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Review

Otitis media with effusion in children: Pathophysiology, diagnosis, and treatment. A review

Pauline Vanneste, Cyril Page*

Department of Otorhinolaryngology and Head & Neck Surgery, Amiens University Hospital, Amiens, France

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ABSTRACT

Otitis media with effusion (OME) is a frequent paediatric disorder. The condition is often asymptomatic, and so can easily be missed. However, OME can lead to hearing loss that impairs the child's language and behavioural development. The diagnosis is essentially clinical, and is based on otoscopy and (in some cases) tympanometry. Nasal endoscopy is only indicated in cases of unilateral OME or when obstructive adenoid hypertrophy is suspected. Otitis media with effusion is defined as the observation of middle-ear effusion at consultations three months apart. Hearing must be evaluated (using an age-appropriate audiometry technique) before and after treatment, so as not to miss another underlying cause of deafness (e.g. perception deafness). Craniofacial dysmorphism, respiratory allergy and gastro-oesophageal reflux all favour the development of OME. Although a certain number of medications (antibiotics, corticoids, antihistamines, mucokinetic agents, and nasal decongestants) can be used to treat OME, they are not reliably effective and rarely provide long-term relief. The benchmark treatment for OME is placement of tympanostomy tubes (TTs) and (in some cases) adjunct adenoidectomy. The TTs rapidly normalize hearing and effectively prevent the development of cholesteatoma in the middle ear. In contrast, TTs do not prevent progression towards tympanic atrophy or a retraction pocket. Adenoidectomy enhances the effectiveness of TTs. In children with adenoid hypertrophy, adenoidectomy is indicated before the age of 4 but can be performed later when OME is identified by nasal endoscopy. Children must be followed up until OME has disappeared completely, so that any complications are not missed.

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* Corresponding author. Service d'ORL et de chirurgie de la face et du cou, Centre Hospitalier Sud, Salouël, rue Laënnec, F-80090, Amiens, France.
E-mail address: page.cyril@chu-amiens.fr (C. Page).

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1. Introduction

In 1976, Mawson defined otitis media with effusion (OME, also referred to as sero-mucous otitis media) as the presence of liquid in the cavities of the middle ear, and the absence of signs of acute infection (Mawson, 1976). This is a chronic form of otitis media in which the tympanic membrane is not perforated. Local inflammation leads to epithelial metaplasia and the collection of liquid in the cavities of the middle ear. The middle ear effusion is mucous or sero-mucous in nature but not purulent. The condition lasts for at least three months; this sets it apart from persistent effusion after acute media otitis, which disappears after two months in 90% of cases (Blanc et al., 2018).

The very youngest children can be affected by OME: 50% of cases occur in infants under the age of 1, and 60% occur in infants under the age of 2 (Casselbrant and Mandel, 2003). The prevalence is especially high (between 60 and 85%) in children with craniofacial malformations (particularly trisomy 21 and cleft palate) (Flynn et al., 2009; Maris et al., 2014). Persistent OME leads to complications such as hearing loss and damage to the tympanic membrane (atrophy, retraction pockets, and cholesteatoma) (Maw et al., 1999). It can also delay language acquisition and lead to behavioural disorders (Aarhus et al., 2015).

The present review is based on a PubMed and Science Direct search for articles published between 1976 and 2018. The following keywords were used: “serous otitis”, “otitis media with effusion”, “tympanostomy tube”, “grommet”, “ventilation tube” and “child”. Articles dealing with OME in adults or with acute otitis media were excluded.

2. The physiopathology of OME

2.1. The inflammatory hypothesis

This pathology is thought to be initiated by inflammatory and immune reactions against rhinopharyngeal infections. The inflammation leads to cytokine production and the secretion of an exudate rich in protein and inflammatory mediators. The associated vasodilatation is responsible for increased gaseous exchanges in the middle ear, which induces an endotympanic pressure drop (LiJ et al., 2013). This pressure drop affects a cavity whose walls are fixed, with the exception of the tympanic membrane. Since the pars flaccida is the most fragile area (given its lack of a fibrous layer), retraction most frequently starts at this site. If the pressure drop is not corrected, tympanic atelectasis progresses at the expense of the pars tensa, and may lead to complete atelectasis of the tympanic membrane.

Prolonged inflammation of the middle ear's mucosae leads to cell differentiation and an increase in the number of mucus cells. An exudate fills the middle ear cavity. Mucus trapped in the Eustachian tube induces an upstream pressure drop in the middle ear, which in turn prevents the mucus from being evacuated (Hilding, 1944).

The inflammatory hypothesis is based on the presence of infectious agents in the cavities of the middle ear. In the past, OME was considered to be a sterile infection because effusion fluid samples gave negative bacterial cultures. In the 1990s, however, PCR assays showed that DNA and RNA of the main pathogens in acute media otitis were also present in OME samples (Fergie et al., 2004; Rayner et al., 1998). In 2006, Stoodley et al. used confocal microscopy to show that 92% of a population of children presenting OME had live bacteria (*Streptococcus pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis*) in their mucosal biopsies (Hall-Stoodley et al., 2006). These metabolically active bacteria might be present in at least half of all cases of OME with sterile bacterial cultures, and are thought to participate in biofilm formation (Van Hoecke et al., 2016).

2.2. Biofilms

Some researchers have estimated that 65% of chronic infections involve biofilms. Biofilm formation on the mucosae has been evidenced in OME (Potera, 1999). A biofilm results from cells trapped within an adherent matrix on an inert or living surface. The film can contain bacterial or fungal cells that are in contact with one another. The matrix contains polysaccharides, nucleic acids, and proteins (Palmer, 2005). The biofilm is created from a bacterial “anchor” that grows into a microcolony and then a mass. The extracellular matrix protects the bacteria against antibodies, phagocytosis, and antibiotics. These bacteria also require less oxygen and nutrients. They can transfer their DNA via plasmids or diversify via adaptive mutations that confer them with antibiotic resistance (Suh et al., 2010). In fact, recent studies have shown that systemic antibiotic treatment is not effective in the eradication of biofilms (Belfield et al., 2015).

2.3. Gastro-oesophageal reflux and allergy

Several other factors are thought to have a role in OME; they include gastro-oesophageal reflux (GOR), pollution, respiratory allergies, and genetic factors (Rovers et al., 2004).

The link between GOR and OME has been suspected ever since pepsins and *Helicobacter pylori* were found in samples of middle ear effusion (Formanek et al., 2015; Dogru et al., 2015). However, a direct causal relationship between GOR and OME has not been demonstrated (Miura et al., 2012; Morinaka et al., 2005).

Likewise, a number of studies have highlighted an association between respiratory (poly)allergy and OME (Luong and Roland, 2008; Alles et al., 2001; Kwon et al., 2013; Kreiner-Moller et al., 2012; Pau and Ng, 2016). Again, a causal relationship has not been proven, and allergy treatment does not modify the progression of OME (Simpson et al., 2011). However, children with chronic rhinitis, turbinate hypertrophy, asthma or allergy should be screened for OME (Mold et al., 2014). Conversely, screening for allergies is only justified when OME is combined with asthma or chronic rhinitis (Seidman et al., 2015).

Otitis media with effusion might be initiated by the activation of mucin genes (Kubba et al., 2000), of which 12 have been identified to date (Gendler and Spicer, 1995; Lapensee et al., 1997; Gum, 1992). MUC1, MUC3 and MUC4 are membrane-bound proteins, and might have a role in microorganism adhesion. Furthermore, MUC5AC and MUC5B might be involved in the accumulation of mucus in the cavities of the middle ear (Suboi et al., 2001).

The high prevalence of OME in children (relative to adults) is explained by the immaturity of the Eustachian tube; the latter is

unable to adequately protection the middle ear from the variations in nasopharyngeal pressure associated with contamination of the middle ear by rhinopharyngeal germs. This dysfunction is due to three age-related factors: the Eustachian tube's angle, length, and ability to close (Bluestone and Klein, 2001).

3. Diagnosis

3.1. Clinical aspects

The physician should consider a diagnosis of OME in children with a hearing disorder, delayed acquisition (particularly language acquisition), difficulties at school, and behavioural and/or sleep disorders. The latter are often reported by the child's parents (Luotonen et al., 1998).

Most cases of OME are diagnosed clinically following an otoscopic examination. The use of a pneumatic otoscope enables the physician to detect middle ear effusion and check the aspect of the tympanic membrane. The use of binocular microscope or telescopic video-otoscopy might improve otoscopy, particularly in children. A liquid film, bubbles, opacity, an ochre or bluish coloration, and central retraction of the tympanic membrane may be apparent. A diagnosis of OME is confirmed if the same signs are present three months later (Legent, 1998).

The tympanogram provides an assessment of tympanic compliance. A type B tympanogram (i.e. a flattened curve) is suggestive of OME (Rosenfeld and Kay, 2003; Shekelle et al., 2002).

The use of nasal endoscopy should be restricted to cases of nasal obstruction or very persistent OME, with a view to confirming the presence or absence of adenoid hypertrophy. Nasal endoscopy also enables the differential diagnosis of a rhinopharyngeal tumour (Quaranta et al., 2013; Elicora et al., 2015).

It is important to screen for an associated palatal disorder (bifid uvula or a submucous cleft palate) because the latter can complicate the treatment of OME. Similarly, craniofacial dysmorphism and polymalformative syndrome are risk factors for the onset, persistence and recurrence of OME (Yaneza et al., 2016).

3.2. Evaluation of the hearing threshold

It is essential to evaluate the impact of OME on the child's hearing, given the disorder's frequent occurrence during the language acquisition period. At frequencies of 500, 1000, 2000 and 4000 Hz, around 50% of children with OME have a loss of more than 20 dB, 20% have a loss of more than 35 dB, and 5–10% lose more than 50 dB. A hearing loss greater than 50 dB should prompt the physician to consider a possible association with inner ear damage (Roberts et al., 2004). Ideally, the hearing assessment should include tonal audiometry with air and bone conduction, and age-appropriate vocal audiometry.

The hearing loss associated with OME is greater in children with a cleft lip and palate. In a study published in 2009, Flynn et al. observed mean hearing losses of 35.71 dB in children with a cleft lip or palate and 26.41 dB in children without clefts (Flynn et al., 2009).

If an audiometric examination is impossible, recording auditory evoked potentials or the auditory steady state response is recommended (Nagashima et al., 2013).

4. Treatments

4.1. Drug treatments

Given the detection (using PCRs) of bacterial genomes (notably those of *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*) in samples of effusion fluid, the treatment of OME with antibiotics has been suggested (Gok et al., 2001). Although many antibiotic drugs have been tested, none has proved long-term efficacy on the symptoms of OME. In fact, a recent Cochrane Collaboration study of 23 studies (with courses of antibiotic treatment ranging from 10 days to 6 months) did not find a positive effect on hearing or a reduction in the frequency of tympanostomy tube (TT) placement. Likewise, the effusion diminished in only 13% of cases (Venekamp et al., 2016).

Although antibiotic treatment is not recommended in the current guidelines, studies have shown that a diagnosis of OME is often followed by the prescription of a course of oral antibiotics – especially in the emergency room, more than in ENT departments (Roditi et al., 2016). For example, some centres prescribe treatment with macrolide antibiotics if OME is combined with rhinosinusitis, since the latter is a trigger for OME. The results of a recent study demonstrated the anti-inflammatory efficacy of macrolides such as erythromycin, clarithromycin, azithromycin and roxithromycin on middle ear effusion in guinea pigs. The researchers suggested that macrolide antibiotics could be used as an antibacterial, anti-inflammatory treatment of OME (Ersoy et al., 2018). However, the international guidelines do not recommend the use of macrolides in the treatment of OME (Simon et al., 2018).

Systemic and intranasal corticoids have also been used to reduce the local inflammation that causes Eustachian tube dysfunction in OME. These drugs might inhibit the synthesis of arachidonic acid and inflammatory mediators in the Eustachian tube and the middle ear. They might also reduce the lymphoid tissue around the Eustachian tube, improve surfactant secretion, and reduce the viscosity of the effusion from the middle ear (Rosenfeld, 1992). In 2011, a literature review of 12 studies found that corticoids had short-term (but not long-term) benefits in the treatment of OME symptoms (Kwon et al., 2013; Kreiner-Moller et al., 2012). A recent prospective, double-blind, randomized clinical trial of oral corticoids in 389 children aged 2 to 8 confirmed the absence of a significant hearing gain upon treatment (Francis et al., 2018). Furthermore, systemic corticoids are associated with a range of adverse reactions, such as diarrhoea, nausea, hyperactivity, and epistaxis. Topical treatments do not have proven long-term efficacy (Williamson et al., 2009). Hence, the risk-benefit ratio rather argues against the use of these medications (Hussein et al., 2017).

Carbocysteine is the only currently recommended mucokinetic agent (in the Japanese guidelines only). It is used optionally with a view to reducing the production of mucus, promoting its excretion, and reducing the inflammation of adjacent organs while waiting for the surgical treatment (Ito et al., 2015). Mucokinetic agents might relieve the symptoms of OME but do not have proven long-term efficacy. A literature review found that 1–3 months of treatment with a mucokinetic agent could avoid the need for TT placement in 20% of affected children (Moore et al., 2001). However, this treatment is not recommended in international guidelines (Simon et al., 2018).

An analysis of 16 studies (totalling 1880 patients) of the efficacy of antihistamines and nasal decongestants (used alone or in combination) did not highlight clinical value in the treatment of OME. A pooled analysis of data from the six studies that evaluated medication-related side effects found a frequency of 17% in the treated group and 6% in the placebo group (Griffin and Flynn, 2011).

The Politzer manoeuvre is a means of relieving dysfunction of the Eustachian tube. By blowing air up the nostril (using a balloon or other device), the child can partially re-open the Eustachian tube. However, the studies performed to date are inhomogeneous. In particular, no double-blind trials have been performed. It has nevertheless been demonstrated that in children over the age of 2, four weeks of Politzerization was associated with improvements in middle ear pressure and in the auditory threshold (Bidarian-Moniri

et al., 2014). A recent literature review of eight controlled, randomized trials (featuring a total of 702 patients) found a trend towards rapid improvement of the symptoms. However, the audiometry and tympanometry results were not statistically significant (Perera et al., 2013). Lastly, this treatment has two potential advantages: its low cost, and the absence of side effects.

Aerosol treatment has also been evaluated in the treatment of OME. Both conventional aerosols and manosonic aerosols have been applied. The advantage of aerosol treatment is the increased diffusion of the active compounds to the nasal and sinus mucosae. In the manosonic aerosol technique, a compressor provides an additional mechanical action and helps to open the Eustachian tube. On average, 12.5 sessions of aerosol therapy with a combination of a corticoid, an antibiotic and a mucokinetic agent are required to normalize the audiometry results in more than 75% of patients (Saga et al., 2009). Again, these treatments have not been evaluated in prospective, randomized trials.

4.2. Tympanostomy tubes and adenoidectomy

The placement of TTs (also referred to as grommets and ventilation tubes) is the benchmark treatment for persistent OME with a functional impact on hearing or with damage to the tympanic membrane (Simon et al., 2018). The indication for TT placement is an audiometric hearing loss of between 25 and 40 dB (Ito et al., 2015; Pediatric Group ENT society of CMA, 2008). It is also necessary to take account of individual difficulties related to this hearing loss, which vary from one child to another and are not always correlated with the hearing threshold.

Tympanostomy tubes help to ventilate the cavities of the middle ear and balance the pressures on each side of the tympanic membrane. Different types of TT can be used in the treatment of OME. Shepard tubes (primarily used in Europe, China, and South Africa) usually fall out about 6 months after placement. Armstrong tubes are preferred in North America, and have an intermediate lifetime - up to 14 months (Rosenfeld et al., 2013). Lastly, T-tubes have a longer lifetime and generally do not fall out spontaneously (Soderman et al., 2016).

Hellström et al.'s literature review of 63 publications found that hearing and quality of life had improved for at least nine months after TT placement. In contrast, their longer-term efficacy could not be demonstrated (Hellström et al., 2011).

Another literature review of 10 randomized studies found that the hearing threshold had improved after TT placement, with a gain [95%CI] of 12 dB (Fergie et al., 2004; Rayner et al., 1998; Hall-Stoodley et al., 2006; Van Hoecke et al., 2016; Potera, 1999) in the first three months and 4 dB (Blanc et al., 2018; Casselbrant and Mandel, 2003; Flynn et al., 2009; Maris et al., 2014; Maw et al., 1999) from 6 to 9 months. However, the review did not find any evidence of a long-term effect of TTs on comprehensive and expressive language development (Browning et al., 2010).

Short-term TTs are used for first-line treatment, and fall out after between 6 and 18 months. Thus, the risk of complications is corresponding lower. Long-term TTs stay in place for two years or more. Even though the complication rate increases with the TTs' duration of use, these devices are still indicated when OME recurs in a child who has already had short-term TTs. They are also recommended in children with chronic Eustachian tube dysfunction (Lindstrom et al., 2004).

Tympanostomy tubes do not prevent the progression of OME towards tympanic atrophy, and their impact on progression towards a retraction pocket has not been determined (Johnston et al., 2004). In contrast, they do prevent the appearance of cholesteatomatous chronic otitis media (Djurhuus et al., 2015). The prevalence of tympanic anomalies increases with TT placement; however, it is not possible to determine the respective responsibilities of OME and the TTs (De Beer et al., 2005).

Wallace et al. have shown that TTs prevent the recurrence of OME after the tubes fall out or are removed. The researchers found that the risk of OME at 2 years was 13% lower than for a wait-and-see approach or for paracentesis (Wallace et al., 2014). However, there are no studies of efficacy beyond 2 years.

In children at risk of language or learning disorders, rapid treatment is recommended in order to limit the impact of additional deafness. This concerns children with autistic spectrum disorders, perception deafness unrelated to OME, a speech delay, a craniofacial syndrome or malformation, blindness (or other visual disorders), a cleft palate or a global development delay (Rosenfeld et al., 2016).

Tympanostomy tubes are inserted under general anaesthesia, and so are associated with an iatrogenic risk. Otorrhoea is the most frequent complication, and occurs in 3–50% of cases immediately after surgery. In most cases, the otorrhoea is usually isolated and does not lead to sequelae (Vlastarakos et al., 2007).

The expulsion, obstruction or removal of the TT is linked to the growth and the progressive migration of the tympanic epithelium. The incidence of obstruction varies from 0% to 37.3%, depending on the study (median: 6.7%), and the incidence of early expulsion is about 3.9%. In 0.5% of cases, the TT migrates into the cavity of the middle ear. The likelihood of these complications depend on the type of TT, the operator's level of experience, and the size of the stoma. For TTs as whole, the frequency of residual perforation varies from 1 to 10% (Kay et al., 2001). The known risk factors are the presence of a large internal flange, previous TT placement, and the TT's lifetime. Myringosclerosis is very frequent; this phenomenon corresponds to proliferation of the fibroblasts in the fibrous layer of the tympanic membrane, with the concomitant deposition of calcium phosphate crystals. In most cases, myringosclerosis does not have clinical consequences; however, very severe cases can lead to transmission deafness by blocking the ossicles (tympanosclerosis) (Kay et al., 2001). Iatrogenic cholesteatoma is very rare, and is thought to result from trapping of the epidermis by the TT (Kay et al., 2001).

The North American (Rosenfeld et al., 2013), (Rosenfeld et al., 2016), (Rosenfeld et al., 2004) and French (Blanc et al., 2018) guidelines recommend a 3-monthwait-and-see period prior to TT placement.

Adenoidectomy may enhance the clinical effectiveness of TTs in OME (relative to treatment with medications or TTs alone) for at least two years (Boonacker et al., 2014). The risk of OME recurrence may be lower, and the time to subsequent TT placement may be significantly longer. The likelihood of subsequent TT placement is thought to be 40% lower in this context (Wang et al., 2014).

According to Mikals and Brigger, the combination of adenoidectomy with TT placement decreases the proportion of children requiring subsequent TT placement from 36% to 17%, although this is only the case in children over the age of 4 (Mikals and Brigger, 2014).

The American guidelines recommend adenoidectomy for the treatment of OME as a function of the child's age. For children under 4, adenoidectomy must only be performed in cases of nasal obstruction or recurrent infections. In children over 4 years, it can be combined with TT placement (Rosenfeld et al., 2016).

Adenoidectomy removes the physical obstruction of the Eustachian tube, restores the drainage of mucus, and equilibrates the pressure in the middle ear. However, a retrospective study of 423 children found that adenoid volume was not correlated with the efficacy of adenoidectomy. In contrast, adenoidectomy was significantly more effective in the treatment of OME when large adenoids were in contact with the torus tubarius than when small adenoids

were not. The viscosity of the middle ear effusion does not influence the effectiveness of adenoidectomy (Skoloudik et al., 2018). Hence, physical blockage may not be the main risk factor for OME.

In animal experiments, Abi Hachem et al. found that biofilm formation was reduced by washing the middle ear with saline solution or children's shampoo. A hydrodebrider can be used to effectively remove biofilms (Abi Hachem et al., 2018).

4.3. Children at risk of OME

In children with cleft lip or palate, OME is more frequent and is more likely to recur (in 26.8%–59.5% of cases, regardless of the type of TT (Iwaki et al., 1998; Valtonen et al., 2005a)) than in children without clefts (35%) (Triglia et al., 2004). These episodes of otitis tend to disappear around the age of 5–6 in the general population, and at around 10–12 for children with cleft lip/palate (Sheahan et al., 2004).

Chin-Lung Kuo et al.'s meta-analysis confirmed the efficacy of the TTs with regard to hearing and language (Kuo et al., 2014). In some studies, hearing improved significantly (Li et al., 2007). In others, the improvement was not statistically significant, although the mean audiometric gain was significantly greater in the TT group than in the non-treated group. With regard to language, Hubbard et al. (1985) found that children treated with TTs at a young age articulated better and required a shorter course of speech therapy.

Several researchers have suggested the use of prophylactic TT placement at the same time as surgery to close the cleft (Paradise et al., 1969; Paradise, 1980; Valtonen et al., 2005b; Tunçbilek et al., 2003). Despite the absence of symptoms, early ventilation of the cavity may enabled normal development and a normal pneumatisation of the mastoid and thus the avoidance of complications. Other researchers (such as Tunçbilek et al. (2003)) recommended TT placement only when the OME was symptomatic (recurrent otitis, hearing loss of more than 30 dB, and tympanic retractions).

5. Conclusion

Otitis media with effusion is a frequent pathology in children; if the condition is not monitored carefully, it can progress into cholesteatomatous chronic otitis. The diagnosis can be performed relatively easily (using otoscopy) during a consultation. Hearing loss must be evaluated before and after treatment. Although pharmacological treatments may have short-term symptomatic effectiveness, the absence of long-term effectiveness (particularly with regard to the auditory threshold), the associated adverse events and the cost mean that they cannot be recommend in the treatment of OME. Tympanostomy tube placement is the only treatment to have been validated by the international scientific community. These devices have proven efficacy with regard to improving the auditory threshold, preventing the recurrence of OME, and protecting against progression to cholesteatoma of the middle ear. Tympanostomy tubes are indicated in cases of OME complicated by transmission deafness or anatomical modifications of the tympanic membrane (i.e. retractions). Adenoidectomy can be combined with TT placement in children over the age of 4 if hypertrophy is detected with nasal endoscopy or under the age of 4 years in the event of nasal obstruction or recurrent rhinopharyngeal infections. The children must be followed up for several years, so that any complications are not missed. Children at risk of language or learning disorders must be monitored closely.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joto.2019.01.005.

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