Acute Mastoiditis in Children – A National Study in Sweden

Enoksson, Frida

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To design guidelines for the management of a disease is a difficult and delicate task. In the case of a very common, and most often self-limiting, infectious disease of childhood it is even more challenging, especially if a small proportion of these children develop serious or, in the worst case, fatal complications. Acute otitis media is such a condition and acute mastoiditis is the most common complication to it, which makes acute mastoiditis an interesting condition to study.

The studies presented in this thesis have contributed to the knowledge on acute paediatric mastoiditis in Sweden today. The findings can contribute to national treatment guidelines on as well the extremely common ear infection and its very uncommon complication.

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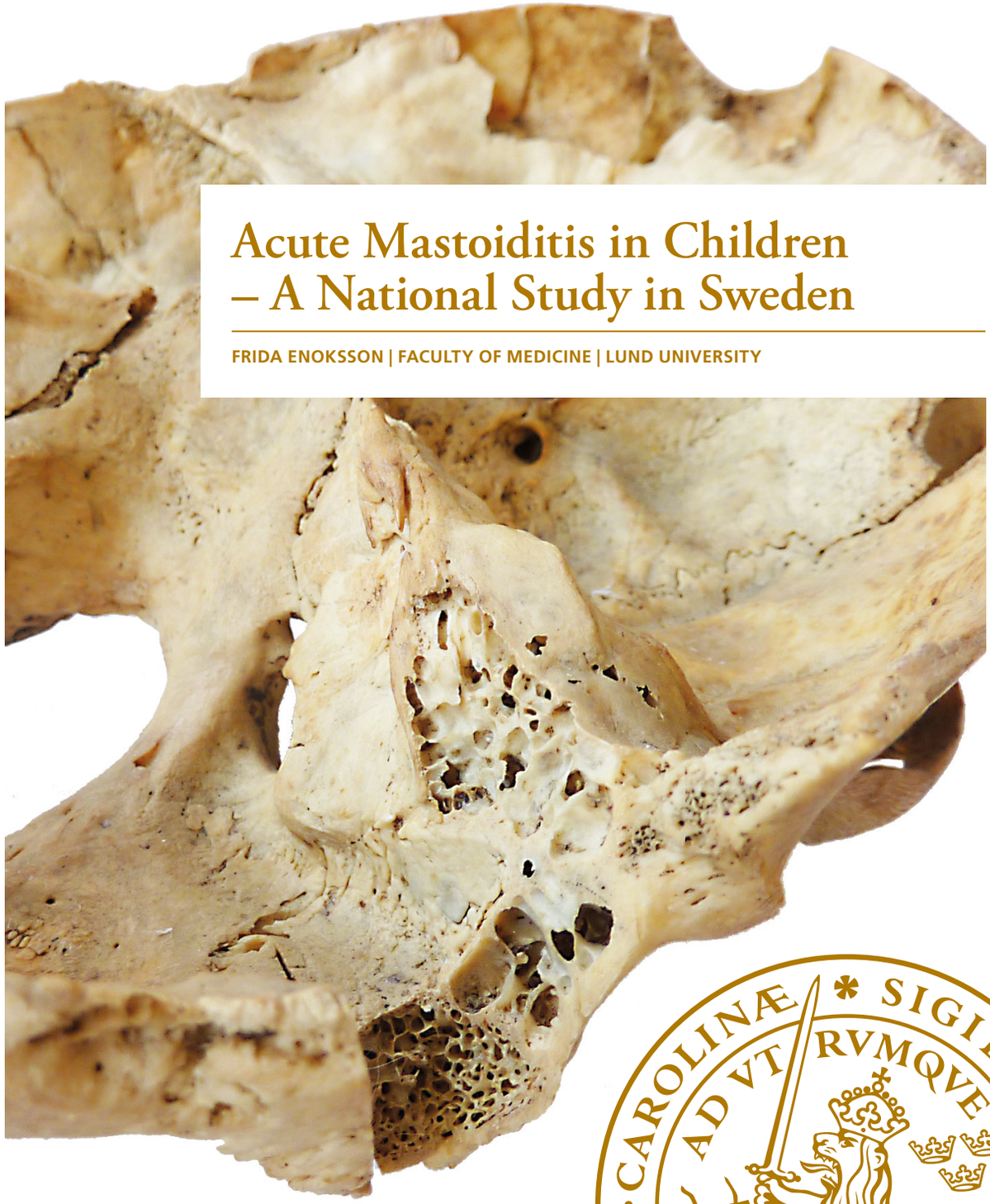

Acute Mastoiditis in Children – A National Study in Sweden

FRIDA ENOKSSON | FACULTY OF MEDICINE | LUND UNIVERSITY

Acute Mastoiditis in Children – A National Study in Sweden

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Abstract:

One of the greatest threats to society today is the development of bacterial resistance to antibiotics. It is commonly accepted that this is mainly due to the use of antibiotics. Acute otitis media (AOM) is responsible for the highest number of antibiotic prescriptions to children although it is in most cases a self-limiting disease. Nevertheless, complications do occur in some case and the most common complication is acute mastoiditis (AM). Treatment guidelines advocating the restrictive use of antibiotics in uncomplicated AOM have been implemented hoping to slow down the development of resistance to antibiotics. This has led to concerns that an increase of complications will arise. Although AOM is extremely common in early childhood, only 20–60 cases of AM in children are encountered per year in Sweden. In the pre-antibiotic era AM was often lethal and the use of antibiotics has revolutionized the clinical course of severe AOM and AM, radically reducing the rate of complications and mortality. In addition to the new guidelines, in the year 2009, immunisation with pneumococcal conjugate vaccine (PCV) against the most invasive serotypes of *Streptococcus pneumoniae*, the most common bacteria causing AOM as well as AM, was introduced into the standard immunisation schedule in Sweden.

The national study "Mastoiditis in Sweden", which formed the basis for the research presented in this thesis, gives a good picture of Swedish paediatric patients suffering from AM. The different ways in which AM symptoms are expressed and their development in different age groups are well described in Paper 1. Different surgical methods for treating subperiosteal abscesses were evaluated in Paper 2. It was found that needle aspiration and/or incision to treat SA had no adverse effects when compared to mastoidectomy. Possible effects of the recently introduced immunisation against pneumococci were investigated in the third study (Paper 3). PCV did not offer a complete protection against the serotypes included in the vaccines, even in fully immunised children. Finally, the effects of the altered guidelines on AOM treatment were explored in an attempt to identify risk factors for AM (Paper 4). No overlooked possible risk factors for AM could be identified. Unfortunately, the retroauricular findings indicating an AM, were found to be overlooked by physicians at the primary assessment of some children, which caused a delayed treatment. Thus the AOM treatment guidelines appear to be sufficient, and the greatest challenge lies in detecting complications arising from AOM.

Key words: acute mastoiditis, paediatric, guidelines, surgical treatment, pneumococcal conjugate vaccine

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“I learn only to be contended”

One possible translation of the inscription
in kanji in the Ryōan-ji tsukubai, Kyoto

Contents

Abbreviations 2

List of papers 5

Preface 6

Thesis at a glance 7

Introduction 9

- Anatomy of the middle ear 9
- History 11
- Antibiotic resistance and the need for watchful waiting 12
- Definitions of and diagnostic criteria for acute otitis media and acute mastoiditis 14

Aims 19

Subjects and methods 21

- Study design 21
  - The retrospective part of Mastoiditis in Sweden 21
  - The prospective part of Mastoiditis in Sweden 24
- Microbiological tests 26
- Statistical analyses 28
- Ethical considerations 28

Results 29

- A summary of the main results 29
- Paper 1: Acute mastoiditis in children aged 0–16 years –A national study of 678 cases in Sweden comparing different age groups 30
- Paper 2: Subperiosteal abscesses in acute mastoiditis in 115 Swedish children 32
- Paper 3: Distribution of Pneumococcal serotypes in paediatric patients with acute mastoiditis in Sweden 34
- Paper 4: Risk factors for paediatric acute mastoiditis in Sweden. 36

Discussion 39
The AM child 39
Definitions and study design 40
Surgical or medical disease? 42
Bacteria and antibiotic resistance 44
The pneumococcal conjugate vaccine 45
Possible additional risk factors 48

Conclusions 51

Populärvetenskaplig sammanfattning på svenska 53
Bakgrund 53
Artikel 1 55
Artikel 2 55
Artikel 3 55
Artikel 4 56
Sammanfattning 56

Acknowledgements 57

References 59

Abbreviations

AM	acute mastoiditis
AOM	acute otitis media
CRP	C-reactive protein, (mg/l)
CT	computerised tomography
GAS	*Streptococcus pyogenes* Group A
GP	general practitioner
Hi	*Haemophilus influenzae*
IPD	invasive pneumococcal disease (severe infections spreading to the blood or passing the brain-blood barrier)
Mc	*Moraxella catarrhalis*
MEF	middle ear fluid
MIC	minimal inhibitory concentration, (mg/l)
n	number
NP	nasopharynx
Pa	*Pseudomonas aeruginosa*
PCV	pneumococcal conjugate vaccine
PCV7	Prevenar™ (Pfizer Inc., New York, USA)
PCV10	Synflorix™ (GlaxoSmithKline plc, Brentford, United Kingdom)
PCV13	Prevenar 13™ (Pfizer Inc., New York, USA)

pnc	*Streptococcus pneumoniae*, or pneumococci
rAOM	recurrent acute otitis media (≥3 separate episodes of AOM within six months or ≥4 in a year)
SA	subperiosteal abscess
SD	standard deviation
SE	standard error of the mean
URTI	upper respiratory tract infection
VT	vaccine type, serotype included in the type of pneumococcal conjugate vaccine a person has received
WBC	white blood cell count, (μl^{-1})

List of papers

This thesis is based on the following papers which will be referred to in the text by their Arabic numerals:

1. Groth A, Enoksson F, Hultcrantz M, Stalfors J, Stenfeldt K, Hermansson A.
Acute mastoiditis in children aged 0-16 years–a national study of 678 cases in Sweden comparing different age groups International journal of pediatric otorhinolaryngology. 2012;76:1494-1500.

2. Enoksson F, Groth A, Hultcrantz M, Stalfors J, Stenfeldt K, Hermansson A.
Subperiosteal abscesses in acute mastoiditis in 115 Swedish children International journal of pediatric otorhinolaryngology. 2015;79:1115-1120.

3. Enoksson F, Eriksson Gonzales C, Hermansson A, Melhus A.
Distribution of Pneumococcal serotypes in paediatric patients with acute mastoiditis in Sweden
Manuscript

4. Enoksson F, Groth A, Hermansson A.
Risk factors for acute paediatric mastoiditis in Sweden
Submitted

Preface

To design guidelines for the management of a disease is a difficult and delicate task. In the case of a very common, and most often self-limiting, infectious disease of childhood it is even more challenging, especially if a small proportion of these children develop serious or, in the worst case, fatal complications. Acute otitis media (AOM) is such a condition, and is so common that most children have experienced at least one episode of it[1, 2]. The most common complication associated with AOM is acute mastoiditis (AM), which is the subject of the research presented in this thesis. Although AOM is extremely common in early childhood, with an estimated annual incidence of nearly 200,000 cases in Sweden, only 20–60 cases of AM in children are encountered per year[3]. The reason for studying such an unusual complication is that it is the most appropriate way of evaluating possible negative effects of the reduction in treatment of AOM with antibiotics. AOM is responsible for the highest consumption of antibiotics in childhood, and lowering the amount of antibiotics prescribed for AOM is thus one way of reducing the development of resistance of bacteria to antibiotics. Since antibiotic resistance is a serious and growing problem, the findings of this research affect not only those affected by AOM, but society as a whole.

The national study "Mastoiditis in Sweden", which formed the basis for the research presented in this thesis, gives a good picture of Swedish paediatric patients suffering from AM. The different ways in which AM symptoms are expressed and their development in different age groups are well described in Paper 1. The observation in a previous study[3] that mastoidectomy was performed less often initiated the evaluation of different surgical methods for treating SA (Paper 2). Possible effects of the recently introduced immunisation against pneumococci were investigated in the third study (Paper 3). Finally, the effects of the altered guidelines on AOM treatment were explored in an attempt to identify risk factors for AM (Paper 4).

In order to understand the study design and conclusions made from the results a background of both AOM and its complication AM is given in the following pages. An overview of the studies carried out is presented in the table below, Thesis at a glance.

Thesis at a glance

Paper	Purpose	Methods	Results	Conclusions
1	To characterise the typical AM child in Sweden.	Investigation of 678 children, aged 0–16, included in the retrospective part of "Mastoiditis in Sweden" study.	No predisposition for ear diseases or allergies. The expression of AM differs with age.	No special risk group was identified. Symptoms vary with age.
2	Evaluation of minimal invasive surgery, needle aspiration/incision in SA.	Comparison of two different surgical methods to treat SA, the most common complication to AM.	No difference in outcome of mastoidectomy versus needle aspiration/incision.	Initial treatment of SA with needle aspiration/incision has no adverse effects.
3	Assessment of whether PCV has affected the pneumococcal serotypes found in AM in Sweden.	Serotyping of pneumococci was performed in 18 AM patients and correlated to their history of pneumococcal immunisation.	Serotypes included in the vaccines caused several cases of AM.	PCV does not protect all immunised children, even against the serotypes included in the vaccine, from developing AM.
4	To investigate possible risk factors for AM in the studied population. To evaluate if the exclusion criteria in the AOM guidelines were sufficient and whether adherence to the guidelines was sufficient.	Parents were interviewed to elucidate possible risk factors not mentioned in the medical records, and to evaluate physicians' adherence to the guidelines.	No additional risk factors were identified. The symptoms of AM were overlooked in 15 cases, leading to a delay in treatment.	The exclusion criteria from watchful waiting appeared to be sufficient. Adherence to the guidelines are acceptable but the number of unrecognized cases of AM is worrying.

Introduction

Anatomy of the middle ear

The anatomy of the middle ear is very complex, as can be seen in Figures 1 and 2. The middle ear is a cavity located in the lateral part of the temporal bone, lined with airway mucosa, and has a volume of about 1.5 ml in adults. The middle ear communicates with the mastoid bone through a series of small, aerated cells lined with a similar mucosa, the mastoid cell system. The size of the mastoid cell system varies between individuals, but has volume of approximately 8 ml in adults. The average area covered by the mastoid cell system in a one-year-old child is approximately 4 cm^2, increasing to 12 cm^2 in adulthood[4]. The gas exchange required to maintain a correct middle ear pressure takes place in this large surface area, which is also an active airway epithelium. Whether and how "size matters" and whether a small cellular system leads to ear problems, or whether ear problems in early childhood lead to a small cellular system in the mastoid bone, has been widely discussed in otology over the years[5, 6].

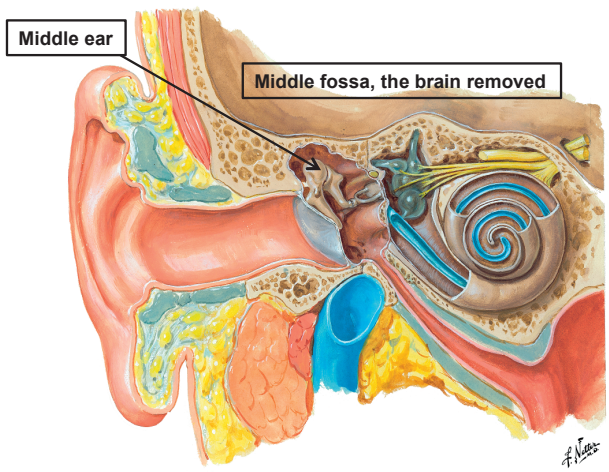

Figure 1:
Coronal section of the temporal bone. Note the close proximity to the middle fossa in which the temporal parts of the brain is located. (Ill. F. H. Netter, illustration used with permission of Elsevier, Inc. All rights reserved. www.netterimages.com)

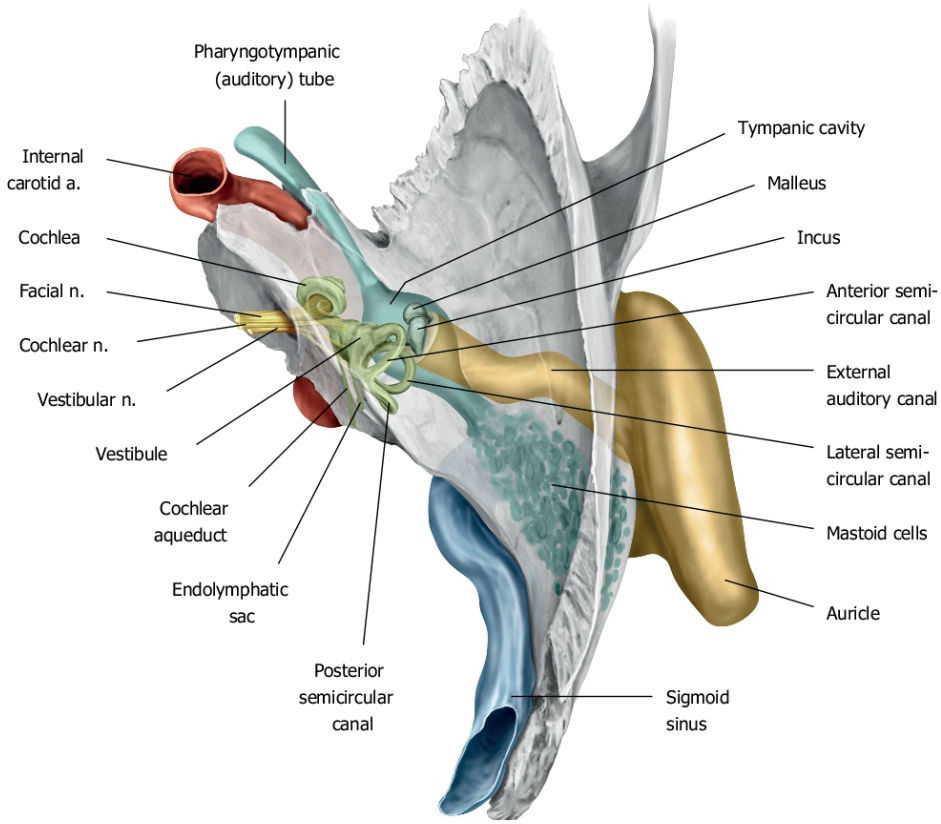

Figure 2:
Anatomy of the middle ear (tympanic cavity) in the temporal bone; superior view from the middle fossa with the brain removed. (From Thieme Atlas of Anatomy 2nd ed., Ill.: Karl Wesker)

Fragile and vital organs, such as the sensory organs of the inner ear, the facial nerve and the brain, are in close proximity to the middle ear (Figures 1 and 2). Thus, infections in the middle ear pose a special medical problem[7]. The spread of infection into the meninges or the inner ear may be lethal, or cause life-long sequelae such as loss of hearing. The most common complication associated with AOM today worldwide is AM[8-11], in which the infection initially spreads beyond the middle ear and the mastoid mucosa into the underlying bone, causing osteitis. Small changes, such as oedema in the mastoid cell mucosa, take place in the middle ear mucosa even during mild infections such as the common cold. The advancement of purulent AOM into the mastoid cells is thought to take place through per continuitatem spread beyond the antrum of the middle ear or by haematogenous spread by draining of the middle ear via the emissary veins. The most common complication to AM is subperiosteal abscess (SA) in which the pus from the infection spreads laterally to the surface of the mastoid process[12, 13]. This complication can be identified by a fluctuation over the SA. The mastoid cavity may be regarded as an enclosed

chamber for infection to which it easily can advance from the middle ear, possibly delaying advancement intracranially or into the inner ear, to a space in which the body´s "battle" can take place without disturbing vital parts. Then, of course, the role of the mastoid cells is not well understood and such hypothetical patho-mechanism is pure speculation.

History

In the pre-antibiotic era, i.e. before antibiotics were discovered and possible to administer the treatment of AM was not very successful. The sulphonamides were introduced as the first efficient antimicrobial agent in the mid 1930s and the first reports on the clinical use of penicillins were published in 1941[14]. The introduction of antibiotics for the treatment of AOM and its complications has led to a remarkable fall in the incidence of complications, and the mortality rate when they do occur[15]. AM can usually be successfully treated in the early stages with antibiotics and the majority of the patients in the developed countries recover completely. In Sweden the antibiotic treatment is most often combined with a myringotomy of the eardrum, thus draining the middle ear from pus. This surgical procedure is usually performed under general anaesthesia shortly after admission. Less than 25% of the paediatric patients with AM in Sweden (Paper 1) were found to require a mastoidectomy, i.e. a more complex surgical procedure in which the mastoid cells are partly removed. The surgical technique of mastoidectomy today, resembles the methods used in the pre-antibiotic era but the facilities and instruments used currently have much improved. In the parts of the world where antibiotics are not readily available, child mortality due to AOM and its complications is still high.

Living conditions have also improved markedly since the 1930s and 1940s and children in the developed countries now have access to good medical care and treatment. Furthermore the nutritional status has improved, and the vast majority of children are now immunised against the most infamous infectious diseases. In Sweden, close to 98% of children are immunised according to the national immunisation schedule, according to national data from The Public Health Agency of Sweden from 2011[16].

It is important to consider the definition of AOM when comparing different studies, and today's definition differs considerably from that of the pre-antibiotic era. For instance, in the often referred-to study by House from 1946[15], the inclusion criteria required admittance to hospital due to otorrhea for at least three days. Today, this would be classified as AOM with spontaneous perforation of the eardrum, requiring immediate antibiotic treatment. Children with self-limiting AOM are currently classified as having a sudden onset of earache, in combination with typical eardrum

findings that recover spontaneously within a few days. Such paediatric patients were probably not assessed by any kind of medical practitioner at the time of House's study, which illustrates how precarious it is to compare pre-antibiotic studies with present day studies.

Antibiotic resistance and the need for watchful waiting

The importance of modern antibiotics cannot be overemphasized, in fact they are fundamental to modern medicine. Without them, procedures such as implant surgery and organ transplantation would not be possible, and both adults and children would die from complications resulting from ordinary infections such as pneumonia and AOM. However the number of sinister reports of microbial resistance against various kinds of antimicrobial agents is growing, and it has even been predicted that we may be approaching a post-antibiotic era[17]. Excessive use of antibiotics is commonly cited as the reason for this[18, 19]. In order to reduce the prescription of antibiotics, the infections mainly responsible for high antibiotic consumption have been identified. One of these is upper respiratory tract infections (URTIs), in children. Among these, the highest prescription rate of antibiotics is seen for AOM. The Dutch were the first to restrict the prescription of antibiotics for AOM already in the 1980s[20], and many other countries have since followed their example. In Sweden, guidelines advocating the restrictive use of antibiotics for the treatment of AOM were introduced in 2000. These made it possible for physicians to refrain from prescribing antibiotics to otherwise healthy children with AOM, aged 2–16 years, whose general condition was not affected. These guidelines were updated in 2010, and "watchful waiting" is now advocated in children aged 1–12 years[21]. A summary of the current Swedish guidelines is given in Table 1.

Table 1:
Summary of the updated Swedish guidelines for diagnosis and treatment of AOM, introduced in 2010

Definition: AOM is defined as a symptomatic purulent infection in the middle ear.

Diagnostic criteria:

- Rapid onset of symptoms; e.g. earache, screaming, irritability, fever, decreased activity/appetite/sleep often during an ongoing URTI
- Signs of inflammation of the tympanic membrane and purulent discharge in the middle ear or in the ear canal

Initial antibiotic treatment:

- Children <1 year and >12 years of age and adults
- All patients with complicating factors such as severe earache despite adequate analgesic treatment, susceptibility to infection due to other concomitant illness/syndrome or treatment, malformations of the facial skeleton or inner ear, sequelae after skull base/maxillofacial fractures, cochlear implant, known middle ear disease or previous ear surgery (not grommets), or known sensorineural hearing disorders
- Bilateral AOM in children <2 years
- Recurrent AOM (≥3/6months or ≥4/12 months)
- Relapsing AOM (within a month)
- AOM with spontaneous perforation of the eardrum independent of age
- AOM with earache ≥48 hours

Watchful waiting: No antibiotics initially, but analgesics if needed:

- Children 1–12 years with sporadic AOM not belonging to the above groups
- If ear pain resolves within the first 24 hours, no need for examination or treatment, otherwise assessment within 24 hours
- Antibiotic treatment if no improvement after 2–3 days or immediately upon deterioration

It has not been easy to implement these guidelines, recommending restrictive treatment of a very common infection capable of causing severe complications or death. Sceptics feared an increase in the incidence of complications, and contradictive reports on rates of AM have been published from countries employing restrictive guidelines[3, 22-27].

It is noteworthy that in the pre-antibiotic part of the study by House from Los Angeles[15], 54% of the 1241 cases admitted to hospital due to AOM with spontaneous perforation recovered spontaneously. Antibiotic treatment is now recommended for AOM patients presenting with a spontaneously perforated eardrum, rather than watchful waiting. In House's study, the rate of mortality due to complications of AOM was 5%; the main cause of death, 70%, being meningitis. In

50% of his AOM patients where bacteriologic data were available, including cases of spontaneous recovery, the bacteria responsible were described as "haemolytic streptococci", probably equivalent to *Streptococcus pyogenes* Group A (GAS), while 6% of the infections were caused by pneumococci, i.e. *Streptococcus pneumoniae* (pnc). The same relation between these bacteria were reported ten years earlier from the San Francisco area[28]. These two bacteria are still responsible for most of the complications associated with AOM, although pnc is now the most common bacterial finding[11, 29-32]. Very little was known about the bacteria causing uncomplicated cases of AOM in the pre-antibiotic era since these patients did not seek or receive any healthcare. The key issue today is to identify patients with AOM at risk of developing severe complications.

Definitions of and diagnostic criteria for acute otitis media and acute mastoiditis

One of the main problems when studying AM is the too often poor description of inclusion criteria and definitions on the conditions studied. AOM is a clinical diagnosis[1, 33], in most cases made by a general practitioner (GP). The definition of AOM in Sweden is in short a combination of rapid onset of symptoms and typical AOM findings in the tympanic membrane (Figure 3). The first is often easy to establish with reasonable certainty. The second, however, can be very difficult to establish, even for a skilled physician, as it can sometimes be difficult or impossible to examine a two-year old with earache. If the eardrum can be examined, it is sometimes difficult to distinguish a red eardrum from the red ear canal wall in a feverish toddler or a red eardrum without fluid in the middle ear as required in AOM. In such cases, correct diagnosis requires evaluation of the mobility of the eardrum using, for example, pneumatic otoscopy, which often is not appreciated by the ill child. The opaque surface of the eardrum in AOM can also be difficult to distinguish from the appearance of secretory, non-infectious, otitis media. In those diagnoses the eardrum is not mobile and to distinguish between them requires an evaluation of the position of the eardrum. It has been found that the best diagnostic tools to evaluate the eardrum and its mobility are a combination of otomicroscopy, which provides stereovision, and pneumatic otoscopy or tympanometry[33, 34]. Many GPs are trained in using these instruments but may lack a trained assistant to hold the child, whereas such a person is usually available at an ENT department. This might partly explain why the frequency of AOM is often lower in studies on AOM performed by otorhinolaryngologists, (from now referred to as ENT specialists) than in similar studies by other medical practitioners[35, 36].

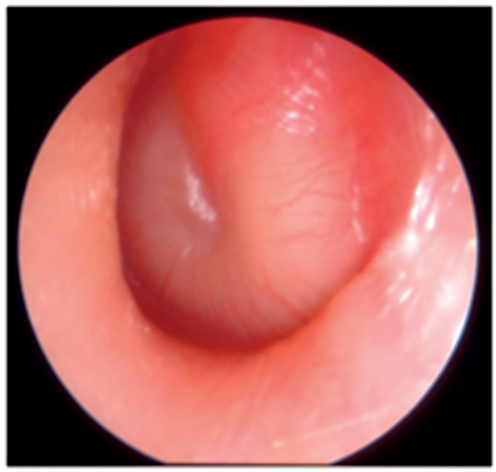

Figure 3:
The bulging, thickened tympanic membrane in a typical case of AOM. (Published with permission by M. Foglé-Hansson)

Acute mastoiditis should be easy to recognize from the typical signs of protrusion of the ear, and redness and oedema over the mastoid, as shown in Figure 4.

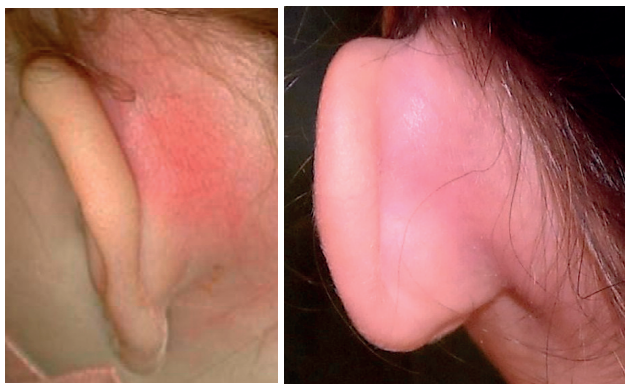

Figure 4:
Typical retroauricular signs of AM with protrusion of the ear and redness and oedema over the mastoid in a young child, (left) and in an older child, (right) (Photos by B Magnuson and F Enoksson)

The unequivocal diagnosis of AM requires histopathological examination of samples of the infected tissue in the mastoid cavity, obtained by mastoidectomy. Today, mastoidectomy is not routinely performed in cases of clinically diagnosed AM, and the diagnosis of AM is based on clinical signs. Unfortunately, there is no consensus on which criteria should be used. Definitions of AM differ between different clinicians and departments in the same country as well as between different

countries, making both national and international comparisons difficult[37]. The definition of AM used in the present work is the combination of AOM with at least two retroauricular inflammatory signs, as is given in Table 2:

Table 2:
The clinical criteria for acute mastoiditis applied in this work

*Clinical signs of acute otitis media (ongoing or within 14 days)
-with bulging eardrum/purulent discharge in the middle ear at myringotomy
-or draining ear without ongoing tube treatment
and
≥2 retroauricular signs of infection
-redness
-protruding ear
-oedema or swollen mastoid
-pain/palpation tenderness over mastoid
and/or sagging of the ear canal (signs of an abscess in the ear canal)
or
*Findings of purulent discharge or acute infection in the mastoid process at mastoidectomy

AM mainly affects young children below the age of two years, just as AOM is most common in this group[2, 38, 39]. The median age of onset of AM was 21 months in Paper 1, (Figure 5).

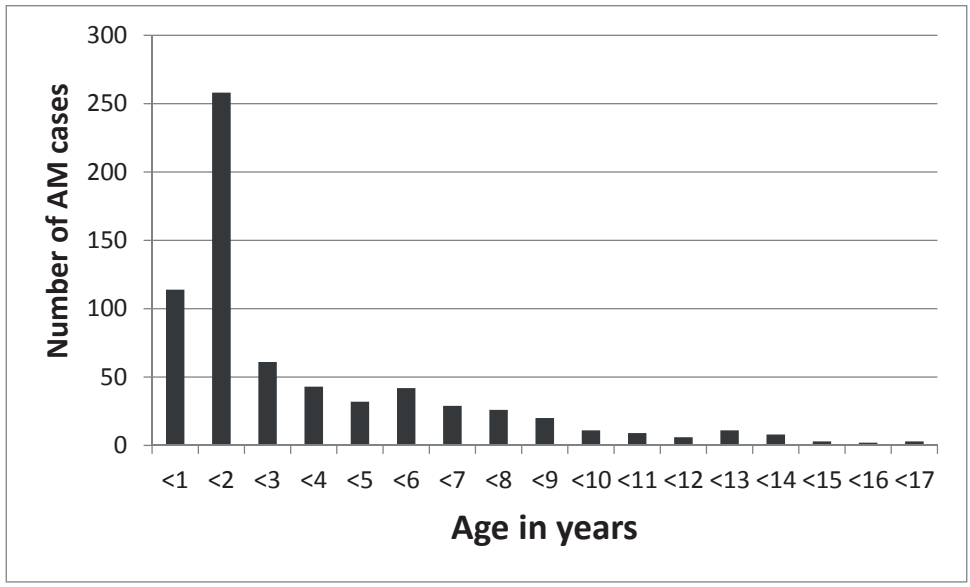

Figure 5:
The age distribution of the included 678 cases in Paper 1.

Detailed retrospective studies[3, 31] revealed some of the pitfalls of studies on registers. For example, the same episode of AM was registered at more than one department, due to referral to a tertiary centre, which would lead to overestimation of the incidence of AM. Some departments used rather wide definition criteria, and others too narrow. These inherent errors of register studies were further analysed in a study on the validity of the diagnostic codes for AM[40] where it was found that reporting in national and ENT departments registers had poor validity, including approximately 25% incorrect diagnoses. A flowchart describing the different ways of validating the codes, in that study is given in Figure 6.

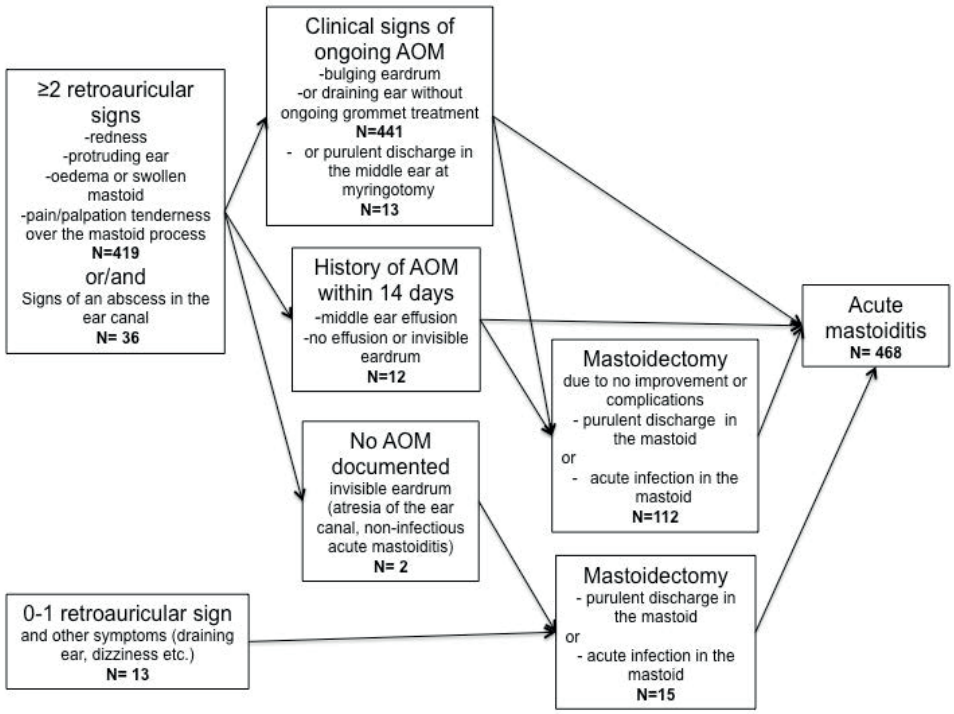

Figure 6:
Flowchart describing the review of medical records with a diagnosis of AM according to predefined criteria[40].

AM is thus a clinical diagnosis based on medical history and clinical examination, where repeated examinations may be necessary to establish the diagnosis. It is important to remember that the final diagnosis may sometimes require myringotomy or mastoidectomy or evaluation of the effects of commenced treatment. Computerised tomography (CT) or surgical procedures were, however, not required to confirm the diagnosis in the present work. Difficulties in establishing uniform and correctly diagnosed patient groups constitute the main obstacle when trying to evaluate possible changes in a very uncommon complication of an extremely common infection.

Aims

The overall aim of the work described in this thesis was to describe the characteristics of paediatric AM in the Swedish population, thus enabling a reliable evaluation of the possible impact of changes in treatment guidelines for AOM and the introduced immunisation on pneumococci.

Four papers are included in this thesis, addressing the following questions.

1. What are the clinical characteristics and the course of events of children with AM aged 0–16 years?

2. Are needle aspiration/incision of a subperiosteal abscess and reduced use of mastoidectomy acceptable changes in the surgical treatment of AM?

3. Has the introduction of pneumococcal conjugate vaccines (PCVs) affected the pneumococcal serotypes that cause AM in fully immunised patients?

4. Are children prone to AM characterised by any particular inherent factors or exposed to any particular factors in their environment? Does adherence to the guidelines for the management of AOM affect the early identification of AM?

Subjects and methods

Study design

A vast amount of data on AM has so far been collected in the national study, "Mastoiditis in Sweden". This study consists of a retrospective and prospective part; the current author being responsible for the prospective part. So far, the findings of this study have led to six publications in international scientific journals including Papers 1 and 2[3, 40-42]. Paper 1 is referred to in a Best Practice Review on AM with a large impact on clinical management in paediatrics[43]. A great deal of effort has been devoted to designing and maintaing the study, and utilizing its findings. This thesis presents some of the aspects concerning paediatric AM that have been analysed so far. The following sections describe the design of the study and the underlying reasons for this design.

The retrospective part of Mastoiditis in Sweden

The primary aims were to establish the true incidence of AM in Sweden, and to investigate any possible effects of the new guidelines advocating restrictive treatment of AOM introduced in 2000. All 34 ENT departments in Sweden treating patients with AM were asked to participate in the study. All but one department accepted the request; the department declining to participate reported only three cases of AM during the period in question. Thus, nearly all of the Swedish population, approximately nine million inhabitants were covered. Medical records of patients with diagnostic codes representing AM and unspecified mastoiditis according to the International Statistical Classification of Diseases and Related Health Problems (ICD) systems, ICD-9 and ICD-10 respectively, were obtained from these departments. In ICD-9, the diagnostic code 383, defines mastoiditis. In ICD-10, H700, H701, H709 and H750 define different kinds of mastoiditis.

In addition to this national investigation, all patients admitted to hospital and treated for AOM with the diagnostic codes for AOM, (382 in ICD-9 and H660 in ICD-10) were investigated at the eight largest departments in Sweden, serving a total of approximately 5 million inhabitants (over half of the population of Sweden). This was performed in order to identify any missed cases of acute mastoiditis in the group

of patients diagnosed as having AOM. The period 1993–2007 was chosen as a suitable study period for the work presented here.

All medical records were reviewed by four members of the study group, all specialists in otorhinolaryngology, (AG, KS, JS, FE, all co-authors in Paper 1), using the criteria for AM given in Table 2. Data on patients with AM of all ages were registered in the database but the studies described in this thesis concern only children in the age groups affected by the AOM guidelines (0–16 years). The data analysed included medical history, age, sex, antibiotic treatment prior to hospital stay, results of clinical examinations and laboratory tests, treatment after admittance, bacterial cultures, duration of ear symptoms and hospital stay, clinical outcome, complications and long-term sequelae. Children with bilateral AM were considered as one case. A new episode of AM or re-admittance to hospital within four weeks was considered to be residual AM. Recurrence after that period was classified as a new episode of AM. Patients exhibiting ear symptoms for longer than 60 days or no purulent infection at mastoidectomy were considered to have chronic mastoiditis and were excluded. Cases with concurrent cholesteatoma or previous surgery for cholesteatoma were also excluded, since cholesteatoma is considered a discrete condition and is therefore usually not included in AM studies in children[37, 44]. All cases exhibiting dry or draining perforations of the eardrum were also classified as chronic otitis media and excluded, even if they had clinical signs of AM. Cases of concurrent or recent head and neck malignancies (rhabdomyosarcoma, neuroblastoma, epipharyngeal neoplasm) were also excluded. Two children with immune deficiencies were excluded, as were three children with atresia of the ear canal who were eventually diagnosed as having cholesteatoma. On the other hand, five children with cochlear implants were included as well as one child with Down's syndrome and two children with cleft palate. A flowchart over the inclusion process is given in Figure 7. Twenty percent of the diagnoses of AM did not meet the definition of AM in this study, most of which had external otitis, grommet drainage or so called CT-verified AM without AM signs. Uncertain diagnoses were discussed in the study group to reach consensus.

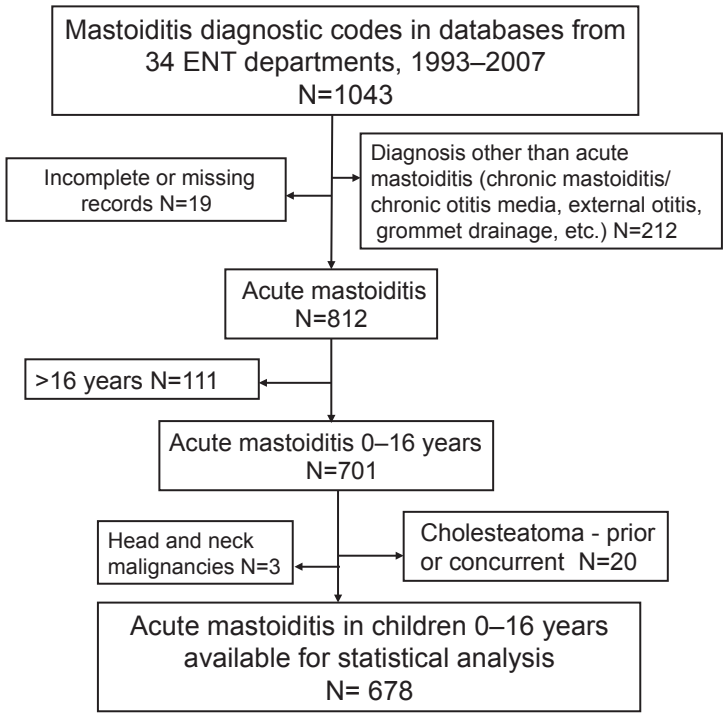

Figure 7:
Flowchart of the inclusion process in the retrospective study.

The study on subperiosteal abscesses

Cases of SA were extracted from the retrospective data and analysed in Paper 2. The diagnosis of SA was defined as the finding of an abscess beneath the periost at mastoidectomy, or retrieval of pus at retroauricular needle aspiration or incision. The use of CT was not required to confirm SA. Cases of abscesses protruding into the ear canal, which might be considered equivalent to SA, were not included. Recurrent episodes of AM were not recorded as new cases in this study, but were reported in order to evaluate the outcome of different methods of treatment. Patients with severe complications in combination with SA were excluded since such patients might require more extensive treatment than patients with SA as the sole complication of AM.

The patients were divided into three groups, as shown in Figure 8. Group 1 included 33 patients treated with a minor retroauricular intervention, i.e. needle aspiration and/or incision of the abscess. Group 2 included 67 patients who had undergone mastoidectomy, and Group 3 included 15 patients who had undergone both minor retroauricular intervention and mastoidectomy. It was impossible to interpret from the medical records why the 15 patients in Group 3 had undergone both minor

retroauricular intervention and mastoidectomy, or whether the minor intervention was intended to be diagnostic or therapeutic. This group could thus consist of cases that had undergone mastoidectomy because the minor intervention failed, and cases where the finding of pus retroauricularly led the surgeon to perform mastoidectomy. Because of this ambiguity, which could lead to erroneous interpretation, these 15 cases were not included in the statistical analysis.

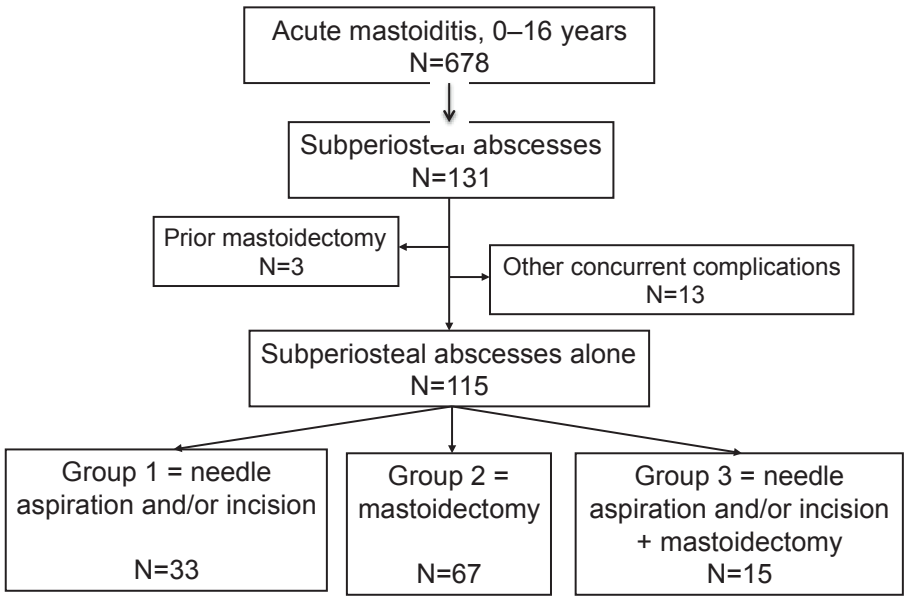

Figure 8:
Flowchart showing the inclusion process in the study on subperiosteal abscesses.

The prospective part of Mastoiditis in Sweden

The prospective study for continued surveillance was designed simultaneously with the retrospective study, and was initiated in 2008. During the period 1993 to 2014, several of the smaller ENT departments in Sweden merged with neighbouring ENT departments, leaving 26 ENT departments in Sweden with inpatient care in 2014. All are participating in the prospective part of the Mastoiditis in Sweden study. The aim of the prospective study is to consecutively include all cases of AM, in patients of all ages, between 2008 and 2017. Agreement to participate in the study, by the patient, but most often by the parent or guardian, grants the investigators permission to study the patients' medical records. The inclusion of each patient depends on clinicians at the participating departments, to remember the study when treating a new patient with AM, and to ask the patient or their parents for consent to

participate. To promote the study, information campaigns are directed towards ENT specialists in Sweden and a website www.helsingborgslasarett.se/mastoidit has been set up to provide easy access to the necessary consent forms. Contact persons at the participating ENT departments also receive regular e-mails reminding them of the study. Despite these measures, some cases are lost, either because they were not asked to participate, or did not give their consent. When investigating a rare condition such as AM it is important to take the loss of cases into consideration, as too general conclusions based on incomplete data could affect the guidelines for treatment of the very common disease AOM. The findings of the retrospective study show that the reporting of diagnosis codes to national registers and registers at the separate ENT departments is poor, revealing an misdiagnosis of 25%[40]. Thus, an analysis of the loss of cases in the prospective study, based on national registers was not considered appropriate. Instead, the medical records of all cases from the participating ENT departments with the ICD-10 codes H700, H701, H709, H742 and H750 were investigated, including those not reported to the national study. An additional ethical review was carried out in 2014 and permission was granted to study these patient records. Parents or guardians of patients fulfilling the diagnostic criteria were sent a letter describing the study and consent forms for retroactive inclusion. A reminder was sent after approximately one month, and if no reply was received, that patient was considered non-consenting. The loss of cases to date at departments where the total number of eligible patients has been verified is approximately 20%. Only the largest departments have been investigated to date, but these cover more than half of the Swedish population.

The interview study

No specific risk factors for AM could be identified in the retrospective study, and in some cases the guidelines for AOM seemed to have been misinterpreted. Both these issues were difficult to evaluate from the medical records alone. By the end of 2014, 242 children aged 0–12 years had been included in the prospective study. An upper age limit of 12 years was used as this corresponds to the upper age limit for watchful waiting in the latest Swedish guidelines on the management of AOM[21]. When the principal investigator and sole interviewer (the present author) received consent from the parent and the medical records of the child with AM, a letter was sent to the parent suggesting an appointment for a telephone interview. In total, 88 appointments were made, and 74 interviews were completed between 2009 and 2014. An extensive questionnaire based on the latest Panel Report from the Ninth International Research Conference on Otitis Media on Risk Factors for AOM[45]was used, including possible risk factors for AOM: perinatal factors, exposure to passive smoking, attending day care and the presence of siblings. 2014 was chosen as the cut-off mainly because it was necessary to evaluate the results in order to plan a future Nordic study on AM. An interview was only arranged if the required consent form and medical records had reached the principal investigator within two months of the diagnosis of AM, ensuring an interview within three months of admission of

the patient. Longer delays were considered inappropriate since the parents may have had difficulties in recalling the episode correctly. Inclusion was thus not randomized, and the cases included may, therefore, not be representative of the typical AM child, which would affect the reliability when evaluating possible risk factors for AM. For this reason, corresponding data were collected from the medical records of the remaining 168 paediatric AM cases included in the prospective part of the Mastoiditis in Sweden study and compared with data from the interview cases.

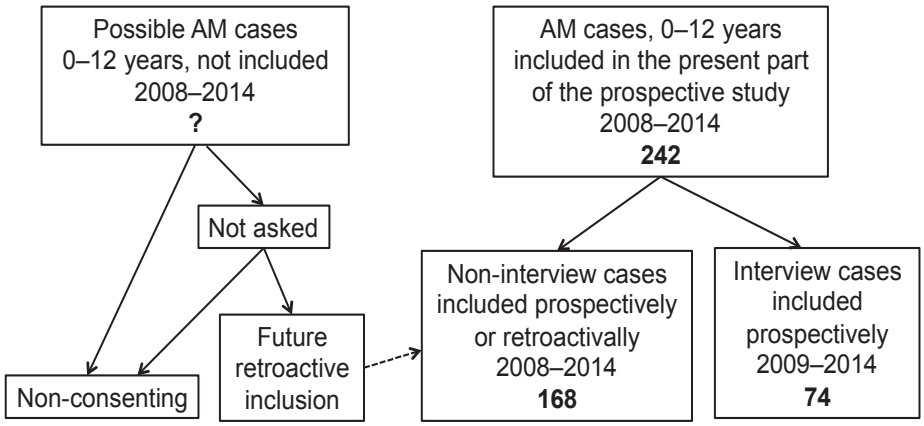

Figure 9:
Flowchart showing the inclusion of cases in the prospective study.

Microbiological tests

Samples for culture in AM are usually retrieved from the nasopharynx (NP) at admission. Carriage of upper airway bacteria is common in the NP in preschool children[46, 47]. Thus, bacteria not responsible for the AOM event that has lead to the current episode of AM can be found in cultures from the NP. For instance, in a toddler it is common to find a mixture of pnc, *Haemophilus influenzae* (Hi) and *Moraxella catarrhalis* (Mc) in NP cultures. In cases of AOM with spontaneous perforation of the eardrum, cultures taken from secretions in the ear canal may show skin bacteria such as *Staphylococcus aureus,* as well as bacteria thriving in a moist environment, such as *Pseudomonas aeruginosa* (Pa), although these may be considered contamination by an opportunist and unlikely to be the causative agent of AOM or AM[23]. For this reason, cultures of samples from the NP and from the ear canal were not considered sufficiently reliable, and only cultures from middle ear fluid (MEF) retrieved after myringotomy and pus from the mastoid cavity or abscesses were reported in the results of both the retrospective and prospective parts

of the study. When a culture from the mastoid cavity tissue or pus from abscesses was not available or negative, the results from the culture of MEF at myringotomy were reported. Blood cultures were seldom performed and in most cases were negative. These were therefore not included.

The bacteria found in cultures with multiple findings were ranked according to virulence. In a few cases, multiple bacteria were found in cultures of pus obtained from the middle ear after myringotomy, but there was a high frequency of negative cultures from MEF. The ranking according to virulence was: GAS, pnc, *Fusobacterium necrophorum,* species of the *mycobacteria,* Hi*, Staphylococcus aureus,* Mc, Pa and miscellaneous species. This ranking system leads to a selection bias in the reports but was based on the findings in previous studies on middle ear infection with cultures performed from NP swabs and in some of the studies, MEF[29, 47-49].

Ten of the participating departments collect samples for culture for further analysis. This procedure was initiated in 2009. One of the most interesting aspects to study is whether the present pneumococcal serotypes are affected by immunisation with pneumococcal conjugate vaccines (PCVs). The vaccine PCV7, covering capsule serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, was officially introduced into the standard Swedish immunisation schedule in 2009, although a few health regions started to use it earlier, in 2008. The vaccine is given at 3, 5 and 12 months of age, free of charge, and the coverage of PCV in the latest national report from the Public Health Agency of Sweden on paediatric immunisation was 97.5%[16]. In 2010, PCV7 was replaced by PCV10 (serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) or PCV13 (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F). Up until 2014, PCV10 was the most commonly used vaccine, but later PCV13 was the most often used, according to sales figures. To ensure that the serotype findings were correlated to the correct type of vaccine, the parents of the children included in the serotype study (Paper 3) were contacted to confirm the type of vaccine given to their child.

When analysing the serotypes in the 18 patients where pnc was the causative microbe, the original samples were analysed at the local microbiology laboratory according to local routines. The isolates were thereafter sent to the Department of Clinical Microbiology, Uppsala University Hospital, for further processing. Pneumococcal isolates were serotyped at the Serum Institute, Copenhagen, Denmark, or in Uppsala, using the polymerase chain reaction (PCR)[50]. This method was slightly modified in that the forward primer for 6A/B was not biotinylated and it was thus not possible to differentiate between serotypes 6A and 6B.

Statistical analyses

In the first study (Paper 1), large groups were available for statistical analysis, and testing for differences between both means and medians was considered appropriate. Pearson's chi-squared test or Fisher's exact test was used to test for homogeneous distribution of qualitative variables. T-tests were also used for quantitative variables to test the equality of means. Equality of medians was tested using the median test. Comparisons were made separately for the younger group, 0–23 months, and the older group, 2–16 years, and for four subgroups of children aged 0–11 months, 12–23 months, 2–7 years and 8–16 years.

The samples sizes in the other studies (Papers 2–4) were relatively small and unevenly distributed. The distribution was evaluated with Shapiro-Wilk's or Kolmogorov-Smirnov's tests. In Paper 3 the sample size was too small for any meaningful statistical analysis. In Papers 2 and 4, non-parametric tests were used for quantitative variables, and the p-value was determined for the medians only, using the Mann-Whitney U-test. Pearson's chi-squared test or Fisher's exact test was used for proportions. The significance level was set at $p < 0.05$. The analyses were performed using SPSS© versions 18 and 22.

Ethical considerations

Both the retrospective and prospective parts of the Mastoiditis in Sweden study were approved by the Ethical Review Board in Lund (H4 143/2007) in accordance with the ethical principles for medical research stated in the Declaration of Helsinki. An additional ethical review was performed in 2014 prior to accessing of medical records for the patients not included in the prospective part of the study. One of the reasons for allowing such access without the patients' or guardians' consent was that patients or parents with incorrect diagnosis codes in the registers might be alarmed by a request for retroactive inclusion in a study on a condition they had never heard of or suffered from. All patient data were recorded in encoded form in databases and access was granted only to the principal investigators. The databases have been registered in accordance with the Swedish Personal Data Act, and approval was obtained from the Swedish Data Protection Authority. A key to the codes is stored at the departments of the principal investigators, and the consent forms and coded medical records are kept in locked storage.

Results

A summary of the main results

This chapter provides the most important results of the studies carried out. Further details can be found in the papers. The findings are commented on in the Discussion.

Paper 1: Acute mastoiditis in children aged 0–16 years – A national study of 678 cases in Sweden comparing different age groups

A total of 678 patients fulfilled the inclusion criteria. The cases were divided into four age groups: 0–11 months, 12–23 months, 2–7 years and 8–16 years of age. Of the children included, 55% were younger than 2 years of age and 69% of these were between 12 and 23 months old. The majority of the children (87%) had previously been healthy. Ten percent had a history of recurrent AOM (rAOM), while 57% had not experienced any previous episode of AOM. The 372 children below 2 years of age were characterised by a lower frequency of prior history of other diseases and ear diseases, and had received antibiotic treatment less often before admission. They also had a shorter duration of symptoms before admission, a shorter duration of hospital stay and lower frequency of complications and mastoidectomies. This group also exhibited a higher incidence of clinical findings and higher C-reactive protein (CRP) levels and white blood cell counts (WBC) than the older children. Pneumococci were found more often in cultures from the youngest children, while cultures from the older children more often exhibited GAS or Pa, or were negative. SAs were found in 20% of all cases. Other extracranial complications were seen in 2%, (facial palsy, postoperative infection, neutropenia, incipient labyrinthitis, torticollis, palsy of the abducens nerve, retrolabyrinthine abscess and persisting perforation of the eardrum), and were found significantly more often in the oldest children (10%). Intracranial complications were seen in a total of 2%, (sinus thrombosis, meningitis, epidural abscess), and were significantly more frequent in the oldest age group (5%). The disease was not lethal in any paediatric case during the period studied.

The younger children showed more rapid progress of symptoms and more distinct retroauricular signs of AM, but had neither more severe AM nor more complications than the older children. The early distinct symptoms of AM are probably the reason why hospital treatment started earlier in the youngest children, which may in turn explain their excellent outcome.

Table 3.
Medical history, symptoms, laboratory findings, treatment and complications in 678 children with acute mastoiditis in different age groups. When data were lacking, the number available is given in the left column. The t-test was used to establish differences between the youngest (0–11 months) and oldest (8–16 years) age groups for which the p-values account. p-values <0.05 indicating statistical significance are given in *italics*

	0–11 months N=114 (17%)	**12–23 months** N=258 (38%)	**2–7 years** N=233 (34%)	**8–16 years** N=73 (11%)	**p-value**	**Total, 0–16 years** N=678 (100%)
Duration of ear symptoms, days (N=661)						
Mean	2.0	2.5	4.4	8.0	*<0.001*	3.7
Median	1.0	2.0	2.0	3.0	*<0.001*	2.0
SD (SE)	2.2 (0.2)	3.3 (0.2)	7.1 (0.5)	12.8 (1.5)		6.5 (0.3)
Retroauricular symptoms:						
Protruding ear	104 (91)	237 (92)	200 (86)	48 (65)	*<0.001*	590 (87)
Retroauricular erythema	102 (90)	235 (91)	195 (84)	55 (75)	*0.001*	587 (87)
Retroauricular pain	37 (33)	108 (42)	141 (61)	51 (70)	*<0.001*	337 (50)
CRP initial value (N=542)						
Mean	93.4	103.7	76.5	64.0	*0.003*	87.8
Median	82.0	93.0	53.5	39.5	*<0.001*	70.0
SD (SE)	58.6 (6.4)	72.5 (5.1)	69.4 (5.0)	59.7 (7.4)		69.4 (3.0)
WBC (N=492)						
Mean	16.6	16.5	14.0	10.7	*<0.001*	14.9
Median	16.4	15.6	13.9	10.9	*<0.001*	14.2
SD (SE)	5.3 (0.7)	8.3 (0.6)	4.8 (0.4)	3.4 (0.4)		6.6 (0.3)
Duration of hospital stay, days (N=677)						
Mean	5.4	5.7	5.7	6.4	*0.03*	5.7
Median	5.0	5.0	5.0	6.0	*0.01*	5.0
SD (SE)	2.9 (0.3)	3.6 (0.2)	3.2 (0.2)	3.2 (0.4)		3.3 (0.2)
Complications, n (%)						
Subperiosteal abscess	23 (20)	45 (17)	46 (20)	19 (26)	0.47	133 (20)
Intracranial	0 (0)	1 (0.4)	7 (3)	4 (5)	*<0.001*	12 (2)
Extracranial	1 (1)	4(2)	3 (1)	7 (10)	*0.001*	15 (2)
Mastoidectomy	17 (15)	52 (20)	62 (27)	29 (40)	*<0.001*	160 (24)

Paper 2: Subperiosteal abscesses in acute mastoiditis in 115 Swedish children

A total of 115 children aged 0–16 years with SA were identified from the retrospective part of the study described in Paper 1. The definition and classification of the groups are given in Subjects and Methods. All patients received intravenous antibiotics and most had undergone myringotomy, but the surgical treatment of the SA differed. The patients were divided into three groups based on the surgical methods used i.e retroauricular needle aspiration and/or incision or mastoidectomy.

Thirty-three children had been treated with minor interventions such as retroauricular needle aspiration and/or incision only (Group 1), while 67 had undergone mastoidectomy (Group 2). The characteristics of the 15 patients in Group 3, which were not compared in the statistical analyses, were similar to those of the remaining 100 patients and are given in Table 4.

Two of the few significant differences found between Groups 1 and 2 were a longer delay between admission and surgery and longer hospital stay in Group 2. More children in Group 1 exhibited retroauricular fluctuation at admission. This difference was almost significant, but difficult to interpret since in some cases the SA developed after admission. A higher, but not statistically significant number of patients in Group 2 suffered from a recurrence of AM.

Table 4.
Comparison between the 115 children aged 0–16 years with AM and SA, divided into three groups according to the surgical treatment of SA. p-values <0.05 indicating statistical significance are given in *italics*

	Group 1 Retroauricular needle aspiration/ incision N=33	**Group 2** Mastoidectomy N=67	**p-value**	**Group 3** Retroauricular needle aspiration/incision and mastoidectomy N=15
Age, months				
Mean	34.5	38.7		49.5
Median	18	25	0.166	48
SD (SE)	40.9 (7.1)	37.6 (4.6)		43.2 (11.1)
Duration of ear symptoms, days				
Mean	2.9	5.0		6.1
Median	2	3	0.060	3
SD (SE)	3.8 (0.7)	10 (14.9)		7.9 (2.0)
Antibiotic treatment prior to admission, n (%)				
	6 (18.2)	26 (38.2)	*0.038*	6 (40.0)
Bacteriological findings, n (%)				
GAS	3 (11.1)	11 (22.4)	*	2 (13.3)
pnc	17 (63.0)	21 (42.9)	*	8 (53.3)
Negative	7 (25.9)	17 (34.7)	0.266*	2 (13.3)
Retroauricular fluctuation noted, n (%)				
	13 (39.4)	14 (20.9)	0.050	1 (6.7)
Time after admission to surgery, (days)				
Mean	0.6	2.0		1.9
Median	0	2	*<0.001*	2
SD (SE)	0.9 (0.2)	1.7 (0.2)		0.9 (0.2)
Duration of hospital stay, days				
Mean	5.7	8.0		6.5
Median	5	8	*0.006*	7
SD (SE)	2.0 (0.4)	4.2 (0.5)		2.2 (0.6)
Recurrent AM, n (%)				
	1 (3.0)	9 (13.4)	0.159	3 (20.0)

*All three culture findings were included in one chi-squared test, and the p-value thus refers to the combination of all three

Paper 3: Distribution of Pneumococcal serotypes in paediatric patients with acute mastoiditis in Sweden

Cultures from paediatric patients, aged 0–12 years with AM were investigated in this study. The samples were collected at ten ENT departments providing cultures for the prospective part of the Mastoiditis in Sweden study. During the period 2009–2013, 51 samples were collected from the ears of paediatric patients, meaning: MEF after myringotomy, pus retrieved at mastoidectomy or, in the case of an SA, samples of pus from the abscess. Pnc was found in 19 of the 51 samples, and it was possible to serotype the bacteria in 18 of these samples. Cultures were were negative in 11 cases, GAS was found in 9 cases, *Fusobacterium necrophorum* in 3 cases and Hi in one case. Miscellaneous findings in the remaining 8 cases consisted of both probable pathogens, i.e. species of the Mycobacteria, 2 cases and *Streptococcus anginosus*, 1 case, as well as less probable pathogens, such as coagulase-negative staphylococci. Mc was not found in any of the cultures.

The results from the 18 serotyped AM cases are given in Table 5. Seven patients were not immunised with PCV, five had received PCV7 and six PCV10. All the vaccinated children were fully immunised, having received all three doses prior to their episode of AM. Pneumococcal serotypes included in the vaccine the patient had received, i.e. vaccine type, (VT), were found in two of the patients immunised with PCV7, serotypes 3 and 18. In the PCV10-immunised patients, VT pnc was found in one case, serotype 6A/B. Serotypes 3 and 19A were the most common findings in all groups. In one child, the isolated 19F serotype showed reduced susceptibility to beta-lactam antibiotics, (MIC = 1.0 mg/l for penicillin G). In all other cases the pnc were fully susceptible.

All patients were otherwise healthy, without prior ear disease or immune disorders. The AOM leading to AM was their first ever in 80 % of the AM patients. In four of the cases the AOM leading to AM had been treated with pcV (in accordance with Swedish guidelines); two patients had finished the five-day course of treatment, one had used it for 3 days and one had only taken a few doses. At admission eight patients received intravenous cefotaxime before myringotomy was performed.

Table 5:
Data on the serotypes found in 18 cases with AM in which Streptococcus pneumoniae was serotyped, including prior PCV immunisation and the origin of culture samples

Year of inclusion	Serotypes found in MEF	Serotypes found in SA	Age at onset of AM, months	oral ab treatment	i.v.ab treatment	Vaccine type causing AM
Not immunised with PCV						
2009	-	3	17	Yes	-	
2009	3	-	13	No	No	
2009	19F	-	11	No	-	
2010	3	-	57	Yes	Yes	
2010	-	3	25	No	Yes	
2011	9V	-	82	No	-	
2012	35F	-	97	No	No	
Immunised with PCV7						
2010	3	-	14	No	No	No
2010	19A	-	16	No	-	No
2010	19F	-	14	Yes	Yes	Yes
2011	3	-	16	No	Yes	No
2011	18	-	19	No	No	Yes
Immunised with PCV10						
2011	19A	-	19	No	Yes	Possible
2012	19A	-	16	No	Yes	Possible
2012	-	15C	15	Yes	Yes	No
2012	6A/B	-	12	No	-	Yes
2013	19A	-	24	No	Yes	Possible
2014	3	-	21	No	No	No

MEF: middle ear fluid; SA: subperiosteal abscess; ab: antibiotic; i.v: intravenous; VT: AM caused by serotype included in the vaccine

Paper 4: Risk factors for paediatric acute mastoiditis in Sweden.

Parents of 74 children completed the telephone interview. It was found that their children were well immunised and had been breastfed for as long as the average Swedish infant. The frequency of rAOM and the frequency of passive smoking also corresponded with that of the average paediatric population. Their background data did not differ from those of the patients whose parents had not been interviewed. Age at the onset of AM was unevenly distributed, with a median of 22.5 months: range 2–144 months. The gender distribution was even. Twelve children had been delivered by Caesarean section, five of which were planned. Three children had been born before gestational week 37; the youngest preterm child was born in week 33+5 and the smallest had a birth weight of 2235 g. In six of the families, one of the parents smoked at least once a day. The median age of the children exposed to passive smoking at the onset of AM was 18 months. The definition of day care attendance required an attendance of 15 hours per week, and was found to apply to 48 children. Thirty of the patients were the firstborn child and 20 children had some history of previous disease, (Table 6). The five children with rAOM one of which had undergone adeno-tonsillectomy, were not treated with grommets at the onset of AM. The duration of preceding general symptoms, most often fever and ear symptoms, was short.

According to the parents, the GP recommended watchful waiting in three cases, despite the fact that the child's symptoms indicated antibiotic treatment according to the treatment guidelines. Two of these children also had retroauricular symptoms of AM at the same consultation, and should have been referred to the nearest ENT department. According to their parents' recollections, another 13 children had retroauricular signs, which in some cases were pointed out by the parent at the consultation, but were overlooked, (Figure 10). The median delay arising from failure to recognise the symptoms of AM was 2 days (range 0–9 days), and 7 of the 15 children in which AM symptoms were overlooked were found to have an SA as a complication of AM.

When the findings of this study were compared with those from the 168 paediatric patients aged 0–12 years whose parents had not been interviewed, few differences were found regarding the severity of symptoms or clinical findings at admission, (Table 7). However, three factors differed significantly between the groups: the general medical condition was more affected in the interview cases, these patients also had a longer hospital stay and, for some unknown reason, bilateral AOM was more common in the interview cases.

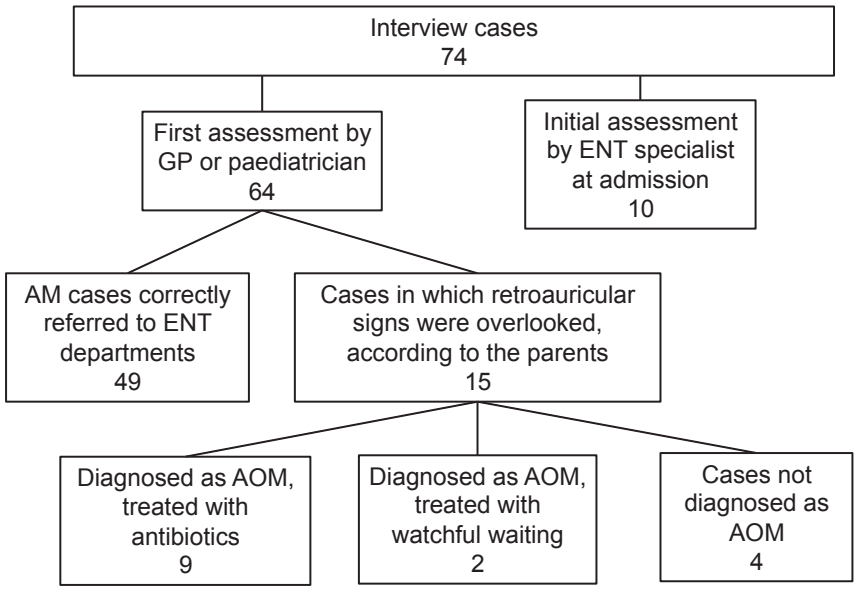

Figure 10:
Flowchart of the initial assessment of the 74 interview cases.

Table 6:
Possible risk factors in the 74 AM cases in the interview group

Attended at:	
Day care, n (%)	48 (65)
Median age at entry, months (range)	16 (12–48)
Median time from entry to onset of AM, months (range)	4 (0–47)
Cared for at home, n (%)	14 (19)
School (>6 years), n (%)	13 (18)
Siblings, n (%)	44 (59)
Exposure to passive smoking, n (%)	6 (8)
Allergies/asthma, n (%)	6 (8)
Recurrent AOM, n (%)	5 (7)
Preterm birth, n (%)	3 (4)
Prior adenotonsillectomy, n (%)	3 (4)
Miscellaneous disease, n (%)	4 (5)

Table 7:
Characteristics and findings of 74 interview cases and 168 non-interview cases, aged 0–12 years, with acute mastoiditis. p-values <0.05 indicating statistical significance are given in *italics*

Characteristic/findings	**Interview group** N=74	**Non-interview group** N=168	**p-value**	**Total** N=242
Median age, months (range)	22.5 (2–144)	25 (1–151)	.581	24
Perforated AOM at admission, n (%)	24 (32)	46 (28)	.446	70 (29)
Bilateral AOM at admission, n (%)	18 (24)	20 (12)	*.017*	38 (16)
Median duration of ear symptoms, days (range)	2 (0–24)	2 (0–35)	.579	2 (0–35)
General condition*, median	2	1	*.012*	1
Complications, n (%)	21 (28)	46 (27)	.877	67 (28)
Days in hospital, median	5	4	*.026*	4

* The general medical condition of the child was stratified according to the NICE recommendations: (1) unaffected, (2) moderately affected and (3) severely affected.

Table 8:
Microbiological results and pneumococcal vaccination in the interview group and non-interview group of 242 children, 0–12 years

Bacterial findings/ Type of PCV	**Interview group** N= 74 n (%)	**Non-interview group** N= 168 n (%)
pnc	21 (28)	44 (26)
GAS	11 (15)	20 (12)
Negative cultures	20 (27)	51 (30)
Miscellaneous findings	9 (12)	35 (21)
Fully or partially immunised with PCV	47 (64)	66 (39)
of which AM was caused by pnc	17/47 (36)	21/66 (32)
Type of PCV received, n=47/66		
PCV7	15 (32)	32 (48)
PCV10	21 (45)	11 (17)
PCV13	11 (23)	23 (35)

Discussion

The national study "Mastoiditis in Sweden", which formed the basis for the research presented in this thesis, gives a good picture of Swedish paediatric patients suffering from AM. The different ways in which AM symptoms are expressed and their development in different age groups are thoroughly described in Paper 1. The observation in a previous study[3] that mastoidectomy was performed less often during the later years of the study, initiated the evaluation of different surgical methods for treating SA (Paper 2). Possible effects of the recently introduced immunisation against pneumococci were investigated in the third study (Paper 3). Finally, the effects of the altered guidelines on AOM treatment were explored in an attempt to identify risk factors for AM (Paper 4).

The AM child

What characterises a typical child with AM in Sweden today? As expected AM is most common in children between one and two years of age, which is the age group in which AOM is most prevalent. This is also a period during which the child's immune system is still immature, breastfeeding is usually terminated and the child thus no longer is given maternal antibodies. Most Swedish children also enter municipal day care between the ages of one and two. The resulting exposure to a multitude of upper airway microbes often causes an increase in the number of URTIs. The question of whether the results of this exposure is more adverse in children coming from naive environments, for instance, the firstborn child, not exposed to other infected children, remains unanswered. The finding that AM occurs predominantly in children of preschool age is in agreement with other studies, although there are some variations[8, 11, 31, 51]. Intracranial complications were found to be more common in children older than seven years (Paper 1) but this was not found in other studies on complicated AM, although it should be borne in mind that those studies included considerably fewer cases[23, 52-54]. From the Swedish perspective, it does not appear to be more dangerous to have AM when very young than at school age. This is probably because there is access to good health care, and the incidence of antibiotic resistance is still reasonably low in Sweden.

Possible reasons for age-dependant differences may be that the youngest children exhibit more apparent retroauricular signs early in the course of the infection. The onset of the disease in these children was also very rapid, in contrast to the previously held common opinion that AM develops slowly from insufficiently treated AOM, but in agreement with the findings of other studies[8, 23, 55]. Many parents recounted how they were able to watch the progress of their child's retroauricular symptoms over a few hours. Rapid onset of AM has also been described in a study on AM in infants based on the retrospective Swedish data[42]. Older children are more often diagnosed as having AOM without any obvious retroauricular signs at onset, and are treated with antibiotics. This may lead to a delay in the diagnosis of mastoiditis allowing the bacteria longer time to spread or cause abscesses[56, 57]. Apart from being young children, no other specific risk factors for AM were found in the present studies. Nevertheless, other factors are important and will be discussed below.

Definitions and study design

The definitions and treatment of AM differ throughout the world. Studying such a small group of patients, knowing that the results might affect the guidelines for treatment of AOM in a very large group of children, requires very strict definitions of both AM and AOM. In many studies on AM, the inclusion criteria for AM are not given, which makes reliable comparisons between studies difficult. In some studies the definitions are very strict, for instance, requiring the signs of an SA, possibly leading to an underestimation of the number of AM. In contrast, when the criteria are too broad, overestimation may occur. The tradition in Sweden that all cases of AM, regardless the severity, are cared for at an ENT department, makes it easier to study AM. In other countries, less severe cases responding to antibiotic treatment are treated by paediatricians who refer severe cases in need of surgery to ENT specialists. In these parts of the world, ENT specialists are exposed to bias by encountering mainly severely ill children with AM. In Sweden, both severe and mild cases of AM are treated at ENT departments throughout the whole course of events, from admission to discharge. Most ENT specialists have treated cases of AM, but their opinions as to what characterises AM and its clinical course may be influenced by the fact that very few cases will be treated at a small department. Differences were found between the Swedish departments regarding the ICD codes used, as mentioned in subjects and methods. Misdiagnosis and double reporting of identic cases can be identified and removed by studying the medical records, providing a more reliable way of evaluating the true incidence in a population. Also, to evaluate the true incidence requires a well defined population as concluded in recent studies[27, 58]. Studies based on registers, sometimes without a defined population often report a falsely high incidence.

AM is a rare condition, the number of paediatric cases in Sweden varying between 20 and 60 per year during the period 1993–2007[3] (Figure 11). This large annual variation must be taken into consideration when performing studies on AM since large normal variations in incidence over a short period of time may be misjudged as a true change of the incidence. This probably explains some reports on rapidly shifting incidence.

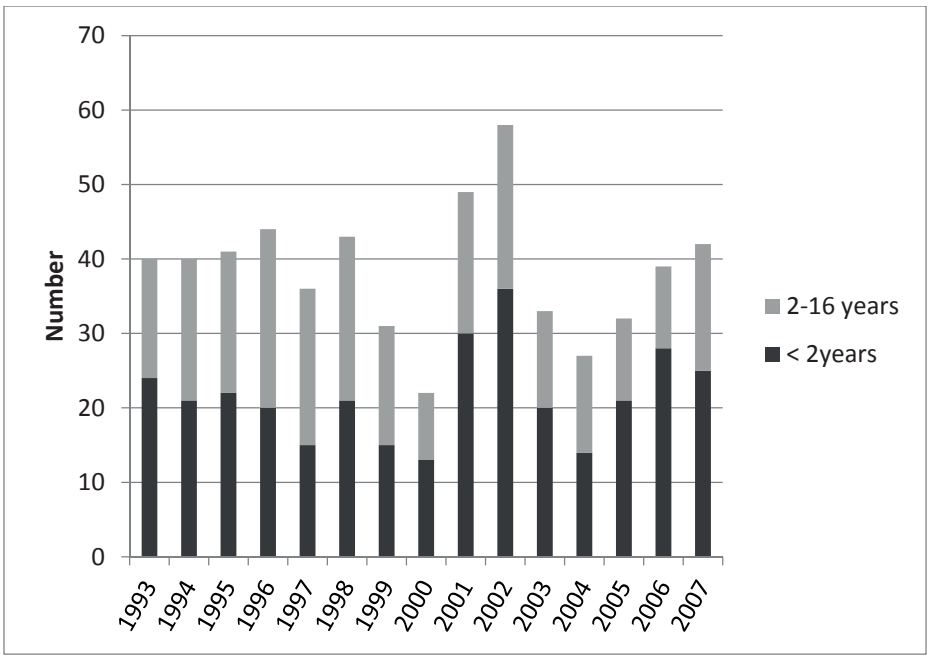

Figure 11:
The number of AM cases per year in younger and older children in Sweden from 1993 to 2007 (from[3])

The study design in Papers 1 and 2 was strictly retrospective and descriptive. In Papers 3 and 4 the design was intended to be prospective, but can at best be considered semi-prospective. All patients were, for obvious reasons, included after the onset of AM, i.e. retrospectively. However, in some cases culture samples were saved for further analysis and in others an extended background story was obtained through telephone interviews with the parents. The study design did not affect the treatment of the children, but followed the routines of the participating departments. It is, however, possible though that reports on the results of the present studies and previous studies have affected routines over the seven years covered in this thesis. The findings of these studies can help in planning future studies on, for instance, diagnostic methods, surgical techniques, antibiotic treatment, follow-up and long-term consequences.

In order to decrease the risk of overdiagnosis at least two retroauricular findings were required in the definition of AM in children in the Mastoiditis in Sweden study, although only one was required in many earlier studies[37]. When reassessing the medical records, 3% of the children were excluded due to too few retroauricular signs[40].

The relationship between AOM and AM in the definition and diagnostic methods used to establish an AOM may cause bias. During the workshops that were held when preparing the Swedish guidelines on the treatment of AOM, the annual incidence of AOM in 2000 was estimated to be 500,000, while the estimate in 2010 was less than 200,000 cases[21]. This apparent considerable reduction in the annual incidence clearly shows the effects of changing the criteria for the diagnosis of AOM, and mainly reflects a massive overdiagnosis before the diagnostic criteria were changed from only requiring a red eardrum, to requiring a bulging and immobile eardrum. The guidelines for treating AOM clearly state that watchful waiting can only be applied after the diagnosis of AOM has been confirmed. This requires an examination by a physician, most often a GP. As earlier mentioned, ENT specialists are more skilled in assessing the eardrum in young children and the diagnosis of AOM by GPs probably caused some overdiagnosis in the estimated incidence of AOM in 2010. On the other hand, the guidelines are sometimes misinterpreted and the parents are advised to apply the watchful waiting at home for a couple of days before their children are given an appointment to see the GP. In such cases, children with self-limiting AOM will never reach the national ICD registers, thus leading to underdiagnosis. Very few studies have been carried out on the validity of the diagnosis of AOM, however, such studies are of great value and interest. From this aspect it must have been easier to be Dr House who only included cases of AOM with spontaneous perforation of the eardrum draining for more than three days in his study[15].

Surgical or medical disease?

Reports of increasing resistance of bacteria to antibiotics are growing more frequent[17]. This may lead to an increase in further complications of AM, and even mortality, due to meningitis, as in the pre-antibiotic era. It has been reported in a study carried out in Spain, where antibiotic resistance is a serious problem[22], that there has been an increase in the incidence of AM, as well as an increase in the need for surgical treatment. The increase in surgical treatment was mainly found in the use of myringotomy to obtain samples for cultures in order to ensure that the appropriate antimicrobial treatment was given, but the incidence of mastoidectomy also increased. In the first study on the retrospective part of the Mastoiditis in Sweden study[3], no increase in complications was seen. Indeed, a statistically non-significant trend was found over the 15 years studied towards performing

mastoidectomy more seldom, and a longer time after admission. It appears that ENT specialists, preferred to monitor the effects of intravenous antibiotic treatment, as suggested by other authors[11, 59]. Treatment strategies in uncomplicated cases of AM differed not only between departments but also within departments, possibly due to the lack of national guidelines on the management of AM. Another explanation might be that the kind of treatment given may also have depended on the competence and surgical skills of the ENT specialist on duty.

These findings led to the investigation of the treatment of paediatric subperiosteal abscesses (Paper 2). The surgical treatment of SAs in Sweden varied between departments and between ENT specialists at the same department. When comparing mastoidectomy with needle aspiration and/or incision of the SA, the outcome was found to be good regardless of the method used which is in agreement with other studies[60, 61]. However, the hospital stay was longer for children treated with mastoidectomy. It is both an advantage and a disadvantage of retrospective studies that the study does not affect the choice of treatment, thus enabling pseudo-randomisation that may arise from the different traditions of treatment among the ENT departments participating in the study. One weakness of the retrospective study design is that it is very difficult to evaluate possible differences in the severity of the SA from the information contained in the medical records. Surgeons in favour of mastoidectomy may claim that the patients successfully treated without mastoidectomy were less severely ill, although the parameters investigated did not indicate this to be the case. In another study on the treatment of SA it was concluded that mastoidectomy should be performed instead of needle aspiration in less than 5 days from admission if AM case did not improve within 5 days of admission[62]. However, the results of that study cannot be compared to the findings in Paper 2 since the median duration of hospital stay was shorter than five days in Paper 2. Nevertheless, early intervention soon after admission, with at least needle aspiration simultaneously as the commonly performed myringotomy seemed to reduce the period of hospitalisation, as well as providing samples for culture, to identifying the bacteria causing AM.

In the case of severe complications and in very ill children, a mastoidectomy may be the only life-saving treatment. Very few severe complications were found in the retrospective study, and most children recovered from AM fully and rapidly following the treatment with antibiotics and most often myringotomy. The most difficult problem facing the clinician is to decide when a paediatric patient is in need of surgical treatment rather than medical treatment. There is no clear boundary between surgical and medical treatment and it is easy to understand the preference of a surgeon to perform surgical treatment to avoid risking sequelae or even death in young children. The confirmation bias arising in seeing very ill children with AM complications must be recognized and respected. However, the negative effects of performing an unnecessary mastoidectomy when medical treatment would have

been sufficient must also be considered. Removing cells that form part of an intricate aerated system by mastoidectomy may lead to loss of a function not well understood. Despite this, most patients seem to be unaffected by such changes in their mastoid anatomy. Unfortunately, mastoidectomy does not protect the patient from new episodes of AM.

It is difficult to study the pathogenesis of recurrent AM due to the very few cases, and the even fewer publications on the topic. In a previous study, it was found that the majority of patients suffering from recurrent AM had previously undergone mastoidectomy[41]. One reason for this could be that the surgeon did not perform a sufficiently radical mastoidectomy on the first occasion, but this is probably not the only explanation. Treatment of children with AM children and SA as the only complication with a less invasive surgical method than mastoidectomy seemed not to be disadvantageous (Paper 2). At least it was apparent that mastoidectomy was not a superior treatment in such cases. Further studies on the need for and timing of mastoidectomy are required. As long as antibiotic treatment can cure most cases of AM, the trend seen in all surgical specialties towards less invasive surgery will probably also be applicable in the treatment of AM.

Bacteria and antibiotic resistance

An important microbiological aspect of AM is changes in the virulence of microbes. In the preantibiotic era, haemolytic streptococci, probably equivalent to GAS, were the most predominant cause of AOM complications in the USA, as well as the remaining western world[15, 28]. The prevalence of GAS in AOM today is much lower, probably due to a change in the definition of AOM, but possibly also due to a lower carriage rate of GAS[29, 63]. The virulence of these "killer bacteria" may also have altered and the incidence of invasive infections caused by GAS varies over time[64, 65]. It is well known that some subclasses of GAS are more invasive than others but the problem is that differences in the virulence of GAS are not distinguishable in the early stages of the infections they cause. The fact that as many as 54% of the complicated AOM cases in the study by House, recovered without antibiotics shows how important individual factors are to fight an infection. In the studies performed in the Mastoiditis in Sweden study, pnc and GAS were found more often in cultures from MEF than Hi and Mc as well as many other studies on AM[11, 23, 29, 31]. This implies that the Hi and Mc found in Swedish patients are less invasive in complicated ear infections. Findings of multiple pathogens in NP cultures can mislead the physician when choosing the appropriate antibiotic for the treatment of AOM. In Sweden, the bacteria most often responsible for AM, pnc and GAS are still largely susceptible to beta-lactam antibiotics.

Due to the ranking of the probable pathogens in the Mastoiditis in Sweden study, the bacterial findings in NP or cultures from pus in the ear canal are not presented in this thesis. Many of the cultures from the ear canal showed Pa, which is often isolated from patients with persistent otorrhea and considered to be contamination[8, 23] although some authors consider it an important and probable causative pathogen[10]. In rare cases Pa causes severe osteitis of the temporal bone, malignant external otitis[66], and might not be completely ruled out as a possible pathogen in AM. On the other hand, malignant external otitis predominantly affects patients predisposed to infections, i.e. diabetics and those whose immune system is compromised in other ways. This category of patients is unusual in paediatric AM in Sweden and findings of Pa are most likely not representing the causative agent of AM. Data from cultures in the Mastoiditis in Sweden study, taken from the NP and ear canal can easily be compared with the already presented in Papers 1 and 3 in future studies, contributing to our knowledge on how culture findings in AM should be interpreted.

Since 1996, a slow but steady increase in the antibiotic resistance of pnc, in terms of reduced susceptibility to beta-lactam antibiotics was noted. In 2004, 6% of the pnc cultured from URTI had a reduced susceptibility to beta-lactam antibiotics, and an increase was predicted[67]. The introduction of treatment guidelines advocating the restrictive use of antibiotics for AOM in Sweden was deemed necessary and introduced in 2000, despite the fact that the problem in Sweden was rather small compared with international levels. The effect of the reduction in the prescription of antibiotics that followed, seems to be positive[68], but the figures on pnc showing decreased susceptibility to antibiotics are difficult to interpret and are probably affected by other factors than the reduction of antibiotic prescriptions[69]. The incidence of AM in Sweden has not increased after the introduction of these guidelines, indicating that they offer a judicious way of dealing with the problem of antibiotic resistance.

Many children, especially in the older age groups, (54% of the children aged 8–16 years) had received antibiotics to treat the AOM that later developed into AM. Most had received between one and four doses but this finding show that antibiotic treatment of AOM cannot always prevent AM which is consistent with earlier results[70].

The pneumococcal conjugate vaccine

Another factor affecting AOM was the introduction of immunisation using PCV. The primary aim of PCV was to reduce the burden of invasive pneumococcal disease (IPD), which has been successful. The vaccines were designed to cover the serotypes most commonly found in IPD[71, 72] but were also found to have a positive,

although rather modest, effect on the frequency of AOM which might be of value in the children affected by severe AOM. Such an effect was considered very difficult to evaluate by Taylor et al[73]. as many other factors affect the incidence of AOM. It was found in a double-blind, placebo-controlled study on PCV in Finland[74], that the prevalence of both AOM and the serotypes included in the vaccine that could cause AOM in the immunised children decreased. These findings have led to expectations that the burden of AOM can be significantly reduced, by using a broad PCV. In the USA, PCV7 was introduced in their standard immunisation schedule in the year 2000, but it was not introduced in Sweden until 2009, nine years after the introduction of watchful waiting.

Within a few years of the introduction of PCV7, serotypes not included in PCV7 emerged in both IPD and AOM, for instance, the serotypes 19A[75]. This serotype is well known to develop resistance to several antibiotics. At that time, IPD was continuously at a lower level than before the introduction of PCV7, but it was reported that some cases of meningitis in infants had become more difficult to treat as they were caused by multi-resistant non-vaccine serotypes[76]. This promoted the development and change to broader PCV, including the newly emerged serotypes but unfortunately a similar serotype shift in IPD after introduction of PCV 13 recently has been reported[77]. The shift in serotypes to previously uncommon pneumococcal serotypes in IPD has also been observed in AOM and AM[78]. The later developed PCV10 was shown to provide more cross-protection against 19A than PCV7[79], although cross-protection had been expected for PCV7. This is the reason that some cases in Paper 3 are categorised as having a possible protection against their causative serotype of AM. A report from southern Israel shows that PCV13 has, both decreased the overall incidence of AOM and near eliminated the serotypes included in PCV13 in MEF from complex AOM (i.e. recurrent, non-responding), children who carry a great deal of the burden of AOM[80]. Findings in NP cultures from PCV13 immunised children with AOM also show a decrease of serotypes included in the vaccine but in all studies the presence of serotypes 11A and 15 are noticed[81, 82].These serotypes are prone to develop multi-resistance and an emergence of them in severe pneumococcal infections may be unfortunate. The overall incidence of pneumococcal AOM decreased in all studies but the authors conclude that surveillance must continue to study the long-term effects of PCV13.

Another aspect of multi-resistant serotypes beautifully reviewed by Song[83] is that these had been increasing in countries with an excessive use of antibiotics, already before the introduction of PCV. To develop antibiotic resistance, bacteria must be exposed to it, and consequently serotypes commonly carried in the NP of children are the most likely to show resistance. The emergence of multi-resistant serotypes reported in studies on the effects of PCV could thus partly be due to the development of multi-resistant serotypes provoked by the overuse of antibiotics in these countries. Also, emerging serotypes not included in the PCV, due to the eradication

of VTs, are selected to a higher exposure to antibiotics and possibly develop multi-resistance. Thus the reduction in virulent serotypes seen as an effect of PCV on serotype selection may lead to an increase in less common but just as aggressive serotypes by giving non-vaccine serotypes more scope to develop. It would be interesting to compare serotype shifts in complicated AOM between countries with high and low levels of multi-resistance in order to test that hypothesis.

Providing protection against Hi and possibly even Mc by vaccination has also been discussed and PCV10 seems to offer some protection due to its conjugation to protein D from NTHi[84]. The introduction of PCV may well have paved the way for other emerging pnc serotypes but also for other bacteria. The findings of an increasing frequency in NTHi in the NP and MEF from PCV7 immunised children with rAOM in Australia[85], may imply that such a development has already begun. On the other hand, a severe case of AM due to NTHi in a child not immunised with PCV was reported from Israel in 2011 and in that study the authors meant that an emergence of NTHi may be related to the very successful immunisation against the extremely aggressive Hi capsule type b (Hib)[86]. Time might tell what impact different vaccines have on upper airway pathogens.

In the present work (Paper 3), it was found that children in Sweden fully immunised with PCV7 or PCV10 developed AM owing to serotypes included in the vaccines they had received. It was also found in Paper 4, that children immunised with PCV13 developed AM, but no serotyping of pnc was performed in this study (Table 8 in Results). The results of a Greek study[87] as well as a study from the USA[88] are similar to the findings presented in Paper 3, but the conclusions were completely different. While the overly optimistic belief in vaccination against the most often self-limiting infection AOM was questioned in the present work, the other authors maintained that broadening the vaccines was necessary in order to avoid complicated AOM. It is possible that the timing of PCV introduction and the introduction of watchful waiting in cases of AOM affects opinions on the necessity and capacity of PCV in different countries. In the USA and Greece the concept of watchful waiting was introduced after PCV, and it may be that PCV was considered a prerequisite for introducing the restrictive use of antibiotics in these countries. Without doubt, the PCVs have saved lives and spared many children the suffering from long-term sequelae encountered by IPD. Nevertheless, the fact that the vaccines soon after introduction needed improvement due to the serotype shift they likely cause, must be acknowledged. No one knows what the long-term effects of using very broad vaccines on as well pnc as other bacteria might be.

Possible additional risk factors

The relation between AOM treatment guidelines and AM were further investigated in Paper 4. All guidelines have exclusion criteria based on supposed risk factors although these vary between countries. We tried to identify possible additional risk factors for AM, as well as investigating whether the guidelines were followed, by interviewing parents of children with AM. No apparent unknown risk factors had been found in an earlier study (Paper 1). No new risk factors could be identified, but according to the parents as many as 20% of the children had exhibited retroauricular signs of AM that were overlooked at the initial examination. This indicates a lack of knowledge on AOM complications, possibly caused by a de-medicalization of the AOM concept[89]. Children with AM are seldom severely affected in the early stages, which is one of the pitfalls in diagnosing AM. To a physician, their general condition, especially after the intake of antipyretic analgesics, may not differ from that of many other children with a common cold or uncomplicated AOM. The cardinal signs are retroauricular findings, and most of the children with such signs were immediately referred to the nearest ENT department. The failure to note signs of AM is very worrying and must be remedied by further training of the clinicians who examine children with suspected AOM.

The lower age limit of one year in the Swedish guidelines for AOM can be questioned. This age limit differs between countries and sometimes no lower age limit is set[90, 91]. It is seldom possible to apply watchful waiting in the case of AOM preceding AM in the youngest children, since many children under one year of age present with signs of AM simultaneously with the diagnosis of AOM. This rapid onset of full symptomatology of complicated AOM facilitates correct diagnosis, and the youngest children with AM are seldom eligible for different AOM treatment choices. This may speak in favour of lowering the age limit for watchful waiting in uncomplicated AOM.

The other exclusion criteria for watchful waiting cannot easily be evaluated, since AM patients with, for example cochlear implants or a history of rAOM, are included in Mastoiditis in Sweden together with previously AOM naive children, in both parts of the study. Children with rAOM, cleft palates, syndromes or cochlear implants shall be excluded from watchful waiting and are to be offered antibiotic treatment when AOM is diagnosed. Thus, children classified as risk patients have most likely been treated with antibiotics, which may have prevented the development of AM. They may thus also be underrepresented in the AM study compared to a hypothetic case in which watchful waiting is applied in all children regardless of other conditions. The possible risk patients were certainly not overrepresented, indicating that the groups excluded from watchful waiting in the AOM guidelines seem to be appropriate. On the other hand, one must consider how the risk groups in the AOM guidelines were identified. It is possible that the

presumed risk patients in the exclusion groups were so few that reliable comparisons were impossible. The fact that the studies described in this thesis were mainly performed on patients included after implementing the AOM guidelines makes it impossible to provide any answers on whether the exclusion criteria were relevant, since the basic data on the AM patients included are affected by the AOM guidelines. Hardly any children with syndromes or other predisposing factors were found. Some children with predisposing factors were initially included, but were later excluded when underlying conditions, i.e. cholesteatoma were discovered. The children included in the Mastoiditis in Sweden study seemed to have been very healthy prior to their episode of AM and the great majority of the cases recovered fully.

Conclusions

The studies presented in this thesis have contributed to the knowledge on paediatric AM in Sweden today. The findings can contribute to national treatment guidelines on AOM as well as AM. The main conclusions of this work are presented below.

- Paediatric AM is, as expected a disease affecting young children aged below two years, and the symptomatology and complication rate differ in children of different ages.

- Treatment of SA as the sole complication of AM with needle aspiration/ incision as compared to mastoidectomy had no adverse effects. The need for early collection of reliable samples for culture cannot be overemphasized.

- Immunisation with PCV does not offer a complete protection against AM, even in fully immunised children.

- No overlooked possible risk factors for AM could be identified. Since AOM seems to have become a harmless condition in the minds of patients and some medical practitioners, knowledge concerning the clinical signs of AM in children must be improved. The AOM treatment guidelines appear to be sufficient, and the greatest challenge lies in detecting complications arising from AOM.

Populärvetenskaplig sammanfattning på svenska

Bakgrund

Man kan fråga sig varför en hel avhandling handlar om något så ovanligt som akut mastoiditit hos barn. Det är den vanligaste komplikationen till öroninflammation men drabbar bara 20-60 barn per år i Sverige. Öroninflammation däremot är en infektion som är så vanlig att nästan alla har haft åtminstone en sådan som barn. I Sverige diagnostiseras upp emot 200 000 fall med öroninflammation per år. Akut mastoidit uppstår när infektionen sprider sig utanför mellanörat och vidare till mastoidbenet bakom örat. Därifrån kan den sedan spridas vidare till, exempelvis, hjärnan som ligger rakt ovanför örat. Utan behandling kan akut mastoidit i värsta fall leda till döden vilket var vanligt innan antibiotika började användas i mitten av 1930-talet. I utvecklingsländer med dålig tillgång till hälsovård och läkemedel är situationen tyvärr densamma nu som då. Skälet till att studera akut mastoidit är alltså sambandet mellan den extremt vanliga barnsjukdomen och dess farliga komplikation.

De små barnens öroninflammationer är oftast självläkande men gör ont. Tidigare behandlades alla öroninflammationer med antibiotika för att bota infektionen och för att skydda mot fruktade komplikationer. Öroninflammation är fortfarande den infektion hos barn som genererar flest recept på antibiotika vid läkarbesök. Detta, sammantaget med att många andra lindriga infektioner antibiotikabehandlades, bidrog till en enorm överanvändning av antibiotika. Det kan leda till att bakterier utvecklar resistens mot antibiotika. När resistensutvecklingen får fäste bland bakterierna i ett samhälle så kommer antibiotika som tidigare hjälpt vid behandlingskrävande infektioner att tappa sin effekt och man måste gång på gång byta till “starkare” antibiotika. Utvecklingen av antibiotikaresistens har tyvärr gått ganska långt och det kommer nu rapporter om superbakterier som överlever alla typer av antibiotika. I värsta fall når vi ett läge med total avsaknad av fungerande antibiotika. Då kommer sannolikt såväl barn som vuxna återigen att dö till följd av infektioner som idag oftast är lättbehandlade, till exempel lunginflammation och öroninflammation.

Vad gör vi då för att hindra denna utveckling? Om man kan minska antibiotikatrycket i samhället så kan man om inte stoppa resistensutvecklingen, så åtminstone bromsa den. Vid öroninflammation skulle det vara möjligt att minska konsumtionen av antibiotika i lämpliga fall. Flera studier har visat att obehandlad öroninflammation varken orsakar mer öronvärk eller mer långvariga besvär hos barn. I Holland införde man antibiotikarestriktiva riktlinjer vid behandling av öroninflammation redan på 1980-talet och nu används liknande världen över. I Sverige infördes sådana, otitkonsensus, år 2000, och de uppdaterades år 2010. Sammanfattningsvis kan man vid öroninflammation hos barn mellan 1 till 12 års ålder avstå från antibiotika om barnet är friskt i övrigt och har god effekt av smärtstillande och febernedsättande läkemedel mot sina öronbesvär. Om symptomen inte gått över efter så kallad "aktiv exspektans" under 2–3 dagar eller om symptomen förvärras ska barnet antibiotikabehandlas. Barn som är yngre än 1 år och barn äldre än 12 år samt vuxna ska alltid antibiotikabehandlas.

Otitkonsensus ifrågasattes kraftigt av bland andra öronläkare, vilka nästan bara behandlar svåra fall av öroninflammation. Man fruktade att komplikationerna till öroninflammation skulle öka och bli svårare. För att kunna utvärdera om en ändrad behandlingsrutin är skadlig för de individer som påverkas är det klokt att studera komplikationen, alltså akut mastoidit. Det blev upprinnelsen till "Mastoidit i Sverige"-studien, som lett fram till bland annat detta avhandlingsarbete. Mastoidit i Sverige-studien består av en retrospektiv del där data om alla fall med akut mastoidit i Sverige mellan 1993–2007 samlats in. Sedan 2008 samlas data från alla nyinsjuknade fall av akut mastoidit i Sverige in och denna prospektiva del av studien pågår fortfarande. Genom dessa studier har vi fått en mycket bra bild av barnen som drabbats av akut mastoidit i Sverige samt vilka bakterier som orsakar deras infektion. Vi vet nu betydligt mer om hur de handläggs och vilka för- och nackdelar som finns vid olika behandlingstyper. Det behövs för att kunna utvärdera kopplingarna mellan förändrade förhållanden kring öroninflammation.

Artikel 1

Som väntat drabbar en komplikation till en barnsjukdom, barn. I Sverige är de drabbade barnen oftast yngre än 7 år och de flesta insjuknar mellan 1 och 2 års ålder. Med tidig intravenös behandling och så kallad paracentes botades nästan alla barn inom några dagar och blev helt återställda. Något oväntat var barnen som drabbades av akut mastoidit oftast mycket friska i övrigt och insjuknandet gick väldigt fort, särskilt hos de riktigt små barnen under två års ålder. De barnen kom ofta till läkare på grund av att en förälder upptäckt att barnet blivit rött bakom örat och att örat börjat stå ut, de klassiska tecknen på mastoidit. Det man sökte sjukvård för var alltså inte att barnet hade öronvärk och att man misstänkte öroninflammation utan för att barnet hade tecken på en komplikation. Många av barnen, särskilt de som var äldre än 7 år, hade hunnit fått antibiotikabehandling mot öroninflammation vilket inte skyddade dem mot att denna öroninflammation utvecklades till mastoidit.

Artikel 2

I denna studie jämfördes olika kirurgiska behandlingstyper av den vanligaste komplikationen till akut mastoidit, subperiosteal abscess, en ytlig böldutveckling över mastoidbenet. I Sverige verkar det inte vara någon nackdel att tömma bölden med enkla metoder som punktion och/eller incision jämfört med att göra en så kallad uppmejsling (mastoidektomi), ett större kirurgiskt ingrepp där man avlägsnar de sjuka delarna av mastoidbenet. Vårdtiden var kortare för de patienter där man i ett tidigt skede tömde bölden med ett mindre ingrepp och man kunde få bättre prover till odling med den metoden, vilket är viktigt för att kunna rikta in antibiotikabehandlingen.

Artikel 3

De bakterier som oftast orsakar såväl öroninflammation som akut mastoidit kallas pneumokocker. Sedan 2009 erbjuds alla barn i Sverige vaccination mot pneumokocker för att skydda mot livshotande pneumokockinfektioner som hjärnhinneinflammation och blodförgiftning. I vaccinet ingår de serotyper av pneumokocker som brukar orsaka de mest aggresssiva infektionerna. I denna studie visade vi att några barn insjuknade i akut mastoidit som orsakats även av den typ av pneumokock som de blivit vaccinerade mot. Pneumokockvaccination ger alltså inte fullt skydd mot komplicerade öroninflammationer.

Artikel 4

En intervjustudie gjordes för att undersöka om det fanns några särskilda faktorer som kunde öka risken för att utveckla akut mastoidit. Inga tidigare okända sådana gick att hitta. Samtidigt försökte vi utvärdera om otitkonsensus hade påverkat handläggningen före inläggning på sjukhus. De läkare som först bedömer barn med mastoiditsymptom, vanligtvis en specialist i allmänmedicin, kände oftast igen tecknen och remitterade genast in patienterna för fortsatt behandling. Tyvärr visade det sig att hos en femtedel av de 74 barn som ingick i intervjustudien uppgav föräldrarna att läkaren missat barnets tecken på mastoidit vid första besöket och därmed fördröjt behandling. Det kan tyda på att man numera ser öroninflammation som en ofarlig åkomma som inte behöver behandlas och att man därmed inte är tillräckligt uppmärksam på de ovanliga men otäcka farorna med den.

Sammanfattning

Studierna i denna avhandling har tillfört värdefull kunskap om akut mastoidit hos barn i Sverige. Denna behövs för att vi i fortsättningen ska kunna utvärdera och förbättra handläggningen av den infektion som de flesta av oss upplevt i barnaåren, öroninflammation. Den behandling som används vid akut mastoidit fungerar bra om barnen får hjälp tidigt i förloppet. Vikten av att behandlande läkare är uppmärksamma på de tidiga tecknen av en svår infektion måste understrykas liksom behovet att vara aktiv vid exspektans vid öroninflammation.

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Paper I

Paper II

Paper III

Paper IV