MIKKO KOTIKOSKI

Acute Myringitis in Children less than Two Years of Age

■

ACADEMIC DISSERTATION

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for public discussion in the small auditorium of Building K,
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ACADEMIC DISSERTATION

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2. ABSTRACT

Acute myringitis is an inflammation of the tympanic membrane that occurs alone or in association with external otitis or acute otitis media (AOM). There are two different types of acute myringitis: bullous and hemorrhagic myringitis. In bullous myringitis one or more blisters are detected on the tympanic membrane. In hemorrhagic myringitis very strong redness is seen on the tympanic membrane.

Although acute myringitis is not a rare disease, the studies dealing with acute myringitis are sparse. The etiology of acute myringitis is unknown. In some acknowledged textbooks acute myringitis is considered a viral infection or an infection caused by *Mycoplasma pneumoniae*, while in others acute myringitis is considered a bacterial infection and the blisters are considered only a manifestation of AOM. The controversial opinions on the etiology of acute myringitis made us to conduct the present study.

In the present study we diagnosed acute bullous myringitis in 82 children. Middle ear fluid (MEF) developed in 97% of cases with bullous myringitis during the course of the disease. Bacteriological pathogens (*S. pneumoniae, H. influenzae* and *M. catarrhalis*) and respiratory viruses detected from the MEF were similar in acute myringitis and AOM. Also the viral detections of nasopharyngeal aspirate (NPA) of acute myringitis were similar to AOM. A bacterial pathogen was detected in 76% of cases of acute myringitis and therefore antibiotics should be recommended for treatment.

The incidence rate of acute myringitis has not been reported previously. In the present study acute bullous myringitis was diagnosed in 6% of children less than two years old during a one-year follow-up. Therefore, it can be estimated that there are about 6400 children under two years of age with bullous myringitis in Finland per year.

The conclusion of our study is that acute bullous myringitis is a severe form of AOM. The etiology is similar to AOM, but the symptoms are more severe and the resolution of MEF is slower than in AOM. In addition, acute bullous myringitis increases the risk for recurrent AOM.

3. TIIVISTELMÄ

Äkillinen tärykalvotulehdus eli akuutti myringiitti tarkoittaa sairautta, jossa tärykalvolla on inflammaatio. Myringiitti voi esiintyä joko yksinään tai korvakäytävätulehduksen tai välikorvatulehduksen yhteydessä. Tärykalvotulehduksia on kahta eri tyyppiä; bulloosi (rakkulainen) ja hemoraginen (verestävä) myringiitti. Bulloosissa myringiitissä tärykalvolla on yksi tai useampi rakkula. Hemoragisessa myringiitissä tärykalvolla on todettavissa voimakas, verestävä punoitus.

Tärykalvotulehdus ei ole kovin harvinainen tauti, mutta tutkimuksia siitä on erittäin vähän. Myringiitin aiheuttajaa ei tunneta. Osa oppikirjoista pitää tautia viruksen tai *Mycoplasma pneumoniaen* aiheuttamana, toiset oppikirjat bakteereiden aiheuttamana. Kyseinen ristiriita etiologiassa sai aikaan tämän tutkimusaineiston keräämisen.

Tässä tutkimuksessa bulloosi myringiitti diagnosoitiin 82 lapsella. Lähes kaikille (97%) lapsille kehittyi bulloosin myringiitin aikana myös välikorvatulehdus. Tärykalvotulehduksen bakteriologisissa analyyseissä välikorvaeritteessä kasvoivat samat bakteerit (*S. pneumoniae, H. influenzae* ja *M. catarrhalis*) kuin välikorvatulehduksen yhteydessä. Myöskään nenänielusta ja välikorvasta otetuista virusnäytteissä ei ollut eroja tärykalvotulehduksen ja välikorvatulehduksen välillä. Koska 76% bulloosissa myringiitissä bakteeri on todettavissa välikorvaeritteessä, on nykykäsityksen mukaan antibioottihoito aiheellinen.

Tärykalvotulehduksen ilmaantuvuudesta ei ole aikaisemmin ollut tietoa. Tutkimuksemme mukaan bulloosi myringiitti esiintyy vuosittain noin 6%:lla alle 2-vuotiaista lapsista. Voidaan arvioida, että Suomessa esiintyy alle 2-vuotiailla vuosittain noin 6400 akuuttia bulloosia myringiittiä.

Tutkimuksen johtopäätöksenä on se, että tärykalvotulehdus on vahvaoireinen välikorvatulehdus. Taudin aiheuttajat ovat samoja kuin välikorvatulehduksessa, mutta oireet ovat voimakkaammat, paraneminen hitaampaa ja lisäksi tärykalvotulehdus lisää lapsen riskiä sairastua toistuviin välikorvatulehduksiin.

4. ABBREVIATIONS

AOM	acute otitis media
BM	acute bullous myringitis
CF	complement fixation test
CI	confidence interval
CRF	case report form
dB	decibel
DNA	deoxyribonucleic acid
EIA	antigen-enzyme immunoassay
FinOM Cohort Study	Finnish Otitis Media Cohort Study
FinOM Vaccine Trial	Finnish Otitis Media Vaccine Trial
HEV	human enteroviruses
H. influenzae	*Haemophilus influenzae*
HM	acute hemorrhagic myringitis
HRV	human rhinoviruses
ICD-10	The International Statistical Classification of Diseases and Related Health Problems
KTL	National Public Health Institute, Finland
M. catarrhalis	*Moraxella catarrhalis*
MEF	middle ear fluid
M. pneumoniae	*Mycoplasma pneumoniae*
NM	not mentioned
NPA	nasopharyngeal aspirate
OME	otitis media with effusion
OR	odds ratio
PCR	polymerase chain reaction
PncCRM	a pneumococcal conjugate vaccine, capsular polysaccharides conjugated to CRM197 protein
PncOMPC	a pneumococcal conjugate vaccine, capsular polysaccharides conjugated to OMPC protein
RAOM	recurrent acute otitis media
RNA	ribonucleic acid
rRNA	ribosomal ribonucleic acid
RR	risk ratio, relative risk
RSV	respiratory syncytial virus
S. pneumoniae	*Streptococcus pneumoniae*
TR-FIA	time-resolved fluoroimmunoassay
URI	upper respiratory infection

5. LIST OF ORIGINAL PAPERS

This dissertation is based on the following publications, which are referred to in the text by their Roman numerals. In addition, previously unpublished results are presented.

I Palmu AAI, Kotikoski MJ, Kaijalainen TH, Puhakka HJ (2001): Bacterial etiology of acute myringitis in children less than two years of age. Pediatr Infect Dis J 20:607-611.

II Kotikoski MJ, Palmu AAI, Nokso-Koivisto J, Kleemola M (2002): Evaluation of the role of respiratory viruses in acute myringitis in children less than two years of age. Pediatr Infect Dis J 21:636-641.

III Kotikoski MJ, Kleemola M, Palmu AAI (2004): No evidence of Mycoplasma pneumoniae in acute myringitis. Pediatr Infect Dis J, in press.

IV Kotikoski MJ, Palmu AAI, Huhtala H, Savolainen H, Puhakka HJ (2003): The epidemiology of acute bullous myringitis and its relationship to recurrent acute otitis media in children less than two years of age. Int J Pediatr Otorhinolaryngol 67:1207-1212.

V Kotikoski MJ, Palmu AAI, Puhakka HJ (2003): The symptoms and clinical course of acute bullous myringitis in children less than two years of age. Int J Pediatr Otorhinolaryngol 67:165-172.

The publishers of the original articles have kindly granted permission to reprint the papers.

6. INTRODUCTION

Acute otitis media (AOM) is one of the most common diseases diagnosed during childhood (Pukander et al. 1982a, Teele et al. 1989, Faden et al. 1998). It has been estimated that children in the United States have a total of 9.3 million episodes of AOM before the age of two years (Berman 1995). AOM causes both direct and indirect economic costs to families and society (Gates 1996, Coyte et al. 1999, Capra et al. 2000). In Finland it has been estimated that each single episode of AOM costs 228 US dollars (Niemelä et al. 1999).

AOM is generally considered a bacterial infection, because in about 50-70% of cases bacteria can be detected from the middle ear fluid (MEF) (Luotonen et al. 1981, Bluestone et al. 1992, Faden et al. 1998, Kilpi et al. 2001) and therefore antibiotic treatment is recommended in most countries (Rosenfeld et al. 1994, Paradise 1995, Froom et al. 1997, Dowell et al. 1998, Klein 1998, Puhakka et al. 1999). However, especially in the Netherlands, withholding antibiotic therapy is preferred in uncomplicated cases of AOM (van Buchem et al. 1981, Froom et al. 1997).

The etiology and pathogenesis of acute myringitis (i.e. inflammation of the tympanic membrane) are not well documented (Gates 1998). The definition of acute myringitis varies between classification panels (Klein et al. 1989, Brook and van de Heyning 1994, WHO 1999). It has also been questioned whether acute myringitis is merely a manifestation of AOM and not a clinical entity (Roberts 1980). The etiology of acute myringitis is controversial in the literature. Some textbooks consider it a viral infection (Brown and Meyerhoff 1991, Balkany and Ress 1998) or an infection caused by *Mycoplasma pneumoniae* (*M. pneumoniae*) (Cherry 1992), while others consider that bacterial etiology is more likely (Bluestone 1999a, Kenna 2000, Paradise 2002). This discrepancy caused us to conduct a study on the etiology of acute myringitis.

Prospective studies dealing with acute myringitis with modern viral detection methods are lacking. In addition, there are practically no data on acute myringitis in children less than two years of age, which is the age group with highest incidence of AOM. It

is important to investigate thoroughly the etiology of this quite common clinical manifestation to enable a more evidence-based treatment of this disease.

In the present study in the Finnish Otitis Media Vaccine Trial (FinOM Vaccine Trial) we focused on the etiology (bacteria, viruses and *M. pneumoniae*), epidemiology and the clinical course of acute myringitis. In addition, we investigated how often MEF develops during the course of acute myringitis and the relationship between bullous myringitis and recurrent AOM (RAOM).

7. REVIEW OF THE LITERATURE

7.1. Anatomy of the tympanic membrane

The tympanic membrane separates the external acoustic meatus from the tympanic cavity and forms the lateral wall of the tympanic cavity. The volume of the tympanic cavity is about 450 mm^3 in infants and 640 mm^3 in adults (Ikui et al. 2000). The shape of the membrane is elliptic; in adults it is approximately 9 to 10 mm wide and 8 to 9 mm high. In infants the size of the tympanic membrane is only slightly smaller than in adults (Ikui et al. 2000). The inferior pole of the tympanic membrane lies further medially than the superior pole, especially in children (Donaldson and Duckert 1991, Duckert 1998). After the development of the hypotympanum the tympanic membrane becomes more vertical (Ikui et al. 2000). The average thickness of the membrane is 0.074 mm. It is thickest (0.09 mm) near the annulus inferiorly and anterosuperiorly, and thinnest (0.055 mm) in the middle of the posterosuperior quadrant (Donaldson and Duckert 1991, Berger et al. 1996, Duckert 1998).

In the middle of the membrane there is a landmark called the umbo, which corresponds to the tip of the manubrium. The handle of the malleus (manubrium mallei) shines through the normal tympanic membrane; in the upper anterior part is the short process of the malleus (processus brevis mallei). The anterior (plica malleolaris anterior) and posterior (plica malleolaris posterior) mallear folds extend from the short process of the malleus to the tympanic sulcus and define the inferior extent of the flaccid portion (pars flaccida, membrana Shrapnelli) of the tympanic membrane. The inferior larger portion of the tympanic membrane is called the pars tensa (Donaldson and Duckert 1991, Duckert 1998). The landmarks of the tympanic membrane are presented in Figure 7.1.

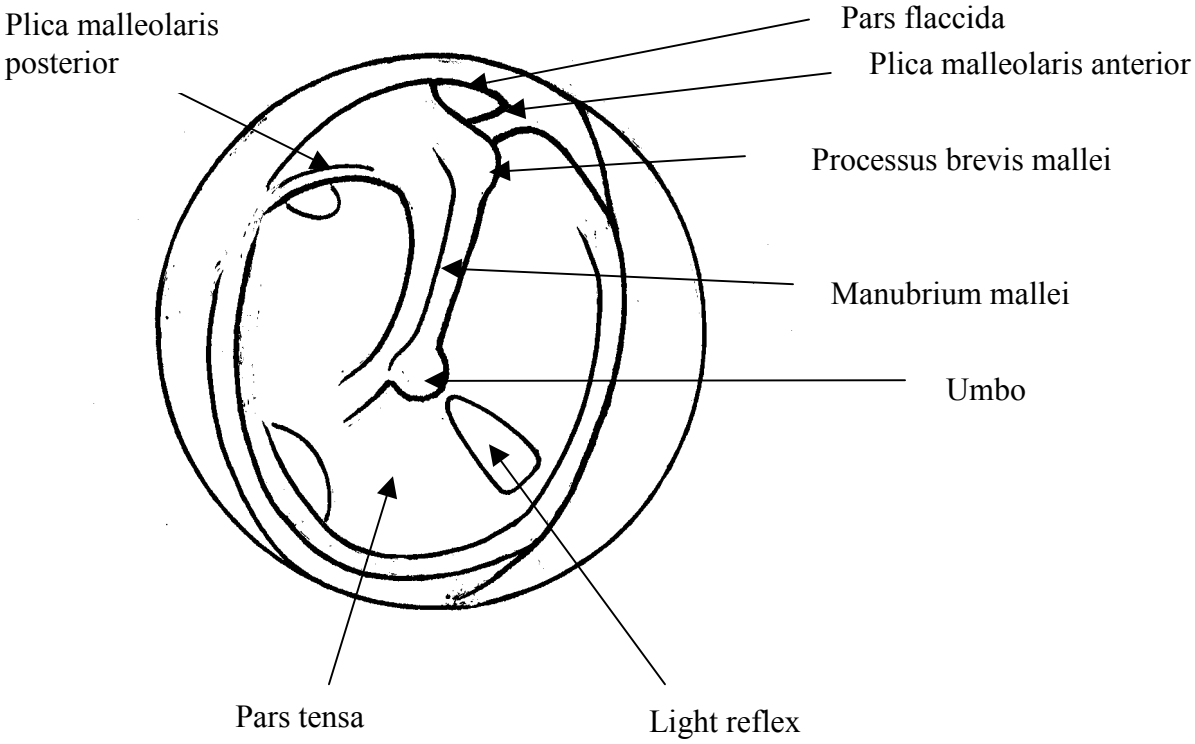

Figure 7.1. The landmarks of right tympanic membrane in the otoscopy.

The pars tensa is composed of five different layers (the lateral, subepithelial, middle, submucosal and medial layers) (Berger et al. 1996) (Figure 7.2.). The lateral layer is continuous with the epithelium of the external auditory meatus and is composed of stratified squamous epithelium (stratum cutaneum). Between the lateral and medial layer is a subepithelial layer composed of loose connective tissue that harbours blood vessels and nerves (Berger et al. 1996). In the middle is a fibrous layer (lamina propria) which consists of two layers of collagen fibers; in the lateral part the fibrous layer runs radially and in the medial part the fibrous layer runs circularly. The radial layer of fibers originates from the handle of the malleus and inserts on the annular ring. Circular fibers originate from the short process of the malleus. Transverse and

parabolic fibers intertwine between these two layers. The exact chemical nature of the fibers is unknown; they probably are neither pure collagen nor elastin. Between the middle and medial layer is a submucosal connective tissue layer identical with the subepithelial layer but thinner than the former and with fewer capillaries (Berger et al. 1996). The medial layer is simple low cuboidal epithelium, which is continuous with the lining of the tympanic cavity. It covers the inner surface of the tympanic membrane. The pars flaccida lacks the fibrous middle layer (Donaldson and Duckert 1991, Ross 2003).

In bullous myringitis the location of the blisters is considered to be in the subepithelial layer (Merifield 1962), although histological evidence for this is lacking (Woo et al. 1992). The blisters may in some instances be present also in the submucosal layer (Biedlingmaier 1994) (Figure 7.2.).

The blood vessels within the epidermal and mucosal surfaces communicate through anastomoses within the subepithelial and submucosal layers and provide the blood supply to the tympanic membrane (Donaldson and Duckert 1991, Duckert 1998). The arterial supply laterally originates from the deep auricular branch of the internal maxillary artery (a. maxillaris interna). Mucosal vessels originate from the anterior tympanic branch of the internal maxillary artery and from the stylomastoid branch of the posterior auricular artery (a. auricularis posterior). The venous blood supply parallels the arterial supply (Donaldson and Duckert 1991, Duckert 1998). In a healthy tympanic membrane the small capillaries are normally not visible, but if the child cries or if an inflammation is present some vessels might be visible.

The sensory nerve fibres of the tympanic membrane join to three different cranial nerves (n. trigeminus, n. glossopharyngeus and n. vagus). The auriculotemporal branch of the trigeminal nerve and the auricular branch of the vagus nerve (Arnold`s nerve) provide the nerve supply to the lateral tympanic membrane. The tympanic branch of the glossopharyngeus nerve (Jacobson`s nerve) supplies sensory fibers to the medial tympanic membrane and the mesotympanum (Donaldson and Duckert 1991, Duckert 1998).

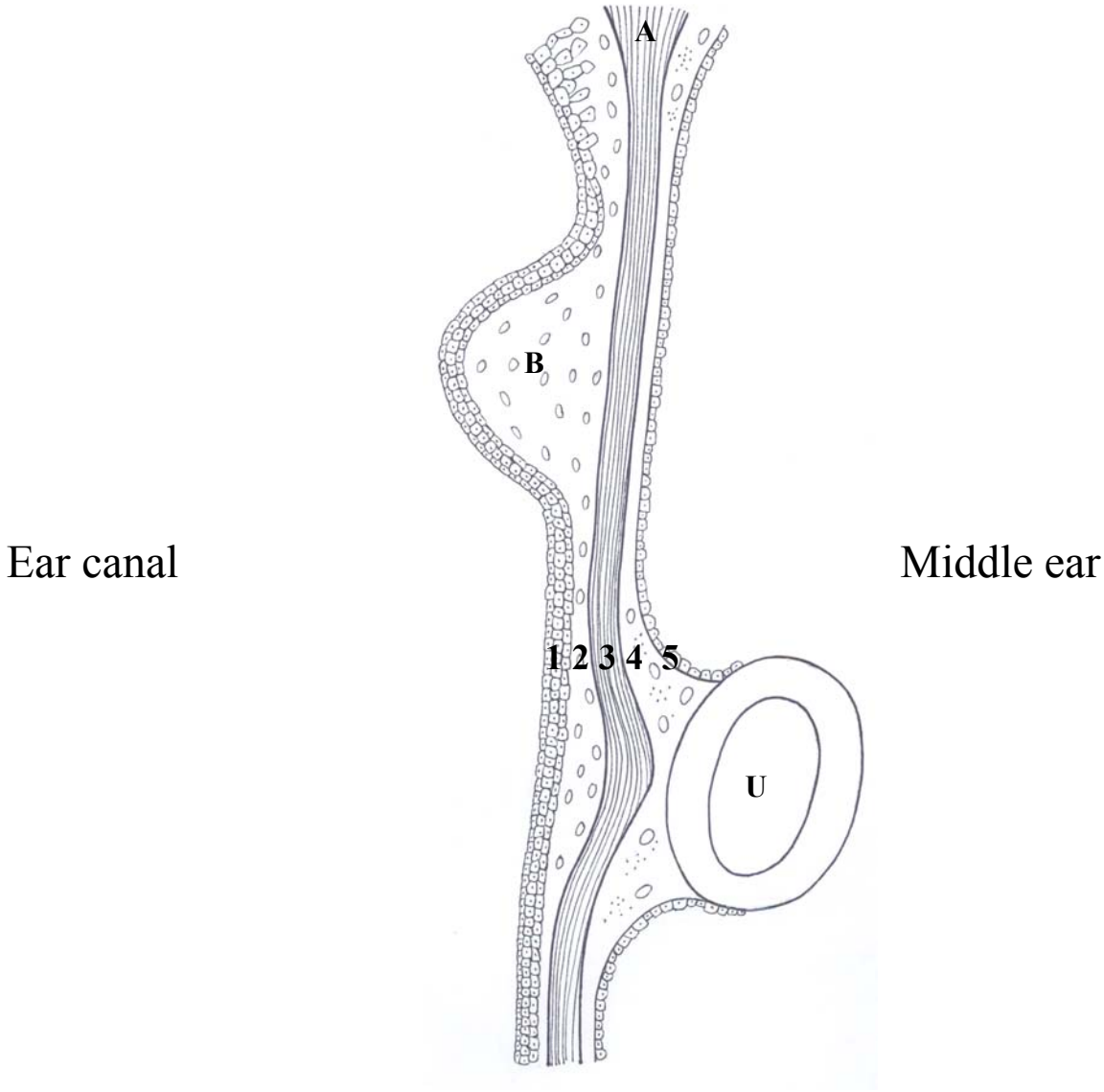

Figure 7.2. The layers of the tympanic membrane in the pars tensa. A blister (B) is located in the subepithelial layer. (U=umbo, A=annulus)

1. Lateral layer
   - stratified squamous epithelium, continuous with the external ear canal
2. Subepithelial layer
   - blood vessels and nerves
   - in bullous myringitis the blisters mostly appear in this layer
3. Middle layer (fibrous layer)
   - radial layer laterally
   - circular layer medially
4. Submucosal layer
   - few blood vessels and nerves
5. Medial layer
   - simple low cuboidal epithelium, continuous with mucosa of the middle ear

7.2. Otologic examination and findings of the tympanic membrane

The tympanic membrane serves as a window into the middle ear. The abnormalities of the tympanic membrane seen in a careful otoscopic examination will help to achieve the proper diagnosis of diseases of the tympanic membrane and the middle ear. Pneumatic otoscopy (or otomicroscopy) is performed in pediatric and otologic practice. In pneumatic otoscopy the focus is on the color, position, translucency and mobility of the tympanic membrane (Rothman et al. 2003). The normal healthy tympanic membrane is translucent, slightly gray and fully mobile. The visualization of the tympanic membrane may sometimes be difficult because of the child's behavior or the narrowness of the ear canal or ear wax obscuring the ear canal. The differentiation of AOM from otitis media with effusion (OME) may also be difficult to assess. Otoscopic findings and a visual assessment of tympanic membrane in normal ear, AOM, bullous myringitis and OME are presented in Figure 7.3.

Color. The color of the tympanic membrane may vary in different pathologic conditions. The healthy tympanic membrane is normally slightly gray. In AOM the color of the tympanic membrane may vary from red to gray. Only 18-50% of tympanic membranes with AOM are red (Karma et al. 1989, Arola et al. 1990). In about 70-80% of ears with AOM the tympanic membrane is cloudy (Karma et al. 1989). In some instances the redness may be extremely strong, as in hemorrhagic myringitis. The color of the tympanic membrane may also be yellow when pus is behind the drum (Rothman et al. 2003). The opaque white tympanic membrane may be a sign of tympanosclerosis or cholesteatoma. After a head injury blood may be present in the middle ear cavity and the color of tympanic membrane is reddish blue or purple.

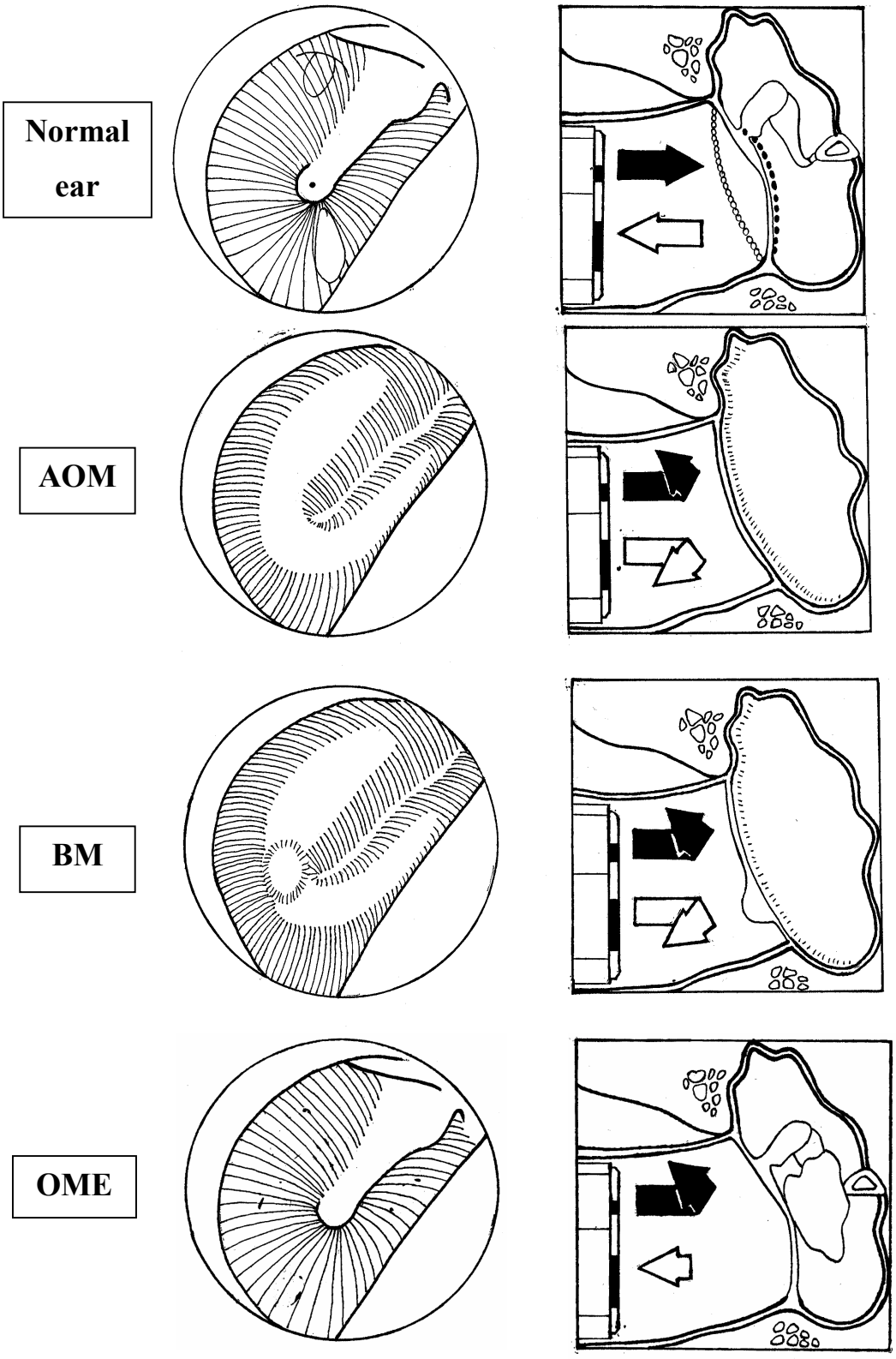

Figure 7.3. Otoscopic findings and a visual assessment of the tympanic membrane: Normal ear, acute otitis media (AOM), bullous myringitis (BM) and otitis media with effusion (OME) (Figures modified from Pelton 1998). The inward movement on positive pressure (black arrow) and outward movement on negative pressure (white arrow) is observed in normal (healthy) ear. The mobility is decreased or absent on both positive and negative pressure in AOM, BM and OME.

Position. The position of the tympanic membrane may be normal, retracted or bulging. In AOM the position is often bulging (Figure 7.3.) In bullous myringitis one or multiple blisters are seen on the tympanic membrane. A bulging membrane with bluish red or purple color may also be due to a glomus tumor (Brown and Meyerhoff 1991). A retraction of the tympanic membrane may be generalized, as in an atelectatic tympanic membrane or a retraction may cover only a small area of the tympanic membrane (for example the pars flaccida) and it may form a retraction pocket. A retracted tympanic membrane is often observed in chronic OME (Rothman et al. 2003).

Translucency. The healthy tympanic membrane is normally translucent. The landmarks that should be visible in a normal ear include the malleus, a light reflex below the umbo and pars flaccida (Rothman et al. 2003). The outline of the incus may also sometimes be visible through the healthy membrane. In AOM the translucency is often turned to opaque. Tympanosclerosis is also a common finding in otoscopy; this is due to abnormal hyalinized collagen in the middle layer of the tympanic membrane. Tympanosclerosis is a benign condition and might be a result of recurrent or chronic otitis media (Brown and Meyerhoff 1991). Granulation tissue may be found on tympanic membrane in some chronic inflammations such as in granular myringitis (Stoney et al. 1992) or granulation tissue may be due to tympanostomy tubes.

Mobility. Checking the movement of the tympanic membrane is an important part of pneumatic otoscopy. The mobility of the tympanic membrane may be normal, impaired, or immobile or it may not be assessable because of perforation or the presence of tympanostomy tubes. If MEF is present the mobility of the tympanic membrane is impaired or immobile. An open Eustachian tube might produce a movement of the tympanic membrane with respiration (Brown and Meyerhoff 1991). In a healthy tympanic membrane a gentle increase of ear canal pressure causes the tympanic membrane to move inwards (medially) (Figure 7.3.). In some pathologic conditions the tympanic membrane may be retracted and the middle ear pressure is negative. In those cases the movement of the tympanic membrane may be seen after negative pressure is applied with a pneumatic otoscope. An atelectatic tympanic membrane may be partly or totally immobile.

Pneumatic otoscopy is a subjective method, and the diagnostic accuracy may be poor, especially in young children (Froom et al. 1990). Furthermore, OME and a retracted tympanic membrane without MEF is frequently misdiagnosed as AOM (Pichichero 2002). Routine use of tympanometry (Palmu et al. 1999) or acoustic reflectometry (Barnett et al. 1998) in otologic examination could lead to more accurate diagnosis. The sensitivity of tympanometry to detect ears with MEF has been 70-93% with the specificity of 79-98% (Koivunen et al. 1997, Palmu et al. 1999). The sensitivity of acoustic reflectometry to detect ears with MEF has been 67-94% and the specificity about 80-99% (Combs and Combs 1996, Block et al. 1998). The additional use of tympanometry reduced the number of AOM diagnoses by over 30% in comparison with the diagnoses based on only a photograph of the tympanic membrane (Blomgren and Pitkäranta 2003). However, general practitioners perform tympanometry on only 1% of patients with AOM in Finland (Honkanen et al. 2002). There are no studies in the literature which are focused on the diagnostic accuracy of acute myringitis.

7.3. Definition of acute myringitis

The Latin word “myrinx” refers to the tympanic membrane; myringitis is a term to describe an inflamed tympanic membrane. The studies dealing with acute myringitis are sparse, and unfortunately in most of those there are no diagnostic criteria of acute myringitis mentioned, although blisters on the tympanic membrane are obviously required for diagnosis. The lack of diagnostic criteria makes the comparability of different studies difficult or impossible.

The strict definition of acute myringitis also varies between different classification panels. In the International Statistical Classification of Diseases and Related Health Problems (ICD-10) acute myringitis (code: H73.0) is defined as an inflammation of the tympanic membrane without middle ear effusion. If MEF is present it should be classified as AOM (codes: H65-H66) (WHO 1999). However, in some other classification panels acute myringitis has also been defined as an acute inflammation of the tympanic membrane that may occur alone or in association with external otitis or otitis media (Klein et al. 1989, Brook and van de Heyning 1994).

The clinical entities of acute myringitis are bullous, hemorrhagic and granulomatous myringitis. In bullous myringitis one or more blisters are seen in pneumatic otoscopy on the tympanic membrane or external ear canal. Hemorrhagic myringitis is defined as hemorrhagic (strong) redness on the tympanic membrane. Acute granulomatous myringitis is a rare entity of myringitis and only five cases have been reported (Hoshino et al. 1998).

7.4. Epidemiology

There are numerous studies dealing with the epidemiology of AOM, but except for a report in 1930's by Karelitz (Karelitz 1937), little information (Wetmore and Abramson 1979, Hahn et al. 1998) is available in English literature dealing with the epidemiology of acute myringitis. The information on incidence, seasonal variation, age distribution, recurrence rate, gender association and possible risk factors are not well documented.

7.4.1. Incidence

AOM is the most common cause of office visits (Freid et al. 1998), antibiotic treatment (Klein 1994, Rautakorpi et al. 1999, Schindler et al. 2003) and surgical operation (tympanostomy tubes and/or adenoidectomy) (Owings and Kozak 1998) in children. In Finland 57% of children have had at least one episode of AOM before the age of 18 months (Sipilä et al. 1987), and 71% before the age of two years (Alho et al. 1991). Furthermore, the incidence of AOM has increased during the past decades (Klein 1994, Lanphear et al. 1997, Joki-Erkkilä et al. 1998).

The incidence of acute myringitis is unknown. Rough estimations of incidence can be made from the studies which have reported the frequency of bullous myringitis in association with AOM. In those studies acute bullous myringitis was present in 1-16% of clinically diagnosed episodes of AOM (Feingold et al. 1966, Halsted et al. 1968, Wetmore and Abramson 1979, Howie and Schwartz 1983, Pukander 1983, Hayden and Schwartz 1985, Arola et al. 1990, Hahn et al. 1998, Rosenblut et al. 2001,

McCormick et al. 2003). The studies are summarized in Table 7.1. However, most of those studies lacked the definition of bullous myringitis.

Table 7.1. The proportion of cases of bullous myringitis (BM) and acute otitis media (AOM) and the age distribution in different study populations.

Study	Design*	BM, n	AOM, n	All, n	(BM/all) %	Age distribution	Proportion of children <2years
Feingold, 1966	P	9	81	90	10.0	0.3 – 11 years	62%
Halsted, 1968	P	4	102	106	3.8	0.2 – 5.5 years	75%
Wetmore, 1979	R	8	99	107	7.5	Mean 19 years	NM
Pukander, 1983	P	27	2227	2254	1.2	0 – 16 years	NM
Howie, 1983#	P	25	805	830	3.0	0 – 17 years	39%
Hayden, 1985	P	19	316	335	5.7	NM	55%
Arola, 1990#	P	32	496	528	6.0	0 – 12 years	53%
Hahn, 1998	R	88	9343	9431	0.9	0 – 17 years	~27%
Rosenblut, 2001	P	27	143	170	15.9	0.3 – 9 years	~36%
McCormick, 2003	P	41	477	518	7.9	0.5 – 12 years	NM
All together		280	14116	14396	**1.9**		
All prospective studies		184	4674	4858	**3.8**		

* P=prospective, R=retrospective

NM = not mentioned

= The numbers of BM are approximations (only the percentage was given)

Hahn et al. (1998) had the largest material (9343 cases of AOM and 88 cases of BM) during a 3-year time period (1987-1990). In their study, cases of bullous myringitis constituted only 0.9% of all cases. However, they speculated that probably AOM was overdiagnosed, because the study was retrospective and the patients with AOM lacked diagnostic criteria (Hahn et al. 1998). According to these AOM studies a physician

must examine 6 to 107 patients with symptoms of AOM to find one case of acute bullous myringitis.

7.4.2. Recurrence rate

Some children have a remarkable tendency for recurrent AOM. About 17-19% of children have three or more episodes of AOM before the age of one year (Sipilä et al. 1987, Teele et al. 1989) and about 6% of children have at least three AOM episodes between their second and third birthday (Teele et al. 1989).

Bullous myringitis recurred in 9 of 87 (10%) children in two weeks to a year after the first attack (Karelitz 1937). In the study of Hahn et al. (1998) a recurrent episode of bullous myringitis occurred in 22 of 88 (25%) patients, with a median follow-up of 52 months.

7.4.3. Risk factors

There are many studies dealing with the risk factors for acute otitis media (AOM). On the other hand, there are no studies of risk factors for acute myringitis, although it is very likely that the risk factors for AOM and acute myringitis are similar. Host-related risk factors include young age (Pukander et al. 1982a, Lundgren and Ingvarsson 1983, Sipilä et al. 1987, Teele et al. 1989, Alho et al. 1991, Jero and Karma 1997), male sex (Teele et al. 1980, Pukander et al. 1982b, Teele et al. 1989, Kilpi et al. 2001), race (Marchant et al. 1984, Schappert 1992, Casselbrant et al. 1995), allergy (Kraemer et al. 1983), craniofacial abnormalities (Paradise et al. 1969, Frable et al. 1985) and genetic predisposition (Kvaerner et al. 1997, Casselbrant et al. 1999).

The environmental factors include upper respiratory tract infection (Henderson et al. 1982, Sarkkinen et al. 1985, Alho et al. 1990), season (Pukander et al. 1982a, Casselbrant et al. 1995, Kilpi et al. 2001), presence of siblings (Pukander et al. 1985, Casselbrant et al. 1995), tobacco smoke at home (Kraemer et al. 1983, Ståhlberg et al. 1986), day care outside home (Pukander et al. 1985, Alho et al. 1993), short-term breast-feeding (Pukander 1982, Saarinen 1982, Teele et al. 1989), the use of a pacifier (Niemelä et al. 1994a, Niemelä et al. 1995) and low socioeconomic status (Paradise et al. 1997).

7.4.4. Seasonality

AOM is frequently a complication of upper respiratory infection (URI); therefore the incidence of AOM is highest during the fall and winter months and lowest in summer months (Henderson et al. 1982, Pukander et al. 1982b, Casselbrant et al. 1995, Kilpi et al. 2001). In acute bullous myringitis 59-67% cases have been diagnosed in winter months and 51-77% had symptoms of URI (Karelitz 1937, Wetmore and Abramson 1979, Hahn et al. 1998).

7.4.5. Age distribution

In AOM the incidence is highest in children less than two years of age (Pukander et al. 1982a, Lundgren and Ingvarsson 1983, Sipilä et al. 1987, Teele et al. 1989, Alho et al. 1991). Acute bullous myringitis has been reported to occur more often in older children, and the majority of cases are diagnosed at the age of 2-8 years (Karelitz 1937, Pukander 1983, Hayden and Schwartz 1985, Hahn et al. 1998, McCormick et al. 2003).

In a study from the 1930`s, the mean age of 87 cases with bullous myringitis was 5.8 years (Karelitz 1937). Only 7% patients were under 2 years of age; about 78% were in age group 2-8 years and 15% were 9 years or older (Karelitz 1937). However, decades ago also the incidence of AOM used to be highest in children around 6 years old ((MRC) 1957).

Pukander (1983) reported that 44% of cases of bullous myringitis occurred in the age group 7-9 years. Hayden and Schwartz (1985) noticed that the proportion of cases of bullous myringitis constituted 3% of cases of AOM in the age group less than two years, while in the age group older than two years the proportion was 9%. Wetmore and Abramson (1979) had two different sets of patients with bullous myringitis (with mean ages 19 and 24 years). They reported that two thirds of patients were between 15-31 years and found that the age distribution was totally different from that of AOM (Wetmore and Abramson 1979). Hoffman and Shepsman (1983) studied bullous

myringitis and sensorineural hearing loss; they examined 15 patients with bullous myringitis (with a mean age of 36 years).

Hahn et al. (1998) studied 88 patients with bullous myringitis with a median age of 5.4 years. About one fourth of patients with bullous myringitis were two years or under (Hahn et al. 1998). In a recent study the children with bullous myringitis were older than AOM children (a median age of 4.3 years in BM children vs. 1.5 years in AOM children) (McCormick et al. 2003). The reason for reported differences in age distribution between bullous myringitis and AOM is unknown.

7.4.6. Gender distribution

Males have a slightly higher incidence of AOM than females (Teele et al. 1980, Pukander et al. 1982b, Teele et al. 1989, Kilpi et al. 2001). Also, in most studies dealing with bullous myringitis a slight majority (50-60%) of patients have been boys (Karelitz 1937, Wetmore and Abramson 1979, Hariri 1990, Hahn et al. 1998, McCormick et al. 2003). The reason for the gender difference is still mostly unclear.

7.5. Pathogenesis

In AOM a viral infection causes congestion of the respiratory epithelium and dysfunction of the Eustachian tube (Bluestone 1999b), which leads to negative pressure in the middle ear and to the accumulation of secretions in the middle ear. The Eustachian tube dysfunction allows microbial pathogens to enter from the nasopharynx to the middle ear and cause an attack of AOM (Bluestone 1999b).

The pathogenesis for the development of the blisters is unknown. It has been speculated that bullous lesions might be simply manifestations of a mechanical injury of the tympanic membrane (Merifield and Miller 1966) or a non-specific tissue reaction to several infective agents (Dawes 1952). In some cases blisters may represent the initial stages of bacterial AOM; in other cases blisters may be due to a viral infectious agent (Gates 1998). Karelitz felt that the fact that in almost all cases of myringitis the URI was present suggests that the pathway is through the Eustachian tube, first causing an inflammation of middle ear and then secondarily the bullous

myringitis (Karelitz 1937). It has also been speculated that the blisters in some cases may be due to blowing one`s nose or sniffing (Gates 1998).

MEF has been frequently found in bullous myringitis, and may have arised as a result of a medial rupture of the bullae to the middle ear (Marais and Dale 1997) or the bullae may have developed secondarily after an inflammation of the middle ear (Karelitz 1937, Marais and Dale 1997). Whether the bullae originate from the middle ear or whether the middle ear effusion is secondary remains unclear.

In human temporal bone studies of AOM it has been shown that the tympanic membrane is thicker in AOM compared with normal ears. This is mostly due to the swelling of subepithelial and submucosal tissue layers of the tympanic membrane (Berger et al. 1996). Furthermore, there are many distended capillaries and an infiltration of inflammatory cells into the swollen subepithelial and submucosal tissue layers (Sano et al. 1994, Berger et al. 1996). Histological studies on bullous myringitis are lacking (Woo et al. 1992), but it is conceivable that in the beginning of the disease a strong inflammatory reaction initiated by pathogen exposure could lead to gross accumulation of fluid between the leaves of the tympanic membrane.

7.6. Etiology

The etiology of acute myringitis has remained controversial, even though the condition was recognized over a hundred years ago (Marais and Dale 1997). In some acknowledged textbooks acute myringitis is considered a virus infection (Brown and Meyerhoff 1991, Balkany and Ress 1998) or an infection caused by *M. pneumoniae* (Cherry 1992). In some other books it is considered a bacterial infection (Bluestone 1999a, Kenna 2000, Paradise 2002).

During the past decades numerous reports have been published suggesting a specific etiology for acute myringitis. Many different viruses, such as influenza (Milligan 1926, Yoshie 1955), adenovirus (Tilles et al. 1967) or Epstein-Barr virus (Kilpatrick 1964, Williams 1980) have been suggested as a causative agent. However, systematic studies on the etiology of bullous myringitis have not been able to confirm any

specific viral agent (Merifield and Miller 1966, Halsted et al. 1968, Wetmore and Abramson 1979). On the other hand, bacterial pathogens similar to those in AOM have been isolated in acute myringitis (Coffey 1966, Feingold et al. 1966). Roberts (1980) concluded from a review of published reports that the etiology of acute myringitis is similar to AOM with common bacterial pathogens (*S. pneumoniae, H. influenzae and M. catarrhalis*). The studies focusing on the etiology of acute myringitis are summarized in Table 7.2.

7.6.1. Viruses

AOM is generally considered to be a bacterial infection. However, there is abundant evidence that viruses play an important role in the pathogenesis of AOM (Ruuskanen and Heikkinen 1994, Pitkäranta et al. 1998, Ramilo 1999, Heikkinen and Chonmaitree 2003). Giebink et al. (1980) performed an experimental animal study and showed that there is an interaction with bacteria and viruses in the pathogenesis of AOM. They inoculated influenza A virus alone, *S. pneumoniae* alone or both pathogens to the nasopharynx of chinchilla. They found that an influenza virus alone resulted in AOM in 4% of animals and *S. pneumoniae* alone caused AOM in 21% of animals. When the animals were exposed to both pathogens AOM developed in 67% of cases (Giebink et al. 1980).

A concomitant virus infection has been confirmed from NPA samples in 30-55% by using the conventional viral diagnostic methods (viral culture and/or antigen-enzyme immunoassay (EIA)) (Klein et al. 1982, Chonmaitree et al. 1986, Arola et al. 1990, Vesa et al. 2001). By using the more sensitive polymerase chain reaction (PCR) method, 62-90% of NPA samples have been reported virus-positive in AOM (Pitkäranta et al. 1998, Heikkinen 2000). MEF samples are virus positive in about 8-25% of cases of AOM with a conventional viral diagnostic method, and 48-74% of AOM cases are virus-positive when using PCR as a diagnostic method (Pitkäranta et al. 1998, Heikkinen 2000). Viruses are detected as the only middle ear pathogens in about 2-15% of cases of AOM (Ruuskanen and Heikkinen 1994).

It has been demonstrated that RSV (Heikkinen et al. 1999) and human rhinoviruses (HRV) (Pitkäranta et al. 1998, Heikkinen 2000) are the main viruses invading the

middle ear during AOM. In addition, parainfluenza viruses, influenza viruses A and B, adenoviruses, human enteroviruses (HEV), human coronaviruses, cytomegaloviruses, herpes simplex viruses, Epstein-Barr viruses and varicella-zoster viruses have been also detected from the MEF (Chonmaitree et al. 1992a, Pitkäranta et al. 1998, Chonmaitree and Henrickson 2000, Shinogami and Ishibashi 2004). The incidence of AOM increases during viral epidemics (Ruuskanen et al. 1989, Arola et al. 1990, Kilpi et al. 2001, Vesa et al. 2001). A concomitant virus infection might cause the treatment failures of AOM (Chonmaitree et al. 1992b).

The evidence that supports a viral etiology is that most episodes of myringitis were preceded by a viral upper respiratory infection (Karelitz 1937, Wetmore and Abramson 1979), and in about 40% of myringitis cases, no bacterial pathogens were isolated (Feingold et al. 1966).

In the 1910`s and 1920`s acute bullous myringitis was seen during the epidemics of influenza and a causal relationship was assumed (Milligan 1926). Otologists of the day were so impressed with the frequent occurrence of bullous lesions of the tympanic membrane in influenza that they considered the bullae were due to influenza. However, it became apparent that this association was not constant. Karelitz (1937) attempted to culture influenza virus from the fluid withdrawn from the blisters of the tympanic membrane in seven cases and failed each time. In the 1940`s a complement fixation and neutralization test was performed to diagnose influenza A and B virus infections from the serum samples of 6 patients with bullous myringitis, but none of those were virus-positive (Senturia and Sulkin 1942). Yoshie (1955) was able to isolate influenza virus from the MEF of 4 out of 10 patients during an influenza epidemic in Japan, but for these cases no general bacterial culture was reported.

Merifield and Miller (1966) studied serum samples for complement-fixing tests against a broad spectrum of common infectious agents, including parainfluenza viruses 1-3, influenza A and B viruses, adenovirus, RSV, psittacosis, mumps, polio 2-3, echo 9, echo 16, rubeola, coxsackie viruses. However, they failed to establish any relationship between the viruses and the cases of bullous myringitis observed (Merifield and Miller 1966).

Tilles et al. (1967) presented a study in which they cultured MEF samples from nine patients with myringitis bullosa and found that adenovirus 3 grew in one sample that was bacteriologically sterile. In the same study population common bacterial pathogens grew in 5 of 9 patients (Tilles et al. 1967).

Halsted et al. (1968) examined 4 cases of bullous myringitis. They performed complement fixation tests for the following antigens: parainfluenza viruses 1-3, RSV, adenovirus, rubeola and *M. pneumoniae*. All MEF and NPA samples remained negative for viruses (Halsted et al. 1968).

Wetmore and Abramson (1979) studied complement fixation antibody titers (including *M. pneumoniae*, adenovirus, influenza virus A and B) on 10 patients with bullous myringitis. There was no evidence of infection by those organisms in any of the studied patients.

There are two reported cases of bullous myringitis with infectious mononucleosis. Kilpatrick (1964) reported one case of bullous myringitis without middle ear effusion associated with infectious mononucleosis. The clinical picture and percutaneus liver biopsy was characteristic of infectious mononucleosis (Kilpatrick 1964). Williams (1980) reported another case in which there were typical bullae on the tympanic membrane and a monospot test was positive and tests for Epstein-Barr virus IgG antibodies were weakly positive on admission and positive 18 days later. IgM antibodies were positive on both occasions (Williams 1980). However, no cultures from the middle ear or from the bullae were taken in either case.

The studies dealing with viral etiology of acute myringitis have several weaknesses. First, the studies have been performed years ago and modern viral diagnostic methods were not used. Second, most studies lacked the diagnostic criteria of acute bullous myringitis. Third, the number of analysed cases of bullous myringitis was low or the articles were single case reports. This makes possible the fact that the diagnosis and a definite viral etiology might be right in the reported case, but it might only present a rare etiology of the disease.

Table 7.2. Studies dealing with the etiology of acute myringitis

Etiological agent	Method	N of patients	N positive	Reference
Virus				
Influenza A or B	Clinical observation	?		Milligan, 1926
	Bulla culture	7	0	Karelitz, 1937
	CF	6	0	Senturia, 1942
	MEF culture	10	4 (40%)	Yoshie, 1955
	CF	10	0	Merifield, 1966
	CF	10	0	Wetmore, 1979
Adenovirus	MEF culture	9	1 (11%)	Tilles, 1967
	CF	10	0	Merifield, 1966
	CF	4	0	Halsted, 1968
	CF	10	0	Wetmore, 1979
RSV and Parainfluenza 1-3	CF	10	0	Merifield, 1966
	CF	4	0	Halsted, 1968
Coxsackie viruses and herpes simplex	CF	10	0	Merifield, 1966
Epstein-Barr virus	Clinical observation	1		Kilpatrick, 1964
	Serology	1	1	Williams,1980
Bacteria				
S. pneumoniae	MEF culture	10	7 (70%)	Coffey, 1966
	MEF culture	9	2 (22%)	Feingold, 1966
H. influenzae	MEF culture	10	4 (40%)	Coffey, 1966
	MEF culture	9	1 (11%)	Feingold,,1966
β-hemolytic streptococcus	MEF culture	9	2 (20%)	Feingold, 1966
St. Albus and diphtheroids	Bulla culture	1	1	Rifkind, 1962
M. pneumoniae				
	Bulla culture	1	0	Rifkind, 1962
	Clinical observation	2		Couch, 1964
	NPA culture	1	1	Sobeslavsky, 1965
	NPA and blister culture	1	1	Clyde, 1967
	CF	23	0	Merifield, 1966
	CF	4	0	Halsted, 1968
	CF	10	0	Wetmore, 1979
	Clinical observation	2		Broome, 1980
	Clinical observation	27		Mansel, 1989

CF = Complement fixation, MEF = middle ear fluid, NPA = nasopharyngeal aspirate, RSV = respiratory syncytial virus

7.6.2. Bacteria

The bacteriology of AOM is well known, with three main pathogens (*S. pneumoniae, H. influenzae and M. catarrhalis*). In about 50-70% of AOM patients pathogenic bacteria can be found from the MEF. *S. pneumoniae* causes 26-39% of the AOM episodes, *H. influenza* 12-25% and *M. catarrhalis* 6-23% (Luotonen et al. 1981, Bluestone et al. 1992, Faden et al. 1998, Kilpi et al. 2001). There are only a few studies dealing with the bacterial etiology of acute myringitis.

Coffey (1966) studied 10 cases of bullous myringitis and all MEF samples were bacteria-positive. *S. pneumoniae* was found in 6 cases, *H. influenzae* in 3 and a mixture of *S. pneumoniae* and *H. influenza*e in 1 case (Coffey 1966). Feingold et al. (1966) examined 9 patients with bullous myringitis and MEF yielded pathogenic bacteria in 5 of 9 (56%) ears. In the same study population, one bacteriologically sterile MEF sample was positive for adenovirus 3 (Tilles et al. 1967). Rifkind et al. (1962) made one needle aspiration of the bulla and the bacterial culture yielded S*taphylococcus albus* and diphtheroids. (Table 7.2.)

Two review articles on acute myringitis concluded that the most common factor that can initiate the development of bullous myringitis in children is AOM caused by *S. pneumoniae, H. influenzae* or *M. catarrhalis* (Roberts 1980, Marais and Dale 1997).

7.6.3. Mycoplasma pneumoniae

Most of the respiratory tract infections caused by *M. pneumoniae* are asymptomatic or minor respiratory illnesses such as pharyngitis or tracheobronchitis (Ferwerda et al. 2001). About 10-40% of community-acquired pneumonia in children is caused by *M. pneumoniae* (Waris et al. 1998, Ferwerda et al. 2001). Although *M. pneumoniae* is a common pathogen in respiratory infections in children, it is a rare pathogen in AOM. It has only twice been cultured from the MEF (Okazaki et al. 1989). By using new gene techniques *M. pneumoniae* was detected in 16 of 380 (4.2 %) of MEF samples in AOM (Räty and Kleemola 2000). The clinical significance of this finding is not clear. The authors speculated that *M. pneumoniae* might have been passively transported from the nasopharynx to the middle ear, or it could have preceded the bacterial AOM,

or it might have acted as a cofactor with bacteria. There is also a possibility that *M. pneumoniae* actually itself caused AOM in some cases (Räty and Kleemola 2000).

M. pneumoniae has been considered as one possible pathogen of acute myringitis. Rifkind et al. (1962) inoculated *M. pneumoniae* (at that time it was called the Eaton agent) to the nasopharynx of 52 adult volunteers and found that 13 of 52 (25%) volunteers developed ear symptoms. The findings in the tympanic membrane varied from mild injection to a severe inflammatory reaction. 5 patients had hemorrhagic areas in the tympanic membrane. Only 2 (4%) cases had bullous myringitis. They cultured one of these bullae, without a success *for M. pneumoniae*. Bacterial culture yielded staphylococcus albus and diphtheroids. The remainder of the ears with myringitis were not punctured for culture because no MEF was seen behind the membrane. They considered that because there was no suppurative middle ear disease present, the myringitis reaction was due to *M. pneumoniae* (Rifkind et al. 1962). In a similar study 2 (3%) of 69 mycoplasma-inoculated adult volunteers developed bullous myringitis, but no ear aspirates were taken (Couch et al. 1964).

In a clinical outbreak of *M. pneumoniae* infection 2 of 115 (2%) patients were reported to have hemorrhagic myringitis (Broome et al. 1980). In another retrospective trial 27 of 148 (18%) patients with laboratory evidence of *M. pneumoniae* pneumonia also had bullous myringitis (Mansel et al. 1989).

M. pneumoniae was detected from the nasopharynx, but not from the MEF, in a case report of a 5-year-old boy with bullous myringitis (Sobeslavsky et al. 1965). In another case report with a 13-month-old boy, *M. pneumoniae* was recovered from both the nasopharynx and fluid aspirated from the bullous lesion (Clyde and Denny 1967). This is the only documented case where *M. pneumoniae* has been found directly from the vesicle fluid in a case of bullous myringitis (Roberts 1980).

A complement fixation test failed to identify any evidence of *M. pneumoniae* in 23 (Merifield and Miller 1966), 4 (Halsted et al. 1968) and 10 (Wetmore and Abramson 1979) patients with bullous myringitis.

7.7. Clinical course

Bullous myringitis is considered to be a benign, self-limited disease, occasionally complicated by a purulent secondary infection (Palmer 1968). However, serious complications like meningo-encephalitis have been reported in some rare instances (Wild and Spraggs 2003).

The characteristic clinical presentation is a patient with a sudden onset of severe ear pain (Karelitz 1937, Merifield 1962, Palmer 1968). However, in young children with AOM the symptoms are usually unspecific (Hayden and Schwartz 1985, Niemelä et al. 1994b, Heikkinen and Ruuskanen 1995, Kontiokari et al. 1998, Palmu et al. 2004), since they can not express their symptoms or the origin of the pain. In acute myringitis the otalgia is often throbbing (Marais and Dale 1997). Pain is usually located within the ear, but may radiate to the mastoid tip, occiput, temporomandibular joint and occasionally the face (Palmer 1968). In most patients the pain subsides in one or two days, but some discomfort is usually present for three to four days (Merifield and Miller 1966). The pain does not entirely disappear after the myringotomy or after the spontaneous rupture of the bulla (Karelitz 1937). The tympanic membrane regains a normal appearance in two or three weeks (Palmer 1968).

The otoscopy reveals an inflamed tympanic membrane with one or more bullae. The bullae are filled with clear, slightly-yellow or hemorrhagic fluid (Wetmore and Abramson 1979, Hahn et al. 1998). Some bullae are barely distinguishable and some occupy a large portion of the tympanic membrane (Palmer 1968, Knappett 1976, Wetmore and Abramson 1979). The bullae appear most often on the posterior or posterior-inferior aspect of the tympanic membrane (Merifield 1962, Palmer 1968, Mertz 1976), or on the posterior canal wall (Palmer 1968). The bullae appear to involve only the subepithelial layer of the tympanic membrane, i.e. the vesicles are beneath the stratum cutaneum (Merifield 1962). However, it has been speculated that blisters may be present on both the outer and inner surface of the tympanic membrane (Biedlingmaier 1994).

In AOM, about 40-60% of infections are bilateral (Pukander 1983, Faden et al. 1998, Kilpi et al. 2001). Bullous myringitis is often detected only unilaterally (Feingold et al. 1966, Wetmore and Abramson 1979, Lashin et al. 1988) while in some studies the proportion of bilateral infection has been 11 to 33% (Senturia and Sulkin 1942, Dawes 1952, Hoffman and Shepsman 1983, Pukander 1983, Hariri 1990). There is only one study in which bilateral involvement appeared in over half (64%) of the cases (Karelitz 1937).

If the bulla ruptures then a serosanguineous discharge of short duration appears in the ear canal (Biedlingmaier 1994), unless complicated by a bacterial invasion when the discharge becomes purulent (Merifield 1962). Minor temperature elevations are usually seen in the initial course of the myringitis (Palmer 1968, Mertz 1976). Most often the bullae disappear by themselves. In a majority of cases the bullae lasted three or four days (Karelitz 1937).

7.8. Presence of middle ear effusion

The definition of bullous myringitis in ICD-10 does not allow the presence of middle ear effusion. However, MEF is frequently found in bullous myringitis (Marais and Dale 1997). The studies reporting the presence of MEF in bullous myringitis are presented in Table 7.3. Karelitz (1937) found that only 14 (10%) of 143 ears with bullous myringitis subsequently developed purulent AOM. Merifield and Miller (1966) found in their series that MEF (serous or mucous) was present in 11 of the 23 (48%) patients. In the study of Hariri (1990) only 1 of 18 (6%) patients developed serous AOM during the course of bullous myringitis. In three other studies MEF was found in all 4 (Halsted et al. 1968), 24 (Lashin et al. 1988) and 41 patients (McCormick et al. 2003) with bullous myringitis. In conclusion, the proportion of cases with MEF during the course of acute myringitis varies from 6 to 100% between different studies.

Table 7.3. The presence of middle ear fluid (MEF) in bullous myringitis (BM).

Study	N of BM ears	MEF present (%)	Age distribution
Karelitz, 1937	143	14 (10%)	0.5 – 30 years
Merifield, 1966	23	11 (48%)	NM
Halsted, 1968	4	4 (100%)	0.2 – 5.5 years
Lashin, 1988	24	24 (100%)	6 – 26 years
Hariri, 1990	18	1 (6%)	10 – 76 years
McCormick, 2003	41	41 (100%)	0.5 – 12 years
All together	253	95 (38%)	

NM = not mentioned

7.9. Differential diagnosis

The typical bullae in the tympanic membrane or external ear canal are characteristic of bullous myringitis. However, syndrome Ramsay Hunt (Herpes zoster oticus) must be differentiated from acute myringitis (Kilpatrick 1964, Palmer 1968, Mertz 1976). There is peripheral facial nerve palsy accompanied by an erythematous vesicular rash on the ear (zoster oticus) or in the mouth in the syndrome Ramsay Hunt and the blisters are seen in most cases in the regions of the concha, antihelix, the fossa of the antihelix or the lobulus. In some cases the blisters are also seen in the ear canal. Varicella zoster virus is the etiological agent of this syndrome (Sweeney and Gilden 2001).

7.10. Treatment

In a meta-analysis of 5400 children the overall rate of spontaneous clinical recovery of AOM in children was 81% (Rosenfeld et al. 1994). Thus, most patients will recover even if they are treated with a placebo. However, effective bacterial eradication has been shown to be beneficial for a clinical outcome (Carlin et al. 1991, Dagan and Leibovitz 2002). Furthermore, the rare but severe complications of untreated AOM (including mastoiditis, meningitis, lateral sinus thrombosis and chronic suppurative otitis media) speak for antibiotic treatment in AOM. On the other

hand, the withholding of antibiotic treatment has been recommended in AOM (van Buchem et al. 1981). Rosenfeld et al. (1994) concluded in their meta-analysis that antibiotics have a modest but significant effect on the short-term resolution of AOM.

In case of an uncomplicated AOM myringotomy is not needed (Bluestone 1994). However, if a child is seriously ill or if the symptoms suggest a complication or if there is no response to antimicrobial therapy then myringotomy should be performed. Two studies (Puhakka et al. 1979, Qvarnberg 1981) have shown an improved outcome of AOM if myringotomy is added to antimicrobial treatment, while other studies could not find any difference whether a myringotomy was performed or not (Engelhard et al. 1989, Kaleida et al. 1991).

7.10.1. Myringotomy/incision of the bulla

During recent decades several different recommendations have been made as a treatment of choice for acute myringitis. Some authors recommended puncturing the bullae (Milligan 1926, Clark 1951), but others doubted whether anything could be gained by incising the bullae and recommended conservative treatment (Karelitz 1937). Myringotomy may increase the risk of secondary infection in the middle ear (Merifield and Miller 1966, Mertz 1976) and the incision of the bullae seldom relieves the ear pain (Palmer 1968).

7.10.2. Antibiotics

Some authors have considered that there is no evidence that systemic antibiotics are of benefit (Palmer 1968) and in the absence of MEF, the use of antimicrobial drugs do not hasten recovery from bullous myringitis (Kilpatrick 1964). Some authors have suggested that antibiotics should be reserved for suppurative otitis media (Knappett 1976, Mertz 1976, Marais and Dale 1997). Furthermore, the use of antibiotics or vasoconstrictors is not necessary because in the majority of cases the disease is self-limited (Merifield and Miller 1966). A careful follow-up has been recommended to find out the possible secondary bacterial infections (Merifield and Miller 1966, Palmer 1968).

The current opinion is that if MEF is not present in bullous myringitis, a treatment with topical eardrops used for acute external otitis is satisfactory (Hirch 2003). If MEF is present, treatment with the same systemic antibiotics as in AOM is preferable (Rowe 1975, Roberts 1980, Biedlingmaier 1994, Marais and Dale 1997, Hirch 2003).

7.11. Effect on hearing

In AOM temporary hearing loss is common; it can be conductive, sensorineural or both. The conductive hearing loss is usually between 15-40 dB and is due to middle ear effusion (Fria et al. 1985). Sensorineural hearing loss (mild, moderate, severe, or profound) has also been reported as a complication of AOM. The hearing loss can be reversible or permanent. Reversible sensorineural hearing loss is mainly related to the stiffness of the round window membrane. In permanent sensorineural hearing loss a middle ear infection or inflammatory products of the middle ear or ototoxic substances such as bacterial toxins spread out to the inner ear (Morizono and Tono 1991, Bluestone 1999a).

There are also some studies with acute myringitis and hearing loss. Karelitz (1937) mentioned that 12 of 87 (14%) patients with bullous myringitis had diminution of hearing and no MEF at the initial office visit or during the follow-up. He did not mention what were the criteria of diminution of hearing, but concluded that a loss of hearing does not necessarily mean that MEF is present (Karelitz 1937).

Merifield (1962) studied 2 patients (3 ears) with bullous myringitis accompanied by mixed hearing loss (40-60 dB); both cases had a complete recovery in 3-4 weeks. In the study of Wetmore and Abramson (1979) reversible sensorineural hearing loss developed in 3 of 22 (14%) patients and a complete recovery appeared in 12 days to 5 months. In one case report one patient suffered from bilateral bullous myringitis with reversible severe (70 dB) mixed hearing loss bilaterally, and the hearing loss subsided slowly within 4 months (Feinmesser et al. 1980).

Hoffman and Shepsman (1983) studied 15 patients (21 ears, aged 17 to 68 years) with bullous myringitis. A total of 67% of the ears developed a sensorineural or mixed

hearing loss. Recovery of hearing was complete in 62% of the ears after one month of diagnosis, while 38% of the ears experienced a persistent, high frequency loss (Hoffman and Shepsman 1983).

Lashin et al. (1988) reported 24 patients (aged 6 to 26 years) with unilateral bullous myringitis. Normal hearing was found in 16 (67%) patients, conductive hearing loss in 1 (4%) patient, mixed hearing loss in 3 (13%) patients and sensorineural hearing loss in 4 (17%) patients. A complete recovery of hearing was found in 7 of 8 (88%) patients at the follow-up visits (Lashin et al. 1988).

Hariri (1990) examined 18 patients (20 ears, aged 10 to 76 years) with bullous myringitis. He found that 3 (15%) had normal hearing, 4 (20%) had conductive hearing loss, 7 (35%) had mixed hearing loss and 6 (30%) had sensorineural hearing loss. Recovery was complete in 12 out of 17 (71%) ears (Hariri 1990).

In conclusion, there is evidence that occasionally (14-67% of patients) sensorineural hearing loss accompanies bullous myringitis. Fortunately, in most cases (57-100% of patients) hearing returns to its original level in a few weeks or months.

8. OBJECTIVES OF THE STUDY

The present study was designed to:

1. Determine the presence of middle ear fluid (MEF) during the clinical course of acute bullous and hemorrhagic myringitis (I).

2. Study the bacteriological findings of the MEF in acute bullous and hemorrhagic myringitis and compare the results with AOM (I).

3. Investigate the virological samples of nasopharyngeal aspirate (NPA) and MEF in acute bullous and hemorrhagic myringitis and compare the results with AOM (II).

4. Assess the role of *M. pneumoniae* in the etiology of acute bullous and hemorrhagic myringitis (III).

5. Report the epidemiological characteristics of acute bullous myringitis (IV).

6. Analyze the symptoms in acute bullous myringitis and compare the results with AOM (V).

7. Study the relationship between acute bullous myringitis and recurrent AOM (IV).

9. MATERIALS AND METHODS

9.1. The Finnish Otitis Media Vaccine Trial

A randomized double-blind cohort study Finnish Otitis Media (FinOM) Vaccine Trial was conducted in Finland from December 1995 through April 1999 (Eskola et al. 2001, Kilpi et al. 2003). The primary objective was to investigate the efficacy of two heptavalent pneumococcal conjugate vaccines (PncCRM and PncOMPC) in the prevention of AOM. Two thirds of the children received pneumococcal conjugate vaccine (either PncCRM or PncOMPC) and one third received a control vaccine (Hepatitis B vaccine). The intramuscular vaccine injections were given at 2, 4, 6 and 12 months of age.

Eight study clinics were located in the communities of Tampere (population, 191,000), Nokia (27,000) and Kangasala (22,000) in Finland. The families living in the study area were informed about the possibility to participate in the vaccine trial by the prenatal health clinics and by public health nurses in child health centers. If the parents were willing to participate they contacted the study clinics in their own area. A total of 2497 children were enrolled in the FinOM Vaccine Trial. The study cohort included 55% of children born in that area during the enrolment phase of the trial. Eighty-seven children (3.5%) discontinued the follow-up before 24 months of age. The children represented normal urban patients of white race from all social layers of the Finnish society.

The children were followed in the study clinics from two months to two years of age. The enrollment visit was at 2 months of age and the prescheduled visits at 4, 6, 7, 12, 13, 18 and 24 months of age. Additionally, the parents were requested to bring their child directly to the study clinic if they had any symptoms of acute respiratory infection. On weekends there was one study clinic open, but there were no appointments during the evenings and nights. In case of upper respiratory tract symptoms the parents of the children were told to contact the study clinics the next morning. About 80% of the diagnoses of AOM were made in the study clinics.

9.2. The satellite study

The data on cases of myringitis were collected in a satellite study of the FinOM Vaccine Trial which was conducted from 1st October 1997 through March 1999. All study clinics except the clinic in Nokia took part in the satellite study. Altogether 2028 children aged 7 to 23 months were included in the follow-up for this study. The follow-up for each child started on October 1, 1997 and ended at 24 months of age or earlier in a case of discontinuation (n = 30, 1.5%). The total follow-up time for the cohort was 1476 person years, ranging from 1 to 531 days per subject (mean 266 days, median 264 days) depending on the age of the child on October 1, 1997. During the satellite study a total of 8207 visits were made to the study clinics. Of those, 4593 were sick visits due to symptoms of respiratory infections and 3614 were follow-up visits.

9.3. Definitions of acute myringitis and acute otitis media

The diagnoses were based on clinical examination by full-time study physicians. Bullous myringitis was defined as one or more blisters seen on the tympanic membrane and/or external ear canal irrespective of other findings in pneumatic otoscopy. Hemorrhagic myringitis was defined as a strong hemorrhagic redness on the tympanic membrane. Extravasal redness was required to classify redness as hemorrhagic. If both blisters and hemorrhagic redness were detected, the event was considered to be bullous myringitis.

The diagnosis of AOM was based on abnormal findings in pneumatic otoscopy suggesting a presence of MEF combined with at least one acute symptom (fever, ear ache, rubbing of ear, a discharging ear not caused by external otitis, excessive crying, restlessness, cough or runny or stuffy nose). Tympanometry was routinely used to aid in the diagnosis of AOM (Palmu 2001).

Because of the nature of myringitis and AOM, the results are reported either by ears, events or episodes, depending on the subject in the focus. An event was defined as an office visit with the disease in focus. In other words, both a unilateral and a bilateral

infection were considered single events. An episode means the same as one event, but a new episode of AOM was considered to have started if at least 30 days had elapsed since the beginning of the previous episode.

A bullous myringitis child (BM child) was defined to have at least one event of bullous myringitis during the follow-up of the study. A child with hemorrhagic myringitis (HM child) was defined to have at least one event of hemorrhagic myringitis during the follow-up of the study. An AOM child was defined to have at least one AOM without any myringitis during the follow-up of the satellite study.

9.4. Treatment and follow-up

If MEF was present, both AOM and acute myringitis were treated with myringotomy and antibiotics. Additionally, a nasopharyngeal aspirate (NPA) sample was obtained for virologic analysis. If MEF was not detected in acute myringitis at the initial visit, an early control visit was scheduled within 10 days to control the ear status and development of MEF.

When acute myringitis was diagnosed a special case report form (CRF) was filled to document the findings of the myringitis. The following characteristics were specifically reported: thorough status of the tympanic membrane, the nature of the myringitis reaction, the number of blisters, area of reaction, presence of ear canal affection and presence of MEF. Additionally, the location of the blisters/hemorrhage was drawn on a schematic image of the tympanic membrane. Otherwise, the data were derived from the FinOM Vaccine Trial.

At the sick visits the following symptoms preceding the visit were recorded: earache, rubbing of the ear, fever, rhinitis, cough, restless sleeping, excessive crying, poor appetite, eye symptoms, vomiting, diarrhea and running ear. The rectal temperature was measured at the office visit in a majority (81%) of cases. Parents followed the recovery from acute bullous myringitis and AOM by reporting the symptoms and signs (earache, rectal fever, restless sleeping and running ear) each day during the

following seven days after the diagnosis. The resolution of MEF after AOM and acute myringitis was checked in the study clinics three to five weeks after the diagnosis.

Data on background information (number of siblings, parental education, parental smoking e.g.) were collected on admission to the FinOM Vaccine Trial. The data on day care was collected at the pre-scheduled healthy visits at 6, 12, 18 and 24 months of age. The number of otological procedures (tympanostomies and adenoidectomies) performed by the end of the follow-up were counted.

9.5. Bacteriological methods

After myringotomy with aspiration was performed, MEF was taken from the suction tip into 0.7 ml of phosphate buffered saline. A10 μl inoculations on an enriched chocolate agar plate and a sheep blood agar plate containing gentamicin (5μg/ml) were incubated overnight in the study clinics. After that they were sent to the bacteriology laboratory of the National Public Health Institute (KTL) in Oulu, Finland for isolation and identification of bacteria.

Bacterial colonies of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* were identified from the MEF using generally accepted methods. Other bacteria were rare findings and were considered non-pathogens or probable contaminants.

For quality assurance written standard operation procedures were followed during the whole trial. All bacteriological data were documented on specific data sheets and data were monitored continuously. Data were checked by several algorithms to find lacking or controversial data.

9.6. Virological methods

Time-resolved fluoroimmunoassay (TR-FIA) was used for the detection of antigens of adenoviruses, influenza viruses A and B, parainfluenza viruses 1, 2 and 3, and

respiratory syncytial virus (RSV) in the NPA and MEF samples (Halonen et al. 1983). The method is based on pairs (capture antibody and detector antibody) of virus-specific monoclonal antibodies provided by the Department of Virology, University of Turku, Finland. Coating, postcoating and washing of the polystyrene microstrips (Labsystems OY, Helsinki, Finland) and the detection of viruses with the Europium-labeled antibody were performed.

The samples were analyzed for human rhinoviruses (HRV) and human enteroviruses (HEV) by reverse transcription polymerase chain reaction (RT-PCR) (Blomqvist et al. 1999). Extraction of viral ribonucleic acid (RNA) from NPA samples was carried out using a commercial RNA isolation procedure (RNeasy®, Qiagen GmbH, Hilden, Germany).

All samples of cases of myringitis were analysed by the viral methods described above. However, for economic reasons, the virologic analyses were performed on only 600 randomly selected FinOM children. NPA and MEF samples of all events of AOM of the selected children were analysed. Of those events we included only the samples which were obtained during the follow-up of the satellite study (samples taken after October 1, 1997) to control for the effect of seasonal virus epidemics. The NPA samples of 165 children in 298 events and the MEF samples of 166 children in 291 events and in 415 ears were available.

9.7. Detection of Mycoplasma pneumoniae

M. pneumoniae was not routinely analysed in cases of acute myringitis and the MEF sample had run out in the previous bacterial and viral analyses in several cases. There was still enough sample for PCR analysis in 30 of 82 (37%) cases of bullous myringitis and in 7 of 18 (39%) cases of hemorrhagic myringitis. In addition, there were 12 cases of bullous myringitis in which the sample taken from the fluid of the blister was available for analysis. Of those, 4 out of 12 were taken from the ears in which a MEF sample was also available.

The extraction of DNA from MEF and blister fluid samples was carried out using a commercial kit (QiaAmp Blood Kit, Qiagen, Hilden, Germany). PCR was carried out using primers from the 16S rRNA gene (van Kuppeveld et al. 1992) and the PCR products were detected by liquid hybridization (Rönkkö et al. 2002).

9.8. Data processing and statistical methods

The data on the visits of the FinOM Vaccine Trial were collected on special case report forms (CRF). The data were optically transformed to an electronic form. Additionally, a normal written case history was available. The SPSS for Windows 8.0.1, Egret for Windows and Stata 7.0 were used for the statistical analyses.

Conditional logistic regression was used for comparison of bacterial etiology between acute myringitis and AOM. Each case of acute myringitis with MEF sample was matched with three controls of AOM by sex, age (+/- 30 days) and vaccine group.

Descriptive analysis was used to report the symptoms and the viral findings of NPA and MEF. Comparison of the etiology (bacteria alone, bacteria and virus, virus alone and no pathogen) between bullous myringitis and AOM was done by the standard chi-square test.

The chi-square test was used to test for differences between the proportions of categorical baseline characteristics. A nonparametric test (Mann-Whitney U test) was used to test for differences between medians for non-normal continuous data. The relative risks (RR) were calculated from 2x2 tables. The Poisson regression model was used to test the variation of incidence of bullous myringitis between different age groups and the dependence between age and seasonal variation of bullous myringitis.

9.9. Ethical consideration

The FinOM Vaccine Trial was conducted according to good clinical practice. Ethical evaluation was carried out in The National Public Health Institute (KTL) and local

trial sites in The Tampere region. Informed consent was obtained from the parents/guardians prior to enrollment in the trial.

10. RESULTS

During the one and half-year follow-up, 86 events of bullous myringitis were diagnosed in 82 children. Four children had a recurrent attack and 6 children had a bilateral infection. Thus, there were 92 ears with a diagnosis of bullous myringitis. The proportion of events of bullous myringitis was 4.6% of the number of all diagnosed AOM events during the follow-up and 1.9% of all sick visits conducted because of respiratory infections.

Hemorrhagic myringitis was found in 37 events and in 40 ears during the follow-up. The proportion of events of hemorrhagic myringitis was 2.0% of the number of all diagnosed AOM events during the follow-up and 0.8% of all sick visits conducted because of respiratory infections.

10.1. Development of middle ear fluid (I)

The development of middle ear fluid (MEF) during the course of bullous and hemorrhagic myringitis is presented in Figures 10.1. and 10.2. In bullous myringitis MEF was present at the time of diagnosis in 83 (out of 92) ears. Those who did not have MEF initially in the acute phase were re-examined in 10 days. Finally there were only 3 ears which apparently did not develop MEF, while 88 out of 91 (97%) ears produced MEF during the episode of acute bullous myringitis (Figure 10.1.).

In hemorrhagic myringitis MEF was present at the time of diagnosis in 20 (out of 40) ears. The ears with no MEF initially were re-examined in 10 days. MEF developed in 31 of 38 (82%) ears during the course of acute hemorrhagic myringitis (Figure 10.2.).

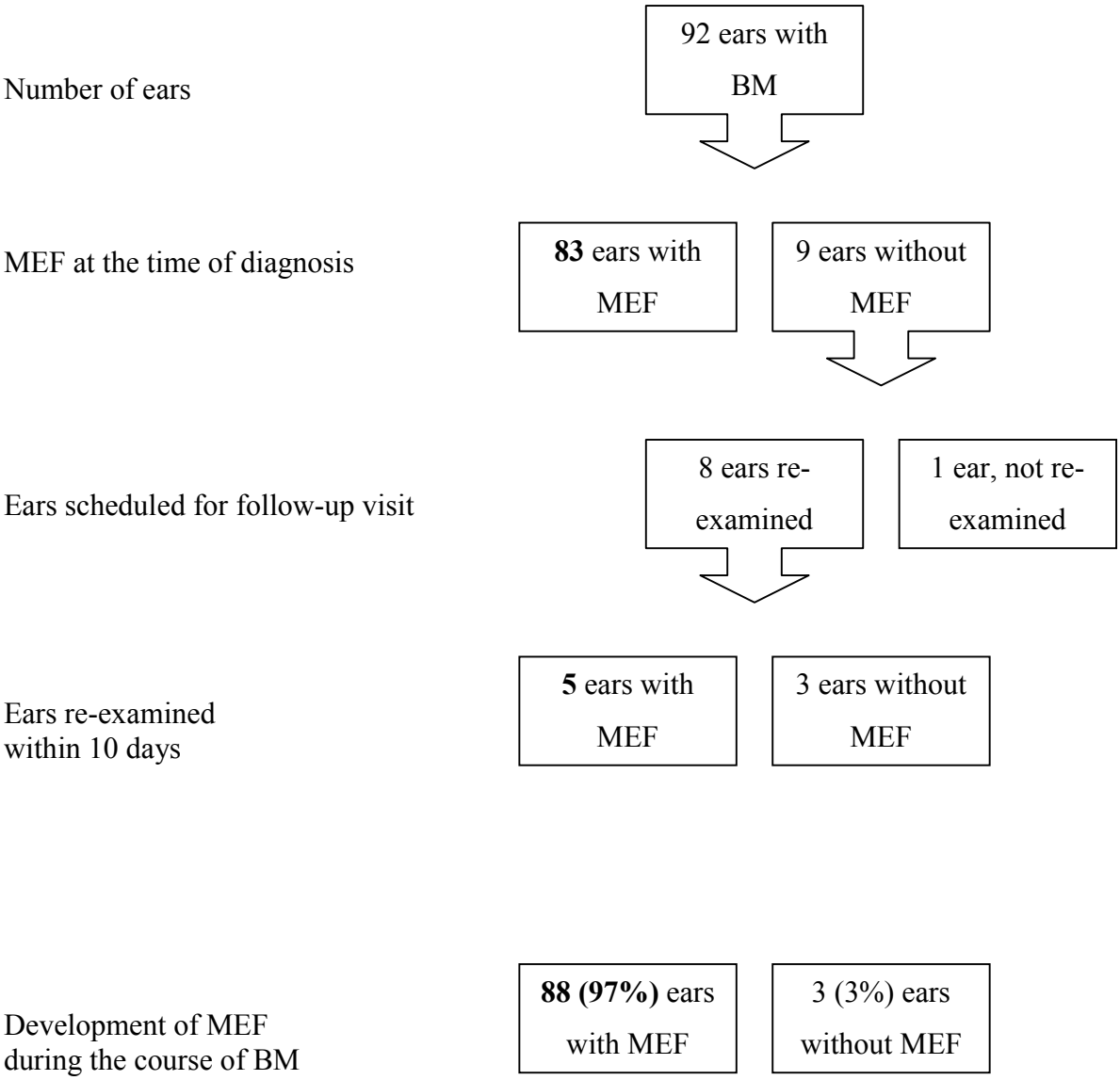

Figure 10.1. The development of middle ear fluid (MEF) during the clinical course of bullous myringitis (BM).

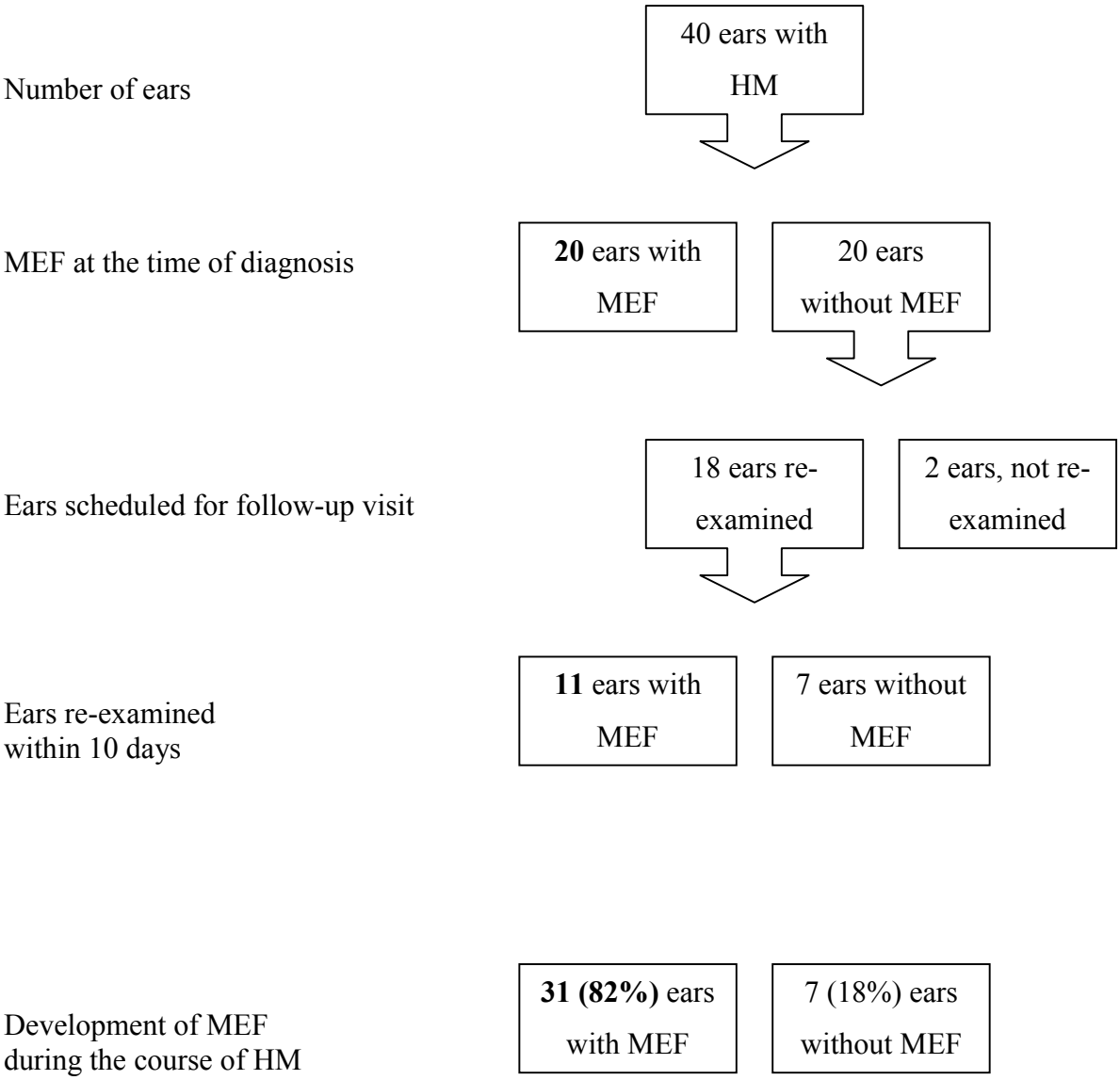

Figure 10.2. The development of middle ear fluid (MEF) during the clinical course of hemorrhagic myringitis (HM).

10.2. Etiology (I-III)

10.2.1. Bacteria

Bacteriological analyses were performed to 74 children with bullous myringitis. The following bacterial pathogens of the MEF were found: *S. pneumoniae* in 24 (32%) children, *H. influenzae* in 22 (30%) and *M. catarrhalis* in 9 (12%). Bacterial culture remained negative or yielded nonpathogenic bacteria in 19 (26%) children (Figure 10.3). *S. pneumoniae* was found more often in bullous myringitis than in AOM (32% vs. 15%) with an odds ratio (OR) of 3.5 (95% CI 1.6-7.5). There was no statistical difference in the proportion of *H. influenzae* (OR 1.6, 95% CI 0.8-3.2) or *M. catarrhalis* (OR 0.96, 95% CI 0.4-2.3) in bullous myringitis compared to AOM.

In hemorrhagic myringitis the bacteriological analyses were performed to 18 children. The following bacterial pathogens of the MEF were found: *S. pneumoniae* in 8 (44%) children, *H. influenzae* in 2 (11%), *M. catarrhalis* in 4 (22%) and negative or non-pathogenic culture in 4 (22%) children (Figure 10.3). *S. pneumoniae* was more common in hemorrhagic myringitis than in AOM (44% vs. 15%) with OR 7.3 (95% CI 1.02-51.7). No significant differences were found for *H. influenzae* (OR 0.5, 95% CI 0.1-3.6) or *M. catarrhalis* (OR 1.5, 95% CI 0.3-8.5).

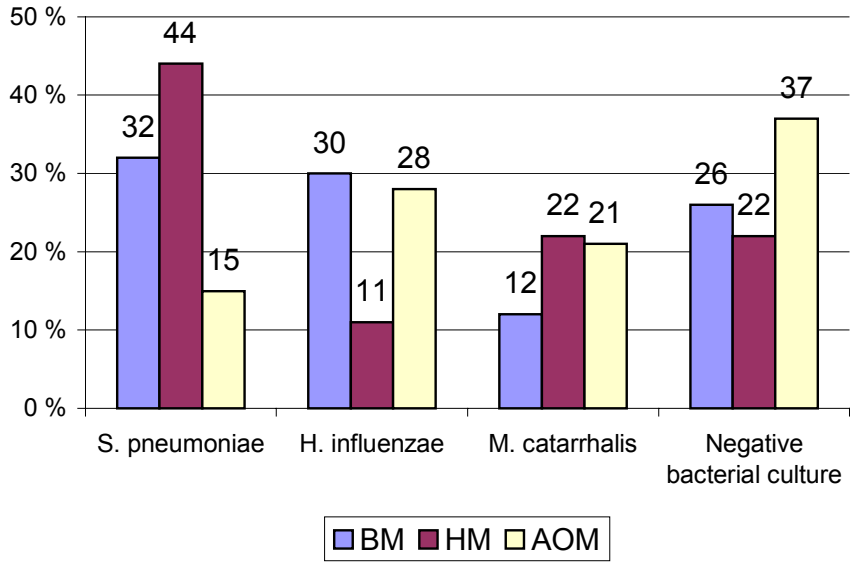

Figure 10.3. The bacterial etiology of bullous myringitis (BM), hemorrhagic myringitis (HM) and acute otitis media (AOM).

10.2.2. Viruses

The viral detections from NPA and MEF are presented in Table 10.1. NPA was analysed in 80 events of bullous myringitis and MEF was detected in 82 ears. In bullous myringitis a viral respiratory tract pathogen was identified from the NPA samples in 56 (70%) events and from the MEF samples in 22 (27%) ears. The detection rates of different viruses in bullous myringitis were rather similar to AOM. In bullous myringitis HRV and HEV were the most common viruses detected from the MEF.

In hemorrhagic myringitis respiratory viruses were identified from the NPA samples in 12 (57%) events and from the MEF samples in 5 (28%) ears. Influenza A virus was more common (11% vs. 1%) in hemorrhagic myringitis compared with AOM, although the number of samples was low (Table 10.1.).

Table 10.1. The detection rates of different respiratory viruses in nasopharyngeal aspiration and middle ear fluid samples in children with bullous myringitis (BM), hemorrhagic myringitis (HM) and acute otitis media controls (AOM).

Virus type	Nasopharyngeal aspirate			Middle ear fluid		
	BM (n=80)	HM (n=21) %	AOM (n=298)	BM (n=82)	HM (n=18) %	AOM (n=415)
Human rhinoviruses	38	29	22	11	6	10
Human enteroviruses	20	5	26	9	6	16
Respiratory syncytial virus	9	5	15	4	6	11
Influenza virus A	6	14	4	2	11	1
Adenoviruses	1	0	3	0	0	0.5
Parainfluenza viruses 1-3	5	5	1	1	0	0.2
Positive for any virus, %	**70**	**57**	**64**	**27**	**28**	**37**
Negative for viruses, %	30	43	36	73	72	63

10.2.3. Mycoplasma pneumoniae

In bullous myringitis all analysed 30 MEF samples were negative for *M. pneumoniae*. In addition, all 12 samples taken from the fluid of the blisters were negative *for M. pneumoniae*.

M. pneumoniae remained negative in all 7 analysed MEF samples of hemorrhagic myringitis.

10.2.4. Combined etiology

The combined bacteriological and viral findings are shown in Figure 10.4. From 82 ears with bullous myringitis a bacterial pathogen (*S. pneumoniae, H. influenzae or M. catarrhalis*) was detected without the presence of any respiratory virus from 41 (50%) ears. Both bacteria and virus were found from 21 (26%) ears. There was only one ear (1%) which was bacteriologically sterile with a virus (HRV) found in the MEF. In bullous myringitis 19 (23%) ears lacked any confirmed evidence of bacterial or viral etiology. Pure viral etiology without concomitant bacterial isolation was more common in AOM than in bullous myringitis (p=0.005).

From 18 ears with hemorrhagic myringitis a bacterial pathogen (*S. pneumoniae, H. influenzae* or *M. catarrhalis*) was detected without the presence of any respiratory virus in 9 (50%) ears. Both bacteria and virus were found in 5 (28%) ears. Respiratory viruses were not detected in bacteriologically sterile samples. Ultimately, 4 (22%) ears with hemorrhagic myringitis lacked any evidence of either bacterial or viral etiology. (Figure 10.4.)

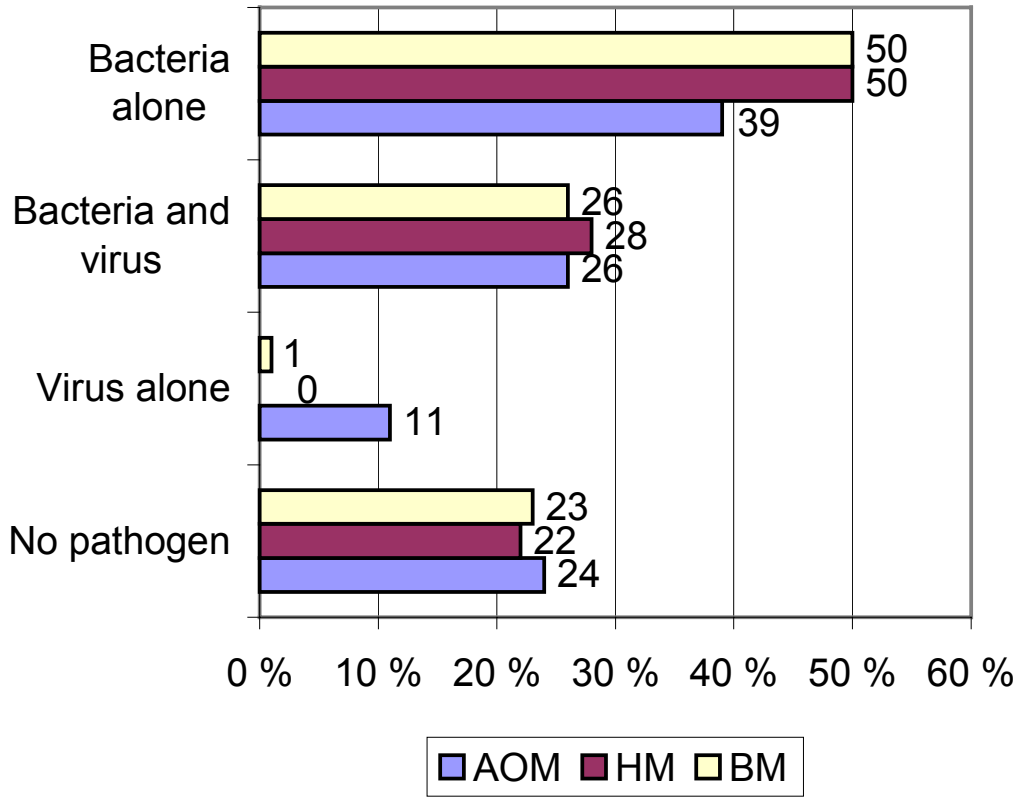

Figure 10.4. The etiology of bullous myringitis (BM), hemorrhagic myringitis (HM) and acute otitis media (AOM).

10.3. Symptoms, clinical course and a short term recovery (V)

The symptoms of the children at the time of diagnosis are presented in Figure 10.5. The symptoms of upper respiratory tract infection (rhinitis and cough) were highly common both in bullous myringitis and AOM. Ear-related symptoms (earache and rubbing of ear) and fever were more common in bullous myringitis compared with AOM. Also unspecific symptoms (restless sleeping, excessive crying and poor appetite) were more common in bullous myringitis than in AOM. The symptoms of hemorrhagic myringitis were similar to bullous myringitis.

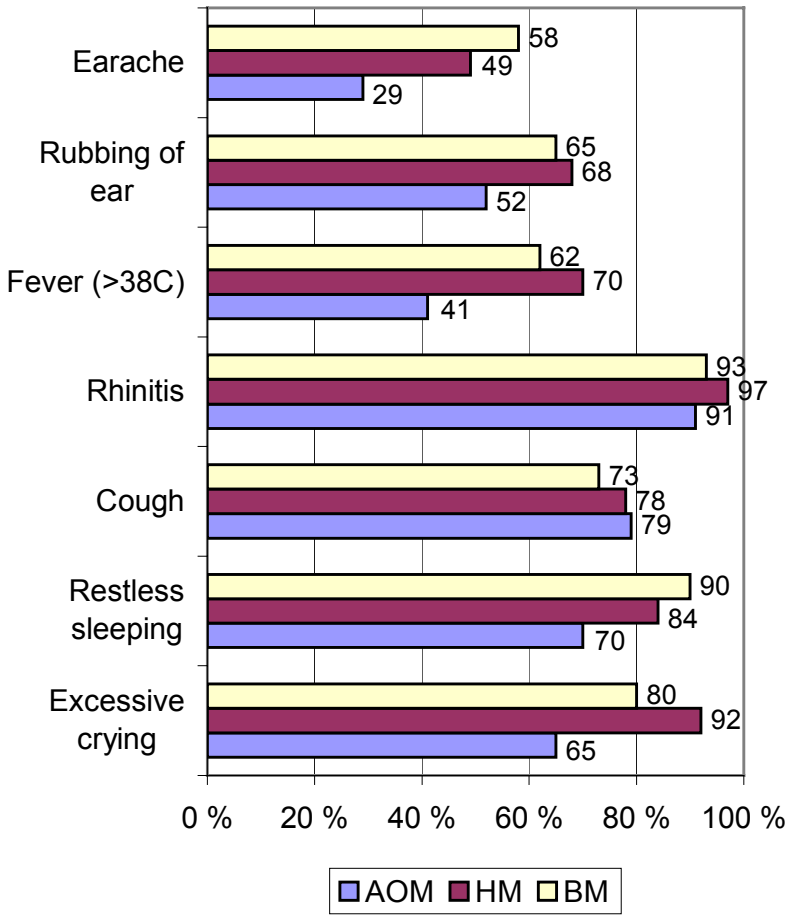

Figure 10.5. The preceding symptoms before the office visit in bullous myringitis (BM, n=86), hemorrhagic myringitis (HM, n=37) and acute otitis media (AOM, n=1876) in children less than two years of age.

The symptoms (earache, fever, restless sleeping and running ear) subsided in 95% of cases in three days. The follow-up visit of the bullous myringitis and AOM was scheduled for three to five weeks after the diagnosis. The resolution of MEF within 5 weeks occurred in 60% of the ears with bullous myringitis and in 68% of the AOM ears. A new AOM event was diagnosed in 37% of cases of bullous myringitis and in 31% of AOM events within 5 weeks after the original diagnosis.

At the time of diagnosis the number of blisters on the tympanic membrane varied from one to three in bullous myringitis. One blister was seen in 71%, two blisters in 24%, three blisters in 2% and a rupture of the vesicle was seen in 3% of ears. Blisters

spread out from the tympanic membrane to the external ear canal in 10% of ears. The area of blisters was less than one third of the area of the tympanic membrane in 49% of ears. About half of the tympanic membrane was affected in 35% of ears, and in 15% of ears more than two thirds of the tympanic membrane was affected. There were no cases of bullous myringitis in ears with patent tympanostomy tubes. Tympanostomy tubes were present in 9% of the ears diagnosed with AOM.

10.4. Epidemiology (IV)

The incidence of bullous myringitis was 5.7/100 person years (95% CI, 4.6-7.1/100 person years) in children < 2 years of age. The incidence of bullous myringitis varied between different seasons. The incidence was lowest (3.2/100 person years) in the summer of 1998 and highest in the winter of 1998-99 (14.9/100 person years).

Since it was possible that pneumococcal vaccine might effect the incidence of bullous myringitis, we calculated the incidences of bullous myringitis separately for children with (n=52) and without (n=30) pneumococcal vaccine. We found no statistical difference between these groups (RR=0.85, 95% CI, 0.5-1.3).

We calculated that up to 6400 events of bullous myringitis occur in the age group < 2 years in Finland per year. About 67% of cases of bullous myringitis were diagnosed in boys. The relative risk for boys was 1.8 (95% CI, 1.2-3.0). A recurrent event of bullous myringitis occurred in 4 of 82 (5%) children.

10.5. Association between acute bullous myringitis and recurrent AOM (IV)

BM children had a mean of 4.8 events (median 5) of AOM before the age of two years. This was higher in comparison with AOM children (mean 3.8 events, median 3, p=0.02) (Table 10.2). The proportions of children with recurrent AOM in BM children and AOM children are presented in Table 10.2. The risk of recurrent AOM (≥3 events) was higher in children with bullous myringitis in comparison with AOM children (RR 1.9 (95% CI, 1.1-3.2)). The results were similar regardless of the definition of recurrent AOM (≥3 events or ≥6 events). The risk of recurrent AOM (≥6

events) in BM children was higher in comparison with AOM children (RR 1.7 (95% CI, 1.01-2.7)).

Table 10.2. The number of events of acute otitis media (AOM) and otological procedures performed before the age of two years in children with at least one event of bullous myringitis (BM children) and in AOM children.

AOM MORBIDITY (2-24 MONTHS OF AGE)	BM children (n=82)	AOM children (n=808)	BM vs. AOM children (p-value)
Number of AOM events (mean)	4.8	3.8	0.02
Number of AOM episodes (mean)	3.7	3.0	0.01
Recurrent (≥3) AOM events, %	74	64	0.02
Recurrent (≥6) AOM events, %	33	23	0.04
Age at first AOM, days (mean)	323	356	0.09
Child with early AOM (<6 months of age), %	26	17	0.06
Otological procedures performed (2-24 months of age), %	34	30	0.39
- tympanostomy tubes, %	34	29	0.33
- adenoidectomy, %	24	21	0.48

In BM children the incidence of AOM before the event of bullous myringitis was 1.8/person year (95% CI, 1.4-2.2/person year) and after the event of bullous myringitis 2.9/person year (95% CI, 2.3-3.5/person year). The results indicate that the event of bullous myringitis actually increases the risk for recurrent AOM. The incidence of AOM was especially high during the first and second month after the

event of bullous myringitis. After that the incidence returned to a level similar to what was before the event of bullous myringitis (Figure 10.6).

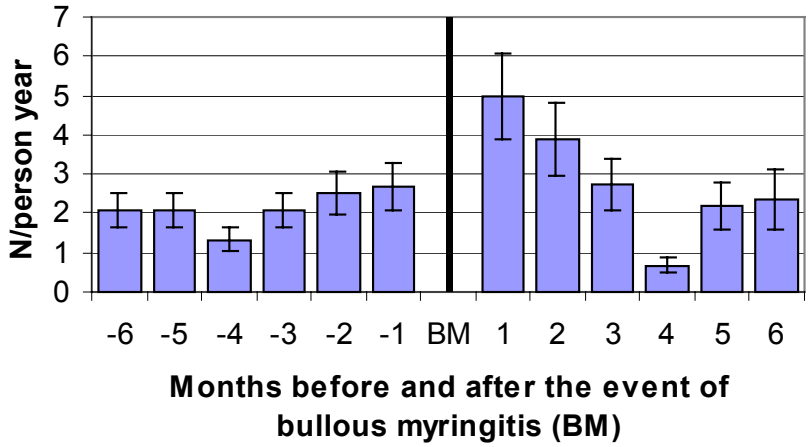

Figure 10.6. The incidence of AOM events in BM children before and after the event of bullous myringitis (BM).

11. DISCUSSION

11.1. Aims of the study

AOM is one of the most common diseases diagnosed during childhood and the most frequent reason for antibiotic therapy in children (Teele et al. 1983, McCaig and Hughes 1995, Freid et al. 1998). It would be very important to find the cases of AOM patients who apparently do not need antibiotics. For decades, acute myringitis has been considered a viral infection and therefore it could be a possible candidate for non-antibiotic treatment. However, the studies focusing on the etiology of acute myringitis are sparse, controversial and old. In addition, most of those studies lacked a strict definition of acute myringitis.

From the published literature we could approximate that bullous myringitis accounts for about 1-16% of the cases of AOM (Feingold et al. 1966, Halsted et al. 1968, Wetmore and Abramson 1979, Howie and Schwartz 1983, Pukander 1983, Hayden and Schwartz 1985, Arola et al. 1990, Hahn et al. 1998, Rosenblut et al. 2001, McCormick et al. 2003). In the United States more than 24 million AOM cases are diagnosed annually (Schappert 1992). It has been estimated that in Finland there about 500,000 AOM events each year in children <7 years old (Niemelä et al. 1999). Therefore, we can count that even if the number of cases of bullous myringitis would be only 1% of the number of AOM cases, still there would be about 240,000 cases of bullous myringitis seen each year in the United States and about 5,000 cases per year in Finland in the age group <7 years.

The main aims of our study were to investigate the etiological (I-III) and epidemiological (IV) aspects of acute myringitis. The FinOM Vaccine Trial provided an excellent opportunity to collect prospectively a large material of cases of acute myringitis. Furthermore, the results of the present study could be directly applied to clinical practice.

11.2. Diagnostic accuracy

The study clinic setting was planned to make the diagnoses as accurate as possible. All study physicians were specially trained; assisting personnel were also employed to each study clinic. At least 30 minutes were scheduled for each office visit. The diagnostic criteria of AOM and acute myringitis were strictly defined and the diagnoses were made by special full-time study doctors. Tympanometry was routinely used and myringotomy was performed if MEF was suspected. All data of the FinOM Vaccine Trial were collected on case report forms (CRF) which were specially designed for this study. All procedures were defined in standard operating procedures to make the diagnostic criteria and treatment consistent with different study clinics and physicians. Additionally, in case of acute myringitis a special CRF was filled to document and describe the finding, including drawn details on a schematic tympanic membrane.

There are many factors that may contribute to diagnostic inaccuracy for AOM or acute myringitis. These include the lack of diagnostic criteria (Hayden 1981), inadequate light sources (Barriga et al. 1986), an inability to visualize the tympanic membrane because of cerumen, a lack of training in pneumatic otoscopy (McCormick et al. 2000), and the withholding of objective tests such as tympanometry (Palmu et al. 1999). Those factors were taken into account in the FinOM Vaccine Trial to make the diagnoses as accurate as possible. The weakness of the present study was that the diagnosis was not confirmed by another doctor, neither was the finding photographed or video-otoscoped (Weiss and Holzmann 2003).

The specificity of detecting blisters on tympanic membrane is obviously high, although in some instances a large bulging membrane may have been diagnosed as bullous myringitis. The term hemorrhagic myringitis was chosen to represent a strong hemorrhagic redness of the tympanic membrane. The diagnosis of hemorrhagic myringitis is more subjective and it is sometimes difficult to determine whether the redness is hemorrhagic or not. Therefore the reliability is likely to be lower in hemorrhagic myringitis than in bullous myringitis. Before we started our trial we

expected to detect more cases of hemorrhagic myringitis than bullous myringitis. Because the number of cases of hemorrhagic myringitis was low and the diagnosis was probably not as reliable as in the cases of bullous myringitis we decided to focus mainly on bullous myringitis. In addition, some cases of myringitis might have been diagnosed outside study clinic during evenings and nights.

An otoscopic finding is always subjective, but we consider the diagnosis of acute myringitis and AOM to be valid and reliable. In our study the diagnostic accuracy is presumably higher than in some recent AOM studies in the USA where only 25% of physicians used pneumatic otoscopy to evaluate a child with an ear complaint and only 6% of doctors reported the mobility of the tympanic membrane (Garbutt et al. 2003). In another study the diagnostic accuracy of otitis media of pediatricians was tested with video-presented ear examinations (Pichichero and Poole 2001). Only 50% of the diagnoses were correctly diagnosed for three categories (AOM, OME and normal tympanic membrane) (Pichichero and Poole 2001).

11.3. Presence of middle ear fluid

Our goal was to investigate the clinical significance of blisters detected on an inflamed tympanic membrane. Therefore, in the present study bullous myringitis was defined as one or more blisters seen on the tympanic membrane or external canal irrespective of the findings in the middle ear. The idea was to study how often the MEF is present at the time of diagnosis and how often MEF develops during the course of acute myringitis.

The main finding of our study was that in almost all cases (97%) of bullous myringitis MEF is present or develops during the course of the disease in the age group studied. ICD-10 defines acute myringitis as an inflammation of the tympanic membrane without a middle ear effusion. If MEF is present it should be classified as AOM (WHO 1999). Also the classification panel of otitis media concluded that acute myringitis (without effusion) might be present during the early stages of AOM or during the stage of resolution (Bluestone et al. 2002).

Our results raise a question: Is there a disease of blisters on the tympanic membrane without MEF in children less than two years old? If we had used the definition of ICD-10, we would have diagnosed only 9 ears with bullous myringitis without MEF (and 20 ears with hemorrhagic myringitis). And of those all but 3 ears with blisters (and 9 ears with hemorrhagic myringitis) developed MEF during the course of disease.

11.4. Etiology

Our study shows that the most important causal agents of bullous myringitis are the common bacterial respiratory pathogens (i.e. *S. pneumoniae, H. influenzae* and *M. catarrhalis*) which are the same as in AOM. Those pathogens were detected from MEF in 76% of the cases of bullous myringitis. Viruses may play a role in the pathogenesis, since a virus was detected from the nasopharynx in 70% and from the MEF in 27% of the cases of bullous myringitis at the time of diagnosis. However, no specific viral pathogen seems to be the causative etiologic agent of acute myringitis. Furthermore there was only one case in which the MEF was virus-positive and bacteria-negative.

We must keep in mind that although we studied the common respiratory bacteria and a wide variety of upper respiratory viruses, it is still possible that there are other etiological agents that were not included in the analyses. In experimental AOM studies with rats it has been demonstrated that any substance (bacterial, nonbacterial or even physiological saline (0.9% NaCl)) which is able to enter the middle ear will induce a sterile or nonsterile inflammatory reaction of the tympanic cavity (Tonnaer et al. 2003). Nevertheless, we suggest the etiology of acute myringitis to be similar to that of AOM with a complex interaction of viral and bacterial pathogens.

The detection rates of viruses are dependent on the sensitivity of the viral diagnostic method used. The conventional viral diagnostic method (time-resolved fluoroimmunoassay was used for the detection of antigens of adenoviruses, influenza viruses A and B, parainfluenza viruses 1-3 and RSV. A more sensitive reverse transcription-PCR method was used for the detection of human rhinoviruses and

human enteroviruses. We might expect that the detection rates of viruses would have been higher if PCR had been performed for all viruses. However, our detection rates are consistent with previous studies in AOM (Pitkäranta et al. 1998, Chonmaitree 2000, Chonmaitree and Henrickson 2000, Heikkinen and Chonmaitree 2000).

One weakness in the present study was that if MEF was not present at the time of diagnosis of acute myringitis then we did not collect an NPA sample either. The missing NPA samples of those cases (n=6 in bullous myringitis and n=16 in hemorrhagic myringitis) might have given us more information on the etiology of acute myringitis. The other weakness was that we did not collect systematically the samples from the blisters. One reason for that was that in many cases the volume of liquid of the blister was very small. It would have been interesting to study the bacteriological and viral distribution of the samples detected from the blisters. Herpes simplex 1 and varicella zoster viruses are generally known to have the potential to develop blisters in skin. However, they are not common in children with respiratory tract infections and therefore those viruses were not included in the study protocol.

In the present study we could not find any *M. pneumoniae* positive cases in acute myringitis. *M. pneumoniae* has been mentioned in the literature as one possible etiological factor of bullous myringitis (Rifkind et al. 1962, Couch et al. 1964, Sobeslavsky et al. 1965, Clyde and Denny 1967). In experimental conditions bullous myringitis has been reported to appear in about 3% of patients if *M. pneumoniae* was inoculated to the nasopharynx (Rifkind et al. 1962, Couch et al. 1964). In clinical trials acute myringitis developed in 2-18% of patients with confirmed *M. pneumoniae* respiratory tract infection (Broome et al. 1980, Mansel et al. 1989). Although acute myringitis has been reported to be present occasionally in experimental and clinical trials with *M. pneumoniae* respiratory infection, there is very little evidence supporting the view that *M. pneumoniae* actually would be a significant etiological agent of acute myringitis.

11.5. Pathogenesis

The developing mechanism of the blisters remains unknown. It has been speculated that the blisters might be simply the manifestations of a mechanical injury of the tympanic membrane and may result from a variety of insults (Eustachian tube insufficiency, fever, etc) (Merifield and Miller 1966). It is probable that bullous myringitis does not have any specific etiological agent; rather, the development of the blisters is due to a non-specific reaction (Roberts 1980). We consider that a strong inflammatory reaction in the middle ear initiated by common bacterial and viral pathogens is the most common triggering factor in the development of the blisters.

The location of the blisters is considered to be in the subepithelial layer of the tympanic membrane (Merifield 1962). There are also small blood vessels and nerves in the same layer. The close location to the nerves and the stretching apart of the layers might be explanations for the severe ear pain that is often present in acute myringitis.

An interesting finding was that we did not diagnose any cases of bullous myringitis with patent tympanostomy tubes on the tympanic membrane. It is possible that tympanostomy tubes prevent the development of blisters. We suggest that the most important explanation is that tympanostomy tubes prevent the strong inflammatory reactions of the middle ear and consequently blisters do not develop on a tympanic membrane with patent tympanostomy tubes. The other possible explanation is that the difference of air pressure between the ear canal and the middle ear might influence the development of blisters during acute ear infection. Also, the presence of tympanostomy tubes may interfere with the eruption of the blisters by tying the tympanic membrane layers closely together. Additionally, it is also possible that the blisters were not diagnosed in some ears with tympanostomy tubes and purulent otorrhea at the office visit.

11.6. Epidemiology

The study population of the FinOM Vaccine Trial represented normal children on a primary care level. A total of 55% of children born in the study area at the enrolment phase of the trial took part in the prospective trial. Only 4% of children discontinued the trial before the age of 24 months. The parents were asked to contact the study clinics directly if their children had any symptoms of acute respiratory infection. The study clinic service was available seven days a week, but there were no appointments during evenings and nights. Over 80% of AOM diagnoses were made in the study clinics. This kind of study design provided the opportunity to diagnose most cases of acute myringitis in the study clinics. Therefore, also the incidence of acute myringitis could be calculated from well-defined and carefully followed population-based material.

In our study bullous myringitis was diagnosed in 5.7% children during a one-year of follow-up in the age group <2 years. The number of events of bullous myringitis was about 2% of all sick visits and about 5% of the number of events of AOM, which is consistent with previous studies (Feingold et al. 1966, Halsted et al. 1968, Wetmore and Abramson 1979, Howie and Schwartz 1983, Pukander 1983, Hayden and Schwartz 1985, Arola et al. 1990, Hahn et al. 1998, Rosenblut et al. 2001, McCormick et al. 2003).

The incidence of AOM is highest in the age group less than 2 years (Pukander et al. 1982b, Lundgren and Ingvarsson 1983, Sipilä et al. 1987, Teele et al. 1989, Alho et al. 1991), but the age distribution of bullous myringitis has been reported to be different from AOM. The majority of cases of bullous myringitis are diagnosed at the age of 2-8 years (Karelitz 1937, Wetmore and Abramson 1979, Pukander 1983, Hahn et al. 1998, McCormick et al. 2003). The narrow age range (from 7 to 24 months) is the major weakness of our study. It would have been interesting also to study the incidence of bullous myringitis in children over 2 years of age.

There is only one retrospective study in which the relationship of bullous myringitis and recurrent AOM (RAOM) has been reported. Hahn et al. (1998) considered that

bullous myringitis occurs in otitis prone patients. Our results are in accordance with that study, because also in our study BM children were more likely to have RAOM than AOM children. However, in our study an interesting finding was that the event of bullous myringitis actually increased the risk for subsequent AOM. The incidence of AOM in BM children was at the same level as in AOM children before the event of bullous myringitis, but after that it was significantly higher. It remained at an especially high level for two months. However, there were no differences in otological procedures between BM and AOM children. All these findings support the view that bullous myringitis is a more severe form of AOM.

11.7. Potential sources of bias

Our satellite study was not started concomitantly with the main trial, but only after the trial had run for nearly two years. At that time the youngest children in the FinOM Vaccine Trial were 7 months of age and the oldest just under two years of age. This kind of design might have resulted in some bias. First, some children had obviously had acute myringitis before the start of the satellite study. Therefore they are not included in the group of BM (or HM) children. Second, in acute myringitis the symptoms are more severe, and some of the cases of acute myringitis might have been diagnosed outside the study clinics. About 20% of the diagnoses of AOM were made outside the study clinics. Third, in the epidemiology part of our study we had divided the children into three age groups (<12 months, 12-18 months and >18 months). All diagnoses of bullous myringitis in the youngest age group were made in the fall of 1997 and the winter of 1997-98. We did not have any children in the youngest age group in the summer of 1998 when the incidence of AOM was lowest. If we expect that the incidence of acute bullous myringitis is lowest in summer, the true incidence rate of the youngest age group might be a little bit lower than we reported. But even if the study design may have led to some confounding factors, we are confident that our population-based cohort study accurately represents children at the general practice level.

In the FinOM Vaccine Trial two thirds of children were vaccinated with either

PncCRM or PncOMPC pneumococcal conjugate vaccine and one third with hepatitis B vaccine. To prevent the effect of vaccine in bacteriological analyses we matched the cases of acute myringitis with AOM controls by age, sex and vaccine group. We found that there is a relative increase in the proportion of *S. pneumoniae* in acute myringitis compared with AOM. Since PncCRM and PncOMPC have a moderate efficacy (25-34%) against culture-confirmed pneumococcal AOM (Eskola et al. 2001, Kilpi et al. 2003) we might expect that the incidence of bullous myringitis might have been a little bit higher if none of the children would have been vaccinated. However, there were no statistical differences in the incidences of bullous myringitis between vaccinated and non-vaccinated children. Therefore, we feel that the use of vaccine in the study protocol did not interfere with the results significantly.

11.8. Treatment

In the present study both the children with acute myringitis and AOM were treated with myringotomy and antibiotics when MEF was suspected. Currently myringotomy is not considered necessary in an uncomplicated case of AOM since it does not improve the resolution of MEF nor the symptoms (van Buchem et al. 1981, van Buchem et al. 1985, Engelhard et al. 1989, Kaleida et al. 1991). However, myringotomy is useful for identifying the causative pathogen. It is also recommended if serious complication is suspected or antibiotic treatment does not respond (Bluestone 1994).

In AOM the spontaneous recovery in children is about 80% and it has been questioned whether antibiotics are needed (van Buchem et al. 1981). Six of every seven children with AOM either do not need antibiotics or will not respond to antibiotic therapy (Laupacis et al. 1988). Unfortunately it is impossible to predict which one of the seven patients would benefit from antibiotics; therefore in clinical practice all seven have to be treated. The conclusion of the meta-analysis of 5400 children was that antibiotics have a significant but modest effect on the short-term recovery of AOM (Rosenfeld et al. 1994). The relief of ear pain also appears faster when antibiotics are used (Del Mar et al. 1997), but about 20 children must be treated

with antibiotics to prevent one child having some pain after two days (Glasziou et al. 2000).

The guidelines for treatment of AOM differ between different countries. In the United States and Canada about 96% of cases of AOM are treated with antibiotics, while in the Netherlands, Norway and Denmark the rates of prescription of antibiotics for AOM are of 31%, 67% and 76%, respectively (Hendley 2002). In Finland, the current recommendation is to treat AOM with a short-term antibiotic (for 5-7 days) (Puhakka et al. 1999). One reason to use antibiotics is the fear of severe complications of AOM. The incidence of acute mastoiditis is higher in the countries where a policy of restricted use of antibiotics for AOM is followed, however the difference amounted to only 2 additional cases of acute mastoiditis per 100,000 children per year (van Zuijlen et al. 2001).

Also in acute myringitis most cases would probably recover without any treatment, but in some case reports severe complications (for example meningo-encephalitis) have been reported (Wild and Spraggs 2003). However, because the bacterial etiology of acute myringitis is similar to AOM, the current opinion supports treating acute myringitis the same as AOM with antibiotics.

12. CONCLUSIONS

1. MEF will develop in a majority of ears during the clinical course of acute bullous and hemorrhagic myringitis in children <2 years of age.

2. The common bacterial pathogens (*S. pneumoniae, H. influenzae* or *M. catarrhalis*) are detected in about three-quarters of ears with acute myringitis. *S. pneumoniae* is more common in bullous and hemorrhagic myringitis compared with AOM.

3. Respiratory viruses are detected from NPA (indicating a concomitant virus infection) in 57-70% of events of acute myringitis.

4. Respiratory viruses are detected from MEF in about one-quarter of ears with acute myringitis. The viral distribution is similar in acute myringitis and AOM, but the pure viral etiology is more common in AOM.

5. *M. pneumoniae* is not a significant etiological agent of acute bullous or hemorrhagic myringitis in children <2 years.

6. Bullous myringitis is diagnosed almost in 1 in every 20 AOM events. During a one-year follow-up about 6% of children <2 years old will get bullous myringitis.

7. The symptoms of acute myringitis in children are unspecific, but earache and fever are more commonly present in bullous myringitis compared with AOM.

8. The children with bullous myringitis are more likely to have recurrent events of AOM compared with the control children. The incidence of AOM remains at a higher level for two months after the event of bullous myringitis.

9. Bullous myringitis is a severe form of AOM regarding the preceding symptoms, resolution of symptoms, resolution of MEF and the increased incidence of AOM after the event of bullous myringitis.

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15. ORIGINAL PUBLICATIONS (I-V)