear inflammation, especially with a bulging of the TM, to differentiate between MEE caused by OME and AOM (Lieberthal et al. 2013). AOM causes otorrhea in children with prior tympanostomy tubes, however, a spontaneous perforation of the TM can be a sign of severe AOM.

Since decisions regarding surgeries for AOM are based on the number of AOM episodes in individual patients, wrong diagnoses may lead to unnecessary tympanostomies and adenotomies. Repetitive antimicrobial treatments may lead to the development of resistant pathogens, and may cause adverse events (vomiting, diarrhea, rash, allergic reactions) (Venekamp et al. 2013). Antimicrobial treatment also has effects on the intestinal microbiome, which may be associated later in life with obesity (Saari et al. 2015).

Spontaneous resolution of AOM without antimicrobial treatment is common and occurs in 80% of patients within 2-3 days (Rosenfeld et al. 2003, Stevanovic et al. 2010, Venekamp et al. 2013). Antimicrobial treatment reduces the duration of MEE by two weeks and patients treated with antimicrobials also have less persistent MEE (5% vs. 24% in placebo group), and less resulting hearing impairment (Tapiainen et al. 2014). So called wait-and-see prescriptions of antimicrobials have been shown to reduce their unnecessary use (Spiro et al. 2006).

Patients with bilateral AOM are more likely to have persistent symptoms if not treated with antimicrobials, are more likely to have bacteria in the MEE, and are younger (McCormick et al. 2007). Children under the age of two benefit from antimicrobial treatment of AOM by a reduction of symptom burden, and shorter times to symptom resolution (Klein 2011, Tähtinen et al. 2011, Hoerberman et al. 2011a, Hoerberman et al. 2013). The expectant observational approach is accepted for most older children with mild disease in high-income countries (Venekamp et al. 2013).

National differences are seen in the prescription rates of antimicrobial treatment; in the Netherlands, antimicrobial treatment is given to 31% of patients with AOM, whereas in most other western countries, over 90% of patients with AOM receive antimicrobial treatment (Schilder et al. 2004). In Sweden, no increase in the incidence of AM in children has been reported following the introduction of watchful waiting as an alternative treatment for AOM (Stenfeldt et al. 2010, Groth et al. 2011). Antimicrobial treatment halves the risk of mastoiditis; the number needed to treat AOM to avoid one case of AM, however, is high (approximately 4,800) (Petersen et al. 2007, Thompson et al. 2009).

Pain medication is an important part of AOM treatment. Oral prednisolone has been shown to be modestly effective as an adjuvant treatment of AOM with tympanostomy tube otorrhea (Ruohola et al. 1999). This study alone, however, does not indicate regular use of steroids for AOM. On the other hand, steroids have been proven efficient in other otological conditions such as labyrinthitis and Bell’s palsy, and since they reduce tissue swelling, they are often used to treat complicated OM (Hartnick et al. 2001, Salinas et al. 2010).

The treatment recommendations for AOM in Finnish current care guidelines have changed over time. Much more active treatment was recommended in the 1970s than currently (Palva...
et al. 1973, Puhakka et al. 1999, Heikkinen et al. 2010). These changes have most likely affected our results, especially regarding otogenic intracranial abscesses. Currently, the following treatment of AOM is recommended: adequate treatment of pain in all patients, antimicrobial treatment (primarily with amoxicillin or penicillin) in most patients with a clear diagnosis of AOM (especially in children under the age of two, in patients with bilateral infection, and in patients with otorrhea), and the possibility of expectant observation with follow-up in 2-3 days (Heikkinen et al. 2010).

Tympanostomy tubes reduce the risk of recurrent AOM by 1.5 episodes of AOM in the 6 months following tube insertion (Gebhart 1981, McDonald et al. 2011, Kujala et al. 2012). Adenotony is beneficial in removing MEE, but has no additional value compared to tympanostomy tube placement in reducing episodes of AOM (van den Aardweg et al. 2010, Kujala et al. 2012). Tympanostomy tubes can also treat OME, having a beneficial effect on hearing for 6 months in children with prolonged OME (>12 weeks) and hearing loss (Browning et al. 2010). It is important to note, however, that tympanostomy tubes may lead to TM perforations, occurring more often with longterm (several years) than short term (8-14 months) tympanostomy tubes (17% vs. 2%, respectively) (Kay et al. 2001). TM perforations may lead to the need for further surgical treatment. According to a recent Danish study, prolonged OM treated with tympanostomy tubes was associated with a higher risk for operatively-treated cholesteatoma (0.17%) than was the risk of completely healthy children (0.01%)(Djurhuus et al. 2015). At the population level, however, the risk of cholesteatoma was lower in the children who had been treated with tympanostomy tubes; each year prior to the first tympanostomy tube insertion increased the risk of cholesteatoma by 54% (Djurhuus et al. 2015).

The treatment of CSOM consists mainly of aural toilet and topical antimicrobial treatment. If these do not result in the resolution of infection, oral or parenteral antimicrobial treatment may be needed. Reconstruction of a perforated TM may be attempted after the acute infection has been treated. In uncomplicated CSOM, mastoidectomy has not been proven more effective than conservative treatment, however, in cholesteatomatous CSOM, surgery is indicated (Mittal et al. 2015).

2.4 Complications of otitis media

The rate of suppurative complications of AOM and OME has been reported to be 0.12-0.24% (Rosenfeld et al. 2003). Complications of OM may develop following an untreated or incompletely treated infection, following infection caused by resistant bacteria, or for unknown reasons. Congenital malformations, and anatomical or immunological conditions may predispose a patient to complications. The thinner bony structures of children may more easily be resorbed by infection (Stenfeldt et al. 2014). Although complications of AOM may develop despite adequate antimicrobial treatment, most patients with AOM have a very good prognosis. The common use of antimicrobial treatment has changed the clinical picture of AOM complications and may mask symptoms and lead to a prolonged, milder form of disease (latent mastoiditis) (Faye-Lund 1989). Thorough examination with bacteriological cultures should be performed, especially if a patient with AOM does not recover and has high fever, severe general symptoms of infection,
secretion from the infected ear, retroauricular signs of infection, hearing problems, dizziness, or neurological symptoms.

OM causes a severe burden in developing countries. According to the WHO, 51,000 deaths occur annually in children under the age of five due to intracranial complications of AOM (Berman 1995). CSOM has been reported as a major cause of hearing impairment in developing countries (Berman 1995). Vaccinations and better treatment of infections are hoped to change this situation.

CSOM with cholesteatoma has been associated with intracranial complications (Osma et al. 2000, Juliano et al. 2013, Prasad et al. 2013). These complications are caused by the chronic infection spreading through bone resorbed by cholesteatoma. In a previous Finnish study, however, more complications were found in adult patients with acute, rather than chronic, OM (Leskinen & Jero 2005).

The complications of OM can be divided into intratemporal and extratemporal (extra- or intracranial) complications.

Intratemporal complications

Intratemporal complications of OM, in order of their prevalence, are: mastoiditis, facial nerve paresis, petrositis, and labyrinthitis (Bluestone 2000, Kitsko et al. 2007). Morbidity rates for the intratemporal complications of OM are reported between 0.4% and 10%, with mortality being extremely rare (Osma et al. 2000, Groth et al. 2012).

Mastoiditis

Mastoiditis develops when a middle ear infection spreads through the aditus to mastoid antrum into the mastoid air cells causing mucosal swelling, local acidosis, ischemia, and resorption of bone. Destruction of the bony mastoid septa occurs in coalescent mastoiditis. Coalescent mastoiditis can have an acute, aggressive course of disease, or a prolonged, silent course of disease known as latent mastoiditis (LM) (Vasquez et al. 2003, Juliano et al. 2013). LM may be difficult to diagnose because the TM and middle ear may appear healthy due to a blocked aditus to mastoid antrum, behind which the mastoid infection continues. The presence of MEE with a simultaneous increase in attenuation of the mastoid cells upon CT, along with signs of mastoiditis, is called incipient mastoiditis (Vasquez et al. 2003). Acute middle ear infections, as well as sub-acute or chronic inflammation, may cause acute mastoid infections. CSOM with cholesteatoma is a common etiology for intratemporal complications (Palva & Pulkkinen 1959, Stahelin-Massik et al. 2008, Maranhao et al. 2014).

Because the diagnosis of mastoiditis is clinical, uniform and accurate diagnostic criteria are essential; the most commonly used diagnostic criteria are: postauricular swelling, erythema, tenderness, protrusion of the pinna, and a recent episode of (sub)acute OM (van den Aardweg et al. 2008, Stalfors et al. 2013). High fever, and a high leukocyte count (WBC) and C-reactive protein (CRP) levels may be signs of complicated AM and warrant close follow-up (Bilavsky et al. 2009). Because the bacterial etiology of AM is more complicated than that of AOM, bacterial cultures of the MEE must always be taken (Luntz et al. 2001, Benito et al. 2007).
Debate regarding the necessity of imaging in AM exists; currently imaging is used in cases with suspected complications, in unclear cases, or in cases that do not respond to conservative treatment (Psarrommatis et al. 2012a, Marom et al. 2016). Because it is not always possible to clinically rule out intracranial complications, some authors suggest CT imaging of all children with AM (Luntz et al. 2012). CT has traditionally been the initial imaging technique for AM; good visibility of the mastoid’s bony structures is achieved and intravenous contrast medium is used for the better evaluation of soft tissues (Saat et al. 2015a) (Figure 6). The overall use of MRI in clinical practice is rising, it is promising in otological conditions. MRI is good at differentiating soft tissues, and at detecting possible intracranial complications (Saat et al. 2015a).

In patients with AM, MRI is suggested when intracranial complications are suspected (Dobben et al. 2000, Vasquez et al. 2003, Minks et al. 2013). Incidental mastoid findings in MRIs of healthy individuals are possible, and AOM patients (with no mastoid infection) can have intramastoid fluid accumulation (Blomgren et al. 2003, Polat et al. 2011, Juliano et al. 2013). It is, however, possible to distinguish between true mastoid infection and incidental MRI findings (Saat et al. 2015b).

**Figure 6.** Left: A child with acute mastoiditis of the left side, protrusion of the pinna, retroauricular swelling, and redness. Right: CT image, in which a subperiosteal abscess is seen (red arrow) (From Laulajainen-Hongisto et al. 2012, with permission of Duodecim)

Mastoidectomy used to be a common treatment for mastoiditis but, currently, more conservative treatment is preferrable (Palva et al. 1959, Chesney et al. 2014). Antimicrobial treatment is often combined with myringotomy or tympanostomy tube insertion, though, in some institutions, retroauricular puncture may be attempted in patients with a subperiosteal abscess (Luntz et al. 2001, Bakhos et al. 2011, Psarrommatis et al. 2012a, Psarrommatis et al. 2012b). Mastoidectomy, as the most reliable and efficient procedure, is suggested in patients who do not respond to more conservative treatment, or those who have intracranial complications (Quesnel et al. 2010, Psarrommatis et al. 2012a, Psarrommatis et al. 2012b) (Figure 7).

In our institution, patients with AM are treated with tympanostomy tube insertion and antimicrobial treatment consisting of either intravenous cefuroxime or penicillin (penicillin in infections caused by StrA), or of other antibiotics according to the results of bacteriological cultures. Additionally topical ear drops (usually ciprofloxacin-hydrocortisone) are given, and steroids are used to reduce inflammation and tissue swelling. Imaging is performed only in cases with suspected complications, or those resistant to treatment in which case, mastoidectomy is also considered (Kajosaari et al. 2014).
Facial nerve paresis

Complicated OM can result in facial nerve paresis, which is usually reversible (Kvestad et al. 2002). Its incidence is currently much lower (0.005%) than in the preantibiotic era (0.5%) (Ellefsen et al. 1996). The tympanic segment of the facial nerve is most commonly affected, especially in patients with dehiscence of the bone covering the facial nerve. Paracentesis or tympanostomy tube insertion should be performed, and bacterial cultures of the MEE should be taken, in patients with facial nerve paresis occurring as a complication of OM (Redaelli de Zinis et al. 2003, Kitsko et al. 2007). Most patients can be treated with parenteral antibiotics (which cover Hi, Streptococci, and Staphylococci). Mastoidectomy, with or without decompression of the facial nerve, may be considered in complicated cases, or in cases not responding to other treatment.

Petrositis

If infection spreads to the apex of the petrous part of the temporal bone (Figure 1) then meningeal inflammation is often present, and due to their close proximity, cranial nerves V (trigeminal nerve) and VI (abducens nerve) may be affected (Juliano et al. 2013). In Gradenigo's syndrome petrous apicitis is accompanied by orbital pain (trigeminal nerve), diplopia (abducens nerve), and otorrhea (Heshin-Bekenstein et al. 2014). Treatment consists of antimicrobials, tympanostomy tube insertion, and surgical treatment.

Labyrinthitis

In labyrinthitis, the inner ear is inflamed due to bacterial infections (suppurative), viral infections, or autoimmune inflammation (serous). Suppurative labyrinthitis may result in permanent hearing loss or vertigo. The infection usually spreads to the labyrinth through an intact round window, or less commonly through the oval window, a congenital perilymphatic fistula, or acquired bone defects. Labyrinthitis may also follow meningitis, in which case infection spreads from the subarachnoid space (Kitsko et al. 2007).
Patients with labyrinthitis suffer from vertigo, nystagmus, and hearing loss. Diagnosis is based on clinical and audiometric findings, though imaging is also useful. MRI is more effective than CT in detecting signs of labyrinthine inflammation (Kitsko et al. 2007, Juliano et al. 2013).

In patients with labyrinthitis, paracentesis should be performed, tympanostomy tube should be placed, and microbiological samples should be taken. Treatment consists of antimicrobials (those covering the most common pathogens of AOM: Pnc, Hi, and Mc), topical ear drops, and steroids; mastoidectomy may be considered in complicated cases or those unresponsive to other treatment (Kitsko et al. 2007).

Labyrinthitis has three stages: acute, fibrous, and ossification (Juliano et al. 2013). The inflammation can result in pathologic ossification of the labyrinth, which may be especially severe after meningitis, and may complicate eventual later insertion of a cochlear implant (Kitsko et al. 2007, Juliano et al. 2013). Steroids are used to prevent ossification in patients with labyrinthitis (Hartnick et al. 2001).

**Extratemporal complications**

Extratemporal complications due to OM can be subdivided into intracranial and extracranial categories.

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**Figure 8.** Extratemporal complications of otitis media. (image by Helena Schmidt, from Laulajainen-Hongisto et al. 2012, with permission of Duodecim)
Extracranial complications

Subperiosteal abscess
In AM, bone destruction may extend to the outer bone cortex through which infection may spread and result in a subperiosteal abscess (Figure 6, Figure 8). If a middle ear infection spreads temporally, it may form a subperiosteal temporal abscess (Luc’s abscess), which does not always involve the mastoid (Weiss et al. 2010, Scrafton et al. 2014).

Bezold’s abscess
If a bone defect exists in the mastoid tip, mastoid infection can spread to the soft tissues of the neck and form an abscess (Betzold’s abscess, Figure 8) (Jose et al. 2003, Vasquez et al. 2003).

Intracranial complications
Intracranial complications of OM are possible due to the close proximity of the brain to the ear. Infection can spread to the intracranial space by direct spreading of infection, bone erosion, retrograde thrombophlebitis, or hematogenous spreading. CSOM with cholesteatoma has been associated with intracranial complications of OM (Penido et al. 2005, Szyfter et al. 2012, Sun et al. 2014). The pathogen that causes the initial, underlying infection would also be the one involved in any resulting intracranial complication. Children with AM caused by anaerobic bacteria may have a higher risk of developing intracranial complications (Zevallos et al. 2009).

Intracranial complications of OM are, however, rare. They include, in order of prevalence: meningitis, dural venous sinus thrombosis, epidural abscess, subdural empyema, and IA (Bluestone 2000). Carotid artery involvement is extremely rare (Vasquez et al. 2003).

The prognosis of patients with intracranial complications of OM, including IAs, has improved over time. However, mortality rates ranging from 9-31% have been reported (Osma et al. 2000, Sennaroglu et al. 2000, Penido et al. 2005, Dubey et al. 2010, Szyfter et al. 2012).

Meningitis
Meningitis is a common intracranial complication of OM. The annual incidence of otogenic meningitis in adults in the United Kingdom is 0.42/100,000, with most cases being due to CSOM (Ibrahim et al. 2010). Meningitis can lead to deafness, even when not caused by OM; thus, early diagnosis is essential (Barry et al. 1999). If an otogenic infection is suspected in a patient with meningitis, myringotomy with bacterial cultures of the MEE should be performed. CT imaging of the ear should be performed if a suspicion of predisposing defects exists, in these cases mastoidectomy should also be considered. Antimicrobial treatment is the first-line treatment for all meningitis patients. Surgery of the ear should only be performed in patients who do not respond to antimicrobial treatment within 48 hours (Slovic et al. 2007).

Intracranial abscesses
Intracranial abscesses (brain abscesses, subdural abscesses, and epidural abscesses) are rare, with an annual incidence of 0.4-0.9/100,000 (Brouwer et al. 2014b). IAs may cause life threatening sequelae, fortunately, however, the prognosis of IA patients has improved over time; case fatality rates have decreased from 40% to 10%, and the rate of patients with full recovery has increased.
from 30% to 70% between the 1970s and 2010s (Brouwer et al. 2014a). Predisposing factors can be identified in most patients: immunosuppressive conditions, acquired or congenital disruptions of anatomical borders of the surrounding structures, or a systemic source of infection (Brouwer et al. 2014b). Although IAs are a rare complication of OM, and have become less common with time, Brouwer et al. found in their recent meta-analysis that 32% of IAs were otogenic (Tarkkanen & Kohonen 1970, Brouwer et al. 2014a). Otogenic IAs (oIA) usually develop as a complication of (prolonged, chronic) middle ear infection via contiguous spreading (Figure 8). The lifetime expectancy of a 30 year-old patient with CSOM developing an oIA is 1/200 (Nunez et al. 1990). The bacteriological etiology of all IAs is affected by their underlying cause; the most common pathogens of oIAs belong to *Streptococcus* spp, *Bacteroides* spp, *Prevotella* spp, and *Enterobacteriaceae* (Brouwer et al. 2014b).

The most common symptom caused by IAs is headache; fever and an altered level of consciousness are often absent, and though eventual other neurological signs become more common as the abscess grows (Brouwer et al. 2014a; Brouwer et al. 2014b). The diagnosis is not always easy to make since the differential diagnosis of IAs include many neurological and infectious conditions (Brouwer et al. 2014b). Prompt treatment is necessary to ensure a better prognosis (Xiao et al. 2005, Dubey et al. 2010). Otogenic IAs should be suspected in patients with prolonged ear infection, headache, and neurological symptoms (Lildal et al. 2014).

CT imaging has resulted in improved diagnostics and has decreased the mortality of IA patients (Mathisen et al. 1997, Ratnaike et al. 2011, Brouwer et al. 2014b). Since the clinical diagnosis of oIAs is difficult, neuroimaging is important, preferably with MRI (Lildal et al. 2014), and imaging of the ear should also be performed. MRI is excellent in differentiating between soft tissues and is a valuable tool in differential diagnostics (Doebben et al. 2000, Lai et al. 2002, Prashanth et al. 2011) (Figure 9).

Antimicrobial treatment should be started as early as possible, usually after the IA puncture (Brouwer et al. 2014b). The initial choice of antimicrobials should be based on the most likely pathogen, often based on the predisposing condition, and should later be modified according to the results of bacterial cultures (Hafidh et al. 2006, Brouwer et al. 2014b). Recommended, initial broad-spectrum antimicrobials are cefotaxime or ceftriaxone with metronidazole; alternatively, meropenem with vancomycin, if *Sa* is suspected (Brouwer et al. 2014b).

Glucocorticoids may also be needed to reduce cerebral edema (Brouwer et al. 2014b). In selected, mild IA cases (also oIAs), only antimicrobial treatment may be attempted (Isaacson et al. 2010).

Neurosurgical treatment is needed to obtain bacteriological cultures, and to reduce the size of the abscess; these can be achieved by puncture, but in some cases extirpation may be needed (Brouwer et al. 2014b). The underlying cause of the infection must also be treated (Osborn et al. 2011). The timing of the operations due to oIAs varies and depends on the clinical condition of the patient (Seven et al. 2005, Wanna et al. 2010). Many authors report treating the ear and IA simultaneously (Kurien et al. 1998, Sennaroglu et al. 2000, Hafidh et al. 2006, Syal et al. 2006, Morwani et al. 2009), with some suggesting treatment of the ear within the first 24 hours (Kuczkowski et al. 2006). In our institution, the IA is usually treated first, followed by treatment of the infected ear once the patient is stabilized.
Brain abscess
Brain abscesses are intracranial abscesses located within the brain tissue. Otogenic IAs are typically located in the temporal lobe, or are cerebellar (Couloigner et al. 1998).

Epidural abscess
Epidural abscess formation usually follows bone destruction associated with coalescent mastoiditis. These abscesses are situated in the epidural space, and patients may be silent of symptoms for them (Vasquez et al. 2003).

Subdural abscess
Subdural abscesses are located in the restricted subdural space. Patients with subdural empyema often have severe symptoms (Vasquez et al. 2003).

Sinus thrombosis
Dural venous sinus thrombosis usually results from an extradural abscess, but may also develop following an epidural abscess, or via osteothrombophlebitis. Infection spreads to the sigmoid sinuses or the transverse sinus, where an infectious thrombus may develop (Vasquez et al. 2003, Stam 2005, Ropposch et al. 2011) (Figure 8). The infected thrombus may continue into the jugular vein, to other dural sinuses, or to the subcutaneous tissue via emissary veins. Patients may have no symptoms, only mild symptoms, or severe infection with neurological symptoms (Stam et al. 2005). CT or MRI are used in the diagnostics of this complication (Vasquez et al. 2003, Stam 2005, Sharma et al. 2015). In otogenic sinus thrombosis, the underlying ear infection should be examined and treated. Treatment of the sinus thrombosis itself, however, remains controversial; ligation of the internal jugular vein and anticoagulants have been used.

Otitic hydrocephalus
If the contralateral sigmoid sinus is hypoplastic in a patient with otogenic sinus thrombosis, absorption of the cerebrospinal fluid may become disturbed resulting in increased intracranial pressure and otitic hydrocephalus. The pathogenesis of otitic hydrocephalus is, however, not completely understood. Symptoms include headache, drowsiness, nausea, blurred vision, diplopia and photophobia; in patients with such symptoms, imaging with MRI should be performed. Both the underlying ear infection and the elevated intracranial pressure must be treated (with steroids, hyperosmolar dehydrating agents, and/or neurosurgery) (Stam 2005, Sadoghi et al. 2007).
3 AIMS OF THE STUDY

The aim of this study was to evaluate the complications resulting from otitis media at our institution.

The specific study aims were:

1. To evaluate the clinical picture of acute mastoiditis caused by different pathogens in children.
2. To study differences in the etiology and clinical picture between acute mastoiditis and hospitalized acute otitis media in children.
3. To study the predisposing factors for the development of otogenic intracranial abscesses.
4. To analyze clinical characteristics of adults hospitalized due to acute otitis media or acute mastoid infections.
4  PATIENTS AND METHODS

4.1  Diagnostic and inclusion criteria

*Acute otitis media (AOM)*

Acute fever (≤14 days), earache, or respiratory symptoms. MEE, bulging, redness, or abnormal mobility of the TM upon otomicroscopy. Recent onset of otorrhea not due to otitis externa.

*Acute mastoiditis (AM)*

Diagnosis of AOM, and at least two of the following symptoms: protrusion of the pinna; retroauricular redness, swelling, pain, or fluctuation; and/or abscess in the EAC; and/or purulent secretions or acute infection in the mastoid process upon mastoidectomy.

*Latent mastoiditis (LM)*

Symptoms of acute mastoid infection in adult patients (≥17 years old) who did not fulfil all the study criteria for AM, or who had a prolonged (> 14 days) duration of symptoms.

*Acute mastoiditis of a chronic ear (AMc)*

Adult patients (≥17 years old) with a history of CSOM in the ear with AM.

*Intracranial abscesses*

The diagnosis was based on clinical findings, laboratory test results, microbiological cultures and imaging studies, intra-operative findings, or findings upon a post-mortem autopsy.

4.2  Patients

Patient data for studies I, II and IV originated in a retrospective search of the hospital's electronic database for data of all patients hospitalized at the Helsinki University Hospital, Department of Otorhinolaryngology between 2003 and 2012. The patients with AOM were hospitalized due to complications, severe symptoms not responding to antimicrobial treatment, or difficulties in outpatient treatment.

Patient data for study III originated in a retrospective search for all patients treated at the Helsinki University Hospital, Department of Neurosurgery due to IA between 1970 and 2012 (Table 1).

*Table 1. Patients included in studies composing this dissertation*

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Age, range (years)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>AM</td>
<td>0-16</td>
<td>56</td>
</tr>
<tr>
<td>II</td>
<td>AOM</td>
<td>0-16</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>IA</td>
<td>0-83</td>
<td>166</td>
</tr>
<tr>
<td>IV</td>
<td>AOM, AM, LM, or AMc</td>
<td>17-91</td>
<td>160</td>
</tr>
</tbody>
</table>
All diagnoses were re-evaluated by the study group according to the diagnostic and inclusion criteria. For studies I and II, only one diagnosis was analyzed per patient; if the patient had both AOM and AM (bilateral infection), they were analyzed as AM. For studies I and II, recurrence after three months was considered a new infection. For study III, all immediate postoperative infection cases were excluded, while favorable recovery was defined as recovery from this infection without severe neurological deficits or health problems and the ability to return to independent life. For study IV, only the first infection of each patient, and only one diagnosis per patient, was analyzed. If a patient (in study IV) had a bilateral infection with both AOM and mastoiditis (AM, LM, or AMc), they were classified as mastoiditis.

The patients were classified as children if they were under the age of 17. For studies I and II, children under the age of two were classified as younger children and those older than two as older children.

The mean age of the patients with IA was 42; 71% were male and 85% were adults. Of the 25 children with IAs, 60% were male (mean age of eight). The mean age of the patients with oIAs was 44; 89% were male and two were children. The mean age of the adults hospitalized for AOM, AM, LM, or AMc was 47 and 42% were male. The mean age of the children hospitalized for AOM was 6 and 45% were male. The mean age of the children hospitalized for AM was 5 and 52% were male.

4.3 Methods

**Children hospitalized due to AM (I) and AOM (II)**

The medical records of all 56 AM and 44 AOM children were retrospectively evaluated. The data analysis included age, gender, medical history, symptoms and signs of infection, pre- and in-hospital medication, surgical treatment, outcome, and results of laboratory tests, bacteriological cultures, and radiological examinations. The samples for bacteriological cultures were taken from MEE through a tympanostomy tube, aspirated from the middle ear through a paracentesis, or taken intraoperatively from the mastoid cavity. The samples were analyzed at the Helsinki University Hospital’s laboratory of microbiology. The data from study I was compared to that of study II.

**Intracranial abscesses (III)**

The study material consists of 166 patients. Patient data was analyzed according to age, demographics, medical history, predisposing condition, symptoms, abscess location, treatment, outcome, and results of bacteriological cultures, laboratory tests and radiological examinations. The bacteriological samples were taken intraoperatively (via puncture or during craniotomy) from the abscess cavity, and were analyzed at the Helsinki University Hospital’s laboratory of microbiology.

**Adults hospitalized due to AOM, AM, LM, or AMc (IV)**

The study material consists of 160 patients. The data analysis included age, gender, medical history, symptoms and signs of infection, pre- and in-hospital medication, surgical treatment,
outcome, and results of laboratory tests, bacteriological cultures, and radiological examinations. Samples for bacteriological cultures were taken from MEE through a tympanostomy tube, aspirated from the middle ear through a paracentesis, or taken intraoperatively from the mastoid cavity. The samples were analyzed at the Helsinki University Hospital’s laboratory of microbiology.

4.4 Statistics

IBM SPSS statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA) was used for studies I-III and IBM SPSS statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA. Released 2013) for study IV.

Fisher’s exact tests and Chi-square tests, as appropriate, were used to determine the significance between categorical variables. The Mann-Whitney U test was used to analyze the equality of medians between continuous variables. A two-sided p-value of below 0.05 was considered statistically significant.

4.5 Ethical considerations

The studies were approved by the Research Ethics Committee of Helsinki University Hospital.
5 RESULTS

Children hospitalized due to AM (I)

The annual incidence of AM in children was 1.88/100,000. The children’s clinical characteristics, symptoms, findings, complications, surgeries, and outcomes are presented in Table 2. The most common symptoms were otalgia, mastoid tenderness, retroauricular redness, and fever.

Antimicrobial treatment had been prescribed prior to hospital admission in 70% of patients (typically amoxicillin, amoxicillin-clavulanate, and cephalosporines), 55% had been diagnosed with a previous AOM.

The bacterial findings are presented in Figure 10. The bacterial cultures were negative in 29% of cases. Of all Pnc (n=21) samples, 48% (n=10) showed reduced susceptibility to common antimicrobials (Table 3); these were clearly overrepresented, relative to the background population (19%, p<0.001). The children with Pnc had less otorrhea (5, 24% vs 19, 54% in others, p=0.03) and more protrusion of the pinna (18, 86% vs 19, 34% in others, p=0.02) than others. The children with StrA had less otalgia than others (3, 50% vs 46, 82%, p=0.004). The children with Ps often had prior tympanostomy tubes (83%). Children with Ps had the lowest CRP values (21) and while retroauricular swelling was not as common in them as others (1, 17% vs. 30, 54%, p=0.04) they all had otorrhea (6, 100% vs. 24, 43% in all, p=0.003). The patients with negative bacterial cultures had less otorrhea (3, 19% vs 21, 38%, p=0.02) and protrusion of the pinna (7, 44% vs 30, 54%, p=0.03), but more dizziness (3, 19% vs 1, 2%, p=0.03) than others.

All patients received intravenous antimicrobial treatment; the most common being cefuroxime (91%), ceftriaxone (16%), and metronidazole combined with another antimicrobe (14%). Steroids were administered to 73%, and topical ear drops to 95%. Oral antimicrobial treatment was continued after hospital discharge in 98%; most commonly cefalosporins (49%) or amoxicillin-clavulanate (33%).

Mastoidectomy was performed on 34% of patients. The children who had been treated with azithromycin prior to hospitalization were more likely to undergo mastoidectomy than others (4, 80% vs 11, 28%, p=0.02). Mastoidectomy also tended to be more common in children with resistant Pnc (6, 60% vs 13, 23%, not significant). No differences emerged in patient outcomes regarding type of pathogen or mastoidectomy status.
### Results

Table 2. Clinical findings, symptoms, surgeries, and outcome of children hospitalized due to AOM or AM.

<table>
<thead>
<tr>
<th></th>
<th>AM (n=56)</th>
<th>AOM (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>27 (48%)</td>
<td>24 (55%)</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>5.0</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 2</td>
<td>15 (27%)</td>
<td>14 (32%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Median CRP (mg/l)</td>
<td>66</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Bilateral infection</td>
<td>9 (16%)</td>
<td>17 (39%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Otalgia</td>
<td>49 (88%)</td>
<td>38 (86%)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>40 (71%)</td>
<td>29 (66%)</td>
<td></td>
</tr>
<tr>
<td>Otorrhea</td>
<td>24 (34%)</td>
<td>22 (50%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (7%)</td>
<td>11 (25%)</td>
<td>0.022</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (7%)</td>
<td>5 (11%)</td>
<td></td>
</tr>
<tr>
<td>Head ache</td>
<td>5 (9%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Hearing problem</td>
<td>5 (9%)</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>Facial paresis</td>
<td>3 (5%)</td>
<td>12 (27%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Retroauricular redness</td>
<td>44 (79%)</td>
<td>10 (23%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retroauricular pain</td>
<td>45 (80%)</td>
<td>7 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retroauricular swelling</td>
<td>31 (55%)</td>
<td>6 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retroauricular fluctuation</td>
<td>10 (18%)</td>
<td>0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Protrusion of the pinna</td>
<td>37 (66%)</td>
<td>3 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subperiosteal abscess</td>
<td>10 (18%)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (2%)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Gradenigo’s syndrome</td>
<td>2 (4%)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Sinus thrombosis</td>
<td>4 (7%)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Imaging performed</td>
<td>28 (50%)</td>
<td>5 (11%)</td>
<td></td>
</tr>
<tr>
<td>Tympanostomy performed</td>
<td>47 (84%)</td>
<td>26 (59%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paracentesis performed</td>
<td>13 (23%)</td>
<td>10 (23%)</td>
<td></td>
</tr>
<tr>
<td>Mastoidectomy</td>
<td>34%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Median hospitalization, days</td>
<td>4.0</td>
<td>3.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Residual TM perforation</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Residual hearing problem</td>
<td>3 (5%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Re-operation performed</td>
<td>7 (13%)</td>
<td>8 (18%)</td>
<td></td>
</tr>
</tbody>
</table>
**Results**

Figure 10. Pathogens of all children with acute mastoiditis (AM) (n=56) and pathogens of younger children (age < 2) with AM (n=15)

Table 3. Resistant S. pneumoniae cases (n=10) in children with acute mastoiditis.
*(MIC = minimal inhibitory concentration, S=susceptible, I=intermediate, R=resistant)*

<table>
<thead>
<tr>
<th>Received antimicrobial treatment</th>
<th>Penicillin (MIC mg/l)</th>
<th>1st and 2nd generation cephalosporin</th>
<th>3rd generation cephalosporin</th>
<th>Sulfamethoxazole-prim</th>
<th>Macrolide</th>
<th>Clindamycin</th>
<th>Mastoidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>I (0.75)</td>
<td>R</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>I (1)</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>I (0.094)</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>I (0.125)</td>
<td>Missing</td>
<td>Missing</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>R (2)</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>R (4)</td>
<td>R</td>
<td>I</td>
<td>R</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>R (4)</td>
<td>R</td>
<td>I</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>I (0.125)</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>9</td>
<td>Yes</td>
<td>I (0.094)</td>
<td>Missing</td>
<td>Missing</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>I (0.75)</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**Children hospitalized due to AOM (II)**

The annual number of children hospitalized due to AOM was 1-9 (over the study’s 10 year period: 12 cases in spring, 7 in summer, 17 in autumn, and 8 in winter). Patient clinical characteristics, symptoms, findings, complications, procedures, and outcomes are presented in Table 2. The most common symptoms were otalgia, fever, and otorrhea.

Antimicrobial treatment had been prescribed to 57% (n=25) prior to hospital admission (typically amoxicillin, penicillin, or cephalosporines).
The bacterial findings are presented in Figure 11. Samples for bacteriological culture were taken from 38 children (86%). Mixed flora was found in the cultures of five children (11%). The cultures were negative in 11 children (25%), typically those who had received antibiotics prior to hospitalization (38% vs 6% in those who had not received antibiotics, p=0.016). Antimicrobial resistance was only seen in one of the Pnc cases (13%) (penicillin MIC (minimal inhibitory concentration) 0.19 mg/l, all were susceptible to cefalosporins). Otorrhea via prior tympanostomy tubes was more common in the children with Ps than others (71% vs 5%, p=0.000). Otorrhea occurred in all children with StrA, which was much more than in children with other pathogens (p=0.021).

All patients received antimicrobial treatment, typically intravenously (75%), with cefuroxime (57%) and ceftriaxone (18%) being most common. Steroids were administered to 55% and topical ear drops to 86%. Per oral antimicrobial treatment was continued after hospital discharge in 95%; amoxicillin-clavulanate (33%), amoxicillin (26%) and cefalosporins (24%) were most common.

![Pie charts showing bacterial findings](image)

**Figure 11.** Pathogens of all children hospitalized due to acute otitis media (AOM) (n=44) and pathogens of younger children (age < 2) hospitalized due to AOM (n=14). Note: Hi was not found in any sample.

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**Comparison of children hospitalized due to AM and AOM (I,II)**

The annual number of hospitalized AOM and AM patients are shown in Figure 12. Prior health problems (such as asthma, diabetes, developmental disorders, ear problems) were more common in children with AOM than AM (48% vs 27%, p=0.037).

Retroauricular symptoms were more common in children with AM than AOM (Table 2), and these signs of infection were rare in patients with facial nerve paresis compared to those without it: retroauricular swelling (0% vs 44%, p=0.001), retroauricular redness (0% vs 64%, p=0.000),
retroauricular pain (7% vs 60%, p=0.0001), and protrusion of the pinna (0% vs 47%, p=0.000).

All children with facial nerve paresis were treated with tympanostomies, while only 68% of those without paresis had the surgery (p=0.009).

*Pnc* was more common in children with AM than AOM (38% vs 18%, p=0.046), especially the resistant strains (48% vs 13% of all Pnc, p=0.021). Younger children were more likely than older children to have infections due to *Pnc* (59% vs 17%, p=0.000) and its resistant strains (24% vs 6%, p=0.013). No significant differences were found in the prevalence of *Ps* or *StrA* between children with AM and AOM. The younger children, however, did not have *Ps* (compared to 18% in the older children, p=0.018) or *StrA* (compared to 17% in the older children, p=0.017). *Sa* was less common in children with AM than AOM (2% vs 14%, p=0.042).

![Figure 12](image_url)

**Figure 12.** Annual number of children hospitalized for acute otitis media (AOM), or acute mastoiditis (AM).


**Results**

**Intracranial abscesses (III)**

The total number of IAs was 166, with a mean annual number of four cases (range 1-8) (Figure 13). The annual incidence of IAs was 0.33/100,000 (2000-2012), and the proportion of children decreased with time (24% in 1970-1989 vs 8% in 1990-2012, p=0.004). The etiology in 18 (11%) patients was otological (Table 4); these oIA cases were most common in 1970-1979 (10 cases, 25%) and their incidence decreased over time (2000-2012: 3 otogenic cases, 5%) (Figure 13). The annual incidence of oIAs (2000-2012) was 0.017/100,000. Over time, cardiac anomalies among IA cases became less common (15, 20% in 1970-1989 vs. 6, 7% in 1990-2012, p=0.001), whereas odontogenic infections became more common.

The median symptom duration of IA patients prior to hospitalization was 10.0 days (0-90 days), though it was shorter in patients with odontogenic infection (4.5 days, p<0.001). Prior to hospitalization, 19% of all IA patients had received antimicrobial treatment; often these were patients with ENT infections (49% vs 3% of all other patients, p<0.001). The most common presenting symptoms were headache (48%), fever (28%), and some focal neurological symptom (21%).

Nearly all IA patients (99%) underwent some imaging, with a singular abscess being found in most cases (87%). Multiple abscesses were more common in children than adults (28% vs 11%, p=0.048). Patients with ENT infections had more temporal abscesses than others (43% vs 12%, p<0.001). Patients with sinusitis had more extra-axial abscesses (i.e. empyemas) than others (40% vs 3%, p<0.001). Temporal abscesses were more common in patients with oIAs than in those with other etiologies (78% vs 12%, p<0.001).

Pathogen results from bacteriological culture are shown in Table 5. *Fusobacteria* were more common in patients with odontogenic infection than others (9, 38% vs 14, 10%, p=0.001). Gram-negative enteric bacteria were more common in patients with oIA than others (4, 22% vs 4, 3%, p=0.005).

Antimicrobial treatment was common during hospitalization (96%); the most common (2000-2012) being: cephalosporins (95%), nitroimidazoles (72%), meropenem (31%), and vancomycin (28%). Preoperative corticosteroids were administered to 74%. Nearly all IAs were treated with surgery (99%).

A favorable recovery was seen in 66%, with 19% being able to return to their prior occupation (12 % in 1970-1989 and 24% in 1990-2012). Those that could return to their prior occupation were typically patients that had no predisposing conditions for their IA (52% vs 28% of others, p=0.018) and were younger (mean age 29 vs. mean age 45).

Twelve patients (11 adults and one child) died due to the IA. Death due to abscess became less common over time (12% in 1970-1989 vs 3% in 1990-2012, p=0.037).
Figure 13. The annual number of otogenic intracranial abscesses (oIA) and of intracranial abscesses of other etiologies (other IA).

Table 4. Intracranial abscesses with ENT or dental predisposing conditions. (* p<0.01)

<table>
<thead>
<tr>
<th></th>
<th>All (166)</th>
<th>Adults (141)</th>
<th>Children (25)</th>
<th>1970-1989 (74)</th>
<th>1990-2012 (92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT infection</td>
<td>37 (22%)</td>
<td>27 (19%)</td>
<td>10 (40%)</td>
<td>21 (28%)</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>Otitis</td>
<td>18 (11%)</td>
<td>16 (11%)</td>
<td>2 (8%)</td>
<td>10 (14%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>15 (9%)</td>
<td>8 (6%)</td>
<td>7 (28%)*</td>
<td>8 (11%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Dental infection</td>
<td>24 (15%)</td>
<td>23 (16%)</td>
<td>1 (4%)</td>
<td>3 (4%)</td>
<td>21 (23%)*</td>
</tr>
</tbody>
</table>

Table 5. Pathogen findings of patients with otogenic intracranial abscesses (oIA) and of intracranial abscesses of other etiologies (other IA). (* p<0.01)

<table>
<thead>
<tr>
<th></th>
<th>oIA</th>
<th>other IA</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus spp</em></td>
<td>33%</td>
<td>42%</td>
</tr>
<tr>
<td>Gram-negative enteric bacteria*</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td><em>Bacteroides spp</em></td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td><em>Fusobacterium spp</em></td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td><em>Haemophilus spp</em></td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td><em>Staphylococcus spp</em></td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Actinomycetales</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>Negative culture</td>
<td>17%</td>
<td>14%</td>
</tr>
</tbody>
</table>
Adults hospitalized due to AOM, AM, LM, or AMc (IV)

The annual incidence of AM in adults was 0.4/100,000, and that of all mastoid infections (AM, LM, or AMc) was 0.8/100,000. The annual number of cases is shown in Figure 14; no significant seasonal variation was seen. Patient clinical characteristics, symptoms, findings, complications, procedures, and outcomes are presented in Table 6. The median duration of symptoms was 8 days and was longest in patients with LM (10 days).

Prior medical conditions (such as asthma, diabetes mellitus, cardiac disease, ear problems) were seen in 99 patients (62%). Cardiac problems were most common in the AMc group (5, 25% vs. 10, 7% in others, p=0.024). While all patients with AMc had CSOM, most patients (73%) had no prior ear problems; only five (3%) had a prior tympanostomy tube. A history of prior ear problems was least common in patients with AM (5, 10% vs. 38, 35% in others, p=0.001), these patients also had fewer general prior medical conditions (26, 50% vs. 73, 68% in others, p=0.036). Prior antimicrobial treatment had been administered to 114 patients (71%) and ear drops to 40 patients (25%). Patients with AMc had received less prior antimicrobial treatment than others (10, 50% vs 104, 74% in others, p=0.034).

Imaging was commonly performed on patients, with CT performed on 104 (65%) and MRI on 35 (22%); AOM patients were least likely to have had imaging. The most common cultured pathogens were StrA (19%), Pnc (14%), and Ps (11%); pathogens are shown according to groups in Figure 15. Hi was only found in the samples of three patients. Of all Pnc cultures, four (18%) had reduced susceptibility for common antimicrobials. Ps (30%, p<0.01), and Sa (25%, p<0.05) were more common in patients with AMc than in others. The results of bacterial cultures were negative for 65 patients (41%), making up 57% of AOM samples, 35% of AM samples, 25% of LM samples, and 30% of AMc samples. Patients with infection caused by Pnc had a longer duration of hospitalization (7 days vs 4 days in others, p=0.000), higher median CRP (216 vs 28 in others, p=0.000) and median WBC levels (14.4 vs 10.5 in others, p=0.009), and more meningitis (5, 23% vs 4, 3% in others, p=0.003) compared to those with infections caused by other pathogens. Otorrhea (83%), TM perforations (57%), hearing problems (83%), and post-infection hearing problems (60%) were common in patients with infection caused by StrA. Additionally, dizziness was relatively common in these patients (57%). Otorrhea (94%) and retroauricular signs of infection were common in patients with infection caused by Ps.

Parenteral antimicrobial treatment was administered to most patients (98%) (cefuroxime 84%, ceftriaxone 11%, and/or metronidazole 10%), as well as peroral antimicrobial treatment to (92%) (cephalexin 55%, amoxicillin-clavulanate 22%, ciprofloxacin 18%). Additionally, topical ear drops (88%) and steroids (79%) were commonly prescribed.

Mastoidectomy was performed on 44% of patients. The mean duration of hospitalization was longer in patients who underwent mastoidectomy (8 days) compared with those who did not (5 days, p=0.001).

Outcomes were better in patients who did not need a mastoidectomy. Full recovery was comparatively less common in patients with infection caused by Ps (24%). Post-infection hearing problems were common in patients with infection caused by Sa (62%) or StrA.
Figure 14. Annual number of adults hospitalized for acute otitis media (AOM), acute mastoiditis (AM), latent mastoiditis (LM), or AM in chronic ear (AMc).
Table 6. Clinical findings, symptoms, surgeries, and outcomes of adults hospitalized due to AOM, AM, LM, or AMc.

<table>
<thead>
<tr>
<th></th>
<th>AOM (60)</th>
<th>AM (52)</th>
<th>LM (28)</th>
<th>AMc (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>67%</td>
<td>60%</td>
<td>43%</td>
<td>45%</td>
</tr>
<tr>
<td>Median age</td>
<td>43</td>
<td>47</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Median CRP (mg/l)</td>
<td>11</td>
<td>81</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Otalgia</td>
<td>97%</td>
<td>100%</td>
<td>86%</td>
<td>95%</td>
</tr>
<tr>
<td>Fever</td>
<td>32%</td>
<td>44%</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>Otorrhea</td>
<td>43%</td>
<td>64%</td>
<td>64%</td>
<td>90%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>53%</td>
<td>44%</td>
<td>43%</td>
<td>30%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>21%</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>23%</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Hearing problem</td>
<td>67%</td>
<td>69%</td>
<td>68%</td>
<td>25%</td>
</tr>
<tr>
<td>Facial nerve paresis</td>
<td>17%</td>
<td>12%</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>Retroauricular redness</td>
<td>2%</td>
<td>23%</td>
<td>4%</td>
<td>40%</td>
</tr>
<tr>
<td>Retroauricular pain</td>
<td>12%</td>
<td>65%</td>
<td>25%</td>
<td>60%</td>
</tr>
<tr>
<td>Retroauricular swelling</td>
<td>0%</td>
<td>23%</td>
<td>4%</td>
<td>45%</td>
</tr>
<tr>
<td>Retroauricular fluctuation</td>
<td>0%</td>
<td>2%</td>
<td>4%</td>
<td>30%</td>
</tr>
<tr>
<td>Protrusion of the pinna</td>
<td>0%</td>
<td>12%</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>Subperiosteal abscess</td>
<td>0%</td>
<td>2%</td>
<td>10%</td>
<td>35%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0%</td>
<td>8%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>38%</td>
<td>15%</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>Sinus thrombosis</td>
<td>0%</td>
<td>4%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Tympanostomy</td>
<td>55%</td>
<td>73%</td>
<td>71%</td>
<td>45%</td>
</tr>
<tr>
<td>Paracentesis</td>
<td>75%</td>
<td>71%</td>
<td>79%</td>
<td>35%</td>
</tr>
<tr>
<td>Mastoidectomy</td>
<td>7%</td>
<td>37%</td>
<td>54%</td>
<td>50%</td>
</tr>
<tr>
<td>Median hospitalization, days</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Residual TM perforation</td>
<td>13%</td>
<td>13%</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>Residual hearing problem</td>
<td>37%</td>
<td>35%</td>
<td>32%</td>
<td>20%</td>
</tr>
<tr>
<td>Re-operations</td>
<td>8%</td>
<td>13%</td>
<td>21%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Figure 15. Pathogens of adults hospitalized for AOM (n=60), AM (n=52), LM (n=28), or AMc (n=20).
Complications of otitis media

According to our results, complications of OM in children and adults are less common in Finland than in other European countries. The annual incidence of AM among Swedish and Dutch children is 2.5-3.8/100,000 (van Zuijlen et al. 2001, Groth et al. 2012). The annual incidence of mastoiditis in Italian adults is 1.0/100,000 with 31% of those due to chronic OM (Palma et al. 2014). In our study, AM was more common in children than adults. The annual incidence of AM in children was 1.9/100,000, whereas the annual incidence of acute mastoid infections (AM, LM, or AMc) in adults was 0.8/100,000. Only 13% of our adult patients had AMc, possibly explaining our lower incidence compared to the Italian study. One explanation for the lower incidence of AM in Finnish children compared to Sweden or the Netherlands, might be the reduced use of antimicrobial treatment in those countries.

Complications due to OM have recently become more common at our institution compared with earlier reports (1990-2004) in which annual OM complication incidences of 1.1/100,000 in children and 0.3/100,000 in adults were reported (Leskinen & Jero 2004, 2005). The diagnostics of OM and its complications have not been altered over this time period, and thus do not explain this change. Reasons for this rise in incidence may be due to changes in the treatment of OM or pathogen virulence.

The annual incidence of IAs, according to a recent meta-analysis, is 0.4-0.9/100,000, with 32% being oIAs (Brouwer et al. 2014a). Some of the studies included in this meta-analysis were old, possibly skewing the incidence rates to appear higher than are currently seen in practice. In our study, the annual incidence for oIA over 2000-2012 was much lower, 0.02/100,000. Our results also show that the incidence of oIA has decreased over time, and that the prognosis of patients with IAs has improved. In our patients, most oIAs were due to CSOM and cholesteatoma, and ear symptoms were common in this group (17 patients, 94%) (unpublished data, Laulajainen-Hongisto et al.). The decrease in the incidence of chronic OM may explain the simultaneous decrease in the incidence of oIAs.

Pathogens of complicated otitis media

The most common pathogens of outpatient AOM in children are Pnc (23%), Mc (18%), and Hi (16%) (Palmu et al. 2004). Studies regarding the pathogens of AOM in adults are scarce, perhaps because outpatient AOM is uncommon in adults; the most common pathogens in adults with AOM have been reported to be Pnc (21%), Hi (26%), StrA (4%), and Mc (3%) (Celin et al. 1991, Bluestone et al. 1992).

Our study results are in accordance with prior literature findings that the bacteriological etiology of complicated OM differs from outpatient AOM (Luntz et al. 2001, Leskinen 2005, Benito et al. 2007); our results show that this difference in bacteriological etiology of outpatient AOM from hospitalized AOM and AM occurs in both children and adults. Therefore, bacteriological cultures should always be taken in complicated cases of OM in order to determine the proper
course of treatment as early as possible. We found that *Pnc*, *StrA*, and *Ps* were the most common pathogens in both adults and children with complicated OM; *StrA* and *Ps* were, however, only seen in adults and children older than two years.

Recent prior antimicrobial treatment was more common in adults (71%) than children (64%). In children, it tended to be more common in AM (70%) than AOM (57%), and in adults it was least common in AMc (50%). Our results show that culture negative bacterial findings were associated with prior antimicrobial treatment; these findings were less common in children (27%) than adults (41%), they were uncommon in adults with AMc (30%). Antimicrobial resistance (especially of *Pnc* to penicillin) is more common in children who have had prior antimicrobial treatment (Leibovitz et al. 1998, Del Castillo et al. 1998).

We found *Pnc* to be common in both outpatient AOM and complicated OM. In this study, *Pnc* was found in 38% of children hospitalized for AM, 21% of adults hospitalized for LM, 19% of adults hospitalized for AM, 18% of children hospitalized for AOM, but not in otAs or adults with AMc. *Pnc*, including its resistant strains, were common in children under two years of age. More *Pnc* strains with resistance to penicillin and 1st and 2nd generation cefalosporins were seen in children with AM (48% of *Pnc*) than in children with AOM (13% of *Pnc*), or in adults (18% of *Pnc*). This might be due to the resistant, more virulent *Pnc* strains being able to more easily cause complicated infections, or due to selection of resistant strains due to prior antimicrobial treatment. Drug-resistant strains are not necessarily more virulent, but may be treated with inefficient antimicrobials more often. Fortunately, a high and frequent-enough dosage of antimicrobials can compensate for the intermediate resistance of *Pnc* to penicillin (Del Castillo et al. 1998, Jalava 2014). Adults had less infections caused by these resistant *Pnc* strains, even though they had received more preceding antimicrobial treatment (71%) compared with children (64%). In children, pneumococcal infections (especially those caused by the resistant strains) caused more severe symptoms and led to more mastoidectomies than infections caused by other pathogens. Multi-drug resistant *Pnc* is, according to the literature, common in complicated AOM (Mattos et al. 2014, Antonelli et al. 1999, Zapalac et al. 2002). More antimicrobial resistance of *Pnc* to penicillin, macrolides, and trimethoprim-sulfonamide was observed in Finland over the period 2009-2011, compared to 2014 (Jalava 2014). Our study fell into this 2009-2011 period, but this does not explain why children with AM, in particular, had such high rates of resistant *Pnc* strains.

In this study, *Hi* was a very rare finding (0-4%) in complicated OM among both children and adults. *Mc* was most often found in children under the age of two who were hospitalized for AOM (14%), but it was not seen in adults or children with AM. Our results confirm the findings of earlier reports, that *Hi* and *Mc* rarely cause complications of OM (Katz et al. 2003, Leskinen & Jero 2003, Segal 2005).

In our study, *StrA* was often found in adults and older children, but not in younger children. It was common in adults hospitalized for AM (27%), LM (25%), and AOM (15%), but not in adults with AMc. In adults, *StrA* caused otorrhea, TM perforations, disturbances in balance, and hearing problems. To enable a faster diagnosis of infections caused by *StrA*, rapid detection from MEE can be used. *StrA* is known to be virulent and locally invasive (Segal 2005, Shulman et al. 2005). The incidence of invasive *StrA* infections in children has tripled within the last 15
years in Finland (Tapiainen et al. 2016). Some strains of StrA have the ability to release bacterial toxins that can, at worst, result in a cytokine storm leading to toxic shock syndrome with tissue damage, disseminated intravascular coagulation, and multiorgan dysfunction (Lappin et al. 2009). Therefore, it is easy to understand how tissue damage caused by bacterial toxins entering the labyrinth or cochlea can result in serious complications.

Ps has been reported to be a common pathogen in AM, especially in children with prior recurrent AOM (Butbul-Aviel et al. 2003). Ps was found in adults with AMc (30%), children hospitalized for AOM (16%) or AM (11%), and adults hospitalized for AM (10%) or AOM (8%), but it was not among the most common pathogens in adults with LM. In our material, Ps caused otorrhea and was found in older children, especially those with prior tympanostomy tubes, as well as adults with chronic OM. In children, the clinical picture of AM caused by Ps was mild.

The bacteriological etiology of AMc was not like that of AOM, LM, or AM. As expected, the bacteriological etiology of AMc - Ps (30%), Sa (25%), and Gram-negative enteric bacteria (20%) - resembled the bacteriology of CSOM (Brook 2005, Yeo et al. 2007, Mittal et al. 2015).

In our material, most patients with oIAs had preceding CSOM with cholesteatoma. An association of CSOM with cholesteatoma, with intracranial complications of OM has been seen previously as well (Penido et al. 2005, Szyfter et al. 2012, Sun et al. 2014). According to the literature, the most common pathogens of oIAs belong to Streptococcus spp, Bacteroides spp, Prevotella spp, and Enterobacteriaceae (Brouwer et al. 2014b), which are similar to those seen in CSOM patients. In our study, Gram-negative enteric bacteria were more common in patients with oIAs (22%) than in others. The bacteriological etiology of oIA resembles that of chronic OM and AMc.

Complicated otitis media in children and adults

In our study, the children with AM were generally younger than those with AOM. However, there were more children under the age of two in the AOM group (32%) than AM group (27%). AM causes a more severe clinical picture in younger children, compared to those who are older (Katz et al. 2003). AM has been reported as very uncommon in infants under the age of six months (17 cases in Sweden over a 15 year period) (Stenfeldt et al. 2014). In our material, AM was clearly less common in children under the age of two than in a Swedish study (55%) (Groth et al. 2012). Although the expectant observation approach for AOM in older children is more clearly suggested in Sweden than Finland, antimicrobial treatment is recommended for AOM in children under the age of two in both countries (Heikkinen et al. 2010, Stenfeldt et al. 2010, Groth et al. 2011). The adults with AOM or AM were younger than those with more prolonged infections (LM, AMc); this may be explained by the complications of OM being along a continuum, starting from AOM, progressing to either AM or LM, which, if not treated, can lead to CSOM and AMc. Most oIAs developed following CSOM, which is more common in adults than children.

Underlying medical problems were more common in children hospitalized for AOM (48%) than AM (27%), while adults with AMc had more prior medical conditions, including ear problems;
this was most likely due to their older age compared with adults in other groups. The chronic ear problems of adults with AMc persisted after the acute mastoid infection.

**Intra- and extratemporal complications of otitis media**

In the present study, subperiosteal abscesses were more common in children with AM (18%) than in adults (6%), probably due to the thinner bone structures in children than adults and the immature immune system of children. Subperiosteal abscesses were more common in adults with AMc than other types of acute mastoid infections or AOM. The patients with AMc probably had more underlying bone destruction due to their chronic middle ear infection.

Facial nerve paresis was more common among children hospitalized due to AOM (27%) than AM (5%). This can be explained by the spread of infection in the direction of least resistance. If the infection spreads toward the mastoid, it causes less pressure on the facial nerve area. In our study, 14% of adults had facial nerve paresis and 23% had labyrinthitis. AOM and AM patients with facial nerve paresis typically have infected tissue and purulent effusion surrounding an uncovered facial nerve.

In our patients, oIAs were usually due to CSOM with cholesteatoma. According to Zevallos et al. (2009), 25% of pediatric patients with coalescent AM may have intracranial complications. We found intracranial complications of AM to be much less common. Additionally, the rate of intratemporal complications due to OM reported in a Brazilian study (0.8%) seems very high compared to our results (Maranhao et al. 2014).

**Diagnostics of complicated otitis media**

The diagnosis of mastoiditis is based on symptoms and clinical findings (protrusion of the pinna, retroauricular redness, swelling, pain, or fluctuation; and/or abscess in the EAC; and/or purulent secretion or acute infection in the mastoid process upon mastoidectomy), not imaging or laboratory tests. Since AOM, AM, LM, and AMc are part of a continuum of middle ear infection, their symptoms overlap.

In our study, children with AM had more protrusion of the pinna than the children with AOM. Also, retroauricular signs of infection were more common in children with AM than AOM. The criteria we chose to use for the diagnosis of AM, therefore, seem appropriate.

Fever, otorrhea, and otalgia did not differ significantly in children with AOM and AM. In our material, fever was more common in adults with AM than in other groups. According to the literature, high fever and elevated infectious parameters (WBC, CRP) may be signs of complicated AM and warrant close follow-up (Bilavsky et al. 2009). We also found that patients with AM had higher CRP levels than those with AOM.

The necessity of imaging in AM has been discussed; currently, imaging is mainly performed to detect complications in unclear cases, or in cases that do not respond to treatment. In concordance with this, imaging was, in our study, less common in children with AOM (11%)
than AM (50%), and less common in adults with AOM (CT 28%, MRI 5%) than LM (CT 93%, MRI 43%). Imaging is crucial in the diagnostics of IAs, as well as in diagnosing the underlying conditions of the ear. CT is efficient in evaluating bony structures, but MRI is superior in evaluating soft tissues and intracranial structures; the choice of imaging technique should be based on the type of anatomical structures in question. The availability of CT is better than that of MRI, and its duration is shorter. Anesthesia may be needed when MRI is performed on small children. All of these factors affect the choice of modality; nevertheless, imaging should be considered in patients with acute infection of the middle ear and signs of mastoid infection that do not respond to conservative treatment (within 48 hours), when surgical treatment is considered, or when complications are suspected.

**Treatment of complicated otitis media**

Ideally, we would be able to identify those AOM patients who are at risk for development of complications as early as possible and treat their infections efficiently before complications develop. Antimicrobial treatment is not only used to avoid complications of AOM, but also to reduce symptoms, shorten the duration of MEE, and to avoid hearing problems in children (Tapiainen et al. 2014). According to Swedish publications, watchful waiting does not seem to increase the incidence of AM (Stenfeldt et al. 2010, Groth et al. 2011). However, the incidence of mastoid complications of AOM in Sweden and the Netherlands, where antimicrobial treatment for AOM is less common, is much higher than in Finland (van Zuijlen et al. 2001, Groth et al. 2012). It is known that antimicrobial treatment reduces the risk of mastoiditis, but the number of treated AOM patients needed to avoid one case of AM is very high (~4800) (Petersen et al. 2007, Thompson et al. 2009). Since spontaneous resolution of AOM is seen within 2-3 days of symptom onset in 80% of patients, those with no known risk for complications can simply be followed (Rosenfeld et al. 2003). Based on the literature and our results, antimicrobial treatment, at least for AOM in children under the age of two, seems adequate (Klein 2011, Tähtinen et al. 2011, Hoberman et al. 2011a, Hoberman et al. 2013).

The factors leading to complications are not entirely known. Complications may develop following untreated infections, incompletely treated infections (LM), or, in some cases, due to unknown causes, despite effective treatment. Anatomical or immunological factors, as well as age, may affect a patient’s predisposition for complications. Additionally, the virulence, or antimicrobial resistance, of a pathogen may affect its ability to cause complicated infections (Antonelli et al. 1999, Zapalac et al. 2002).

In our study, children with AM had received more antimicrobial treatment prior to hospitalization (70%) than children with AOM (57%). Many of the pathogens of OM are naturally resistant to macrolides. In our study, the children with AM who had been treated with macrolides underwent more mastoidectomies (80%) compared to the whole group (34%). Macrolides should not be used to treat AOM since almost all Hi strains, and 14-27% of Pnc, are resistant to them.

All study patients with AOM or mastoid infection received antimicrobial treatment; cefuroxime was the most common, followed by ceftriaxone, clindamycin, and metronidazole. Ciprofloxacin-hydrocortisone ear drops were commonly administered to the patients (~90%) to treat the
infection and keep the tympanostomy tube open. In order to reduce inflammation and tissue edema, oral or parenteral steroids were given to 55-73% of children and 79% of adults.

We advise that the antimicrobial treatment of complicated OM should always cover *Pnc* and *StrA*. In the Finnish current care guidelines for treatment of AOM, the suggested amoxicillin dose is 40mg/kg/day, whereas guidelines from the United States suggest an amoxicillin dose of 80-90mg/kg/day (Heikkinen et al. 2010, Lieberthal et al. 2013). Since antimicrobial resistance of *Pnc* was common in our pediatric sample of AM, and most *Pnc* cases were intermediately resistant to penicillin, a higher dose of antimicrobials should be considered for this group.

The patients with AM required longer hospitalization and more surgeries than those with AOM. In adults, surgeries were more common in the patients with prolonged mastoid infections (LM, AMc) than in those with AOM or AM. Paracentesis was performed more commonly in adults (69%) than children (23%), and tympanostomies less commonly in adults (63%) than children (73%). Tympanostomy was more common in children with AM (84%) than with AOM (59%). Although the treatment of mastoiditis has become more conservative, mastoidectomy is still required in AM resistant to conservative treatment (Chesney et al. 2014). Mastoidectomy was performed on 34% of children with AM, and on 44% of all adult patients with AM, LM, or AMc. In adults, mastoidectomy was most common in LM (54%). The adult patients that underwent mastoidectomy had worse outcomes than those who did not, however, none had perioperative complications. Patients requiring mastoidectomy had infections that were already severe prior to the surgery. The overall outcomes across all patient groups in our study are similar to those reported in prior literature (Osma et al. 2000, Sennaroglu et al. 2000, Penido et al. 2005, Dubey et al. 2010, Groth et al. 2012). In our material, the outcome of children was better than that of adults, probably because children have less chronic ear infections.

Since the acute infections of patients with CSOM may lead to serious complications (AMc, oIAs), they must be efficiently treated. In patients with complicated CSOM, the common pathogens are *Ps*, *Sa*, and Gram-negative enteric bacteria. Patients who have already developed chronic OM should be efficiently treated and followed. Antimicrobial treatment of complicated chronic OM should efficiently cover the most common bacterial pathogens of CSOM (*Ps*, *Sa*, and Gram-negative enteric bacteria).

The treatment of oIAs was not specifically analyzed in this thesis. Most patients with IAs in this study received antimicrobial treatment, the only exception were patients arriving at the hospital in critical condition, dying before treatment was possible. Almost all patients (99%) with IAs underwent surgery for their abscess. At our institution, the underlying (ear) infection is treated when the patients are stable, usually after the initial treatment of the IA.
**Future perspectives**

PCVs were added to our national immunization protocol in September 2010 and our data collection period ended in 2012. Our aim, however, was not to evaluate the effect of PCVs on OM complications. Although PCVs are effective against invasive pneumococcal disease, against AOM caused by *Pnc*, and have resulted in a reduction in tympanostomies among children, they seem not to have resulted in a reduced incidence of AM (Eskola et al. 2001, Poehling et al. 2007, Sarasoa et al. 2013, Whitney et al. 2003, Palmu et al. 2013). *Pnc* replacement by non-vaccine serotypes has been reported, some of these serotypes are virulent and have a tendency to develop antimicrobial resistance (Casey et al. 2010, Hoberman et al. 2011b). Multivalent PCVs are available, however, and may, in the future, change the prevention landscape. The effect of PCVs on the development of AOM complications is important to monitor in the future.

Anatomical conditions may exist that predispose a person to developing complications from OM. For example, the size of the mastoid might affect development of mastoid infections; this too warrants further study. Genetic susceptibility for the development of complicated OM is also an interesting issue for future research, as well as the use of steroids in the treatment of OM complications.
7 CONCLUSION

Acute complications of OM are rare in Finland compared with other European countries. However, their incidence has risen over the last decade.

1. The clinical findings in children with AM differ depending on the causative pathogen. *Pnc*, particularly the resistant strains, often cause severe symptoms and lead to mastoidectomy. *Ps* typically causes milder symptoms and affects mainly older children with prior tympanostomy tubes.

2. Children hospitalized due to AOM or AM have a different bacteriological etiology than those with outpatient AOM. The typical AOM pathogens, *Hi* and *Mc*, were uncommon in the complicated (hospitalized) patients. *Pnc*, especially its resistant strains, was less common among patients hospitalized due to AOM than AM. Children with AOM required less surgical interventions and had a shorter hospitalization period than those with AM. *StrA* and *Ps* were linked to otorrhea and were only found in older children.

3. Otogenic IAs have become less common over time and are usually due to CSOM, often in connection with cholesteatoma.

4. In adults, the bacteriological etiology of hospitalized AOM, AM, and LM (*Pnc*, *StrA*, and *Ps*) differs from that of AMc (*Ps*, *Sa*, and Gram-negative enteric bacteria). LM and AMc lead to more surgical procedures than do the acute complications of AOM or AM.
ACKNOWLEDGEMENTS

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Helsinki, May 2016
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