The Etiology, Pathophysiology, and Management of Otitis Media with Effusion

Christopher C. Butler, MD, and R. Gareth Williams, MPhil, FRCS*

Address
*Department of General Practice, University of Wales College of Medicine, Llanedeyrn Health Centre, Cardiff CF23 9PN, UK.
E-mail: butlercc@cf.ac.uk

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Otitis media with effusion (OME) is a common and important condition that may result in developmental delay in children, and significant health care resources are devoted to its management. Newer techniques including polymerase chain reaction are implicating organisms not previously considered important in etiology. The role of gastroesophageal reflux as a cause of OME is likely to receive greater research attention. Regarding prevention, more is being learned about potentially modifiable risk factors such as environmental smoke, care outside the home, and breast feeding. Although immunization may to play a role in the future, existing evidence suggests that the general population of children should not be immunized in order to prevent OME. Several major studies have recently added to the understanding of epidemiology and management. Large trials in the United States, the Netherlands, and the UK suggest that OME is not an appropriate condition to include in a screening program. In addition, the advantages of early treatment with ventilation tubes over watchful waiting in terms of language development tend be modest and diminish by about 18 months. Treatment with hearing aids should be further evaluated. The search for effective medical management continues, and better ways are being identified of targeting interventions to those children with OME who are most likely to benefit.

Introduction

Otitis media with effusion (OME) is a chronic inflammation of the middle ear in which a collection of fluid is present in the middle ear space, in the absence of acute inflammation, and where no perforation of the ear drum is present [1,2]. Refractory OME is a common problem in children and may be associated with hearing loss and delayed language development [3–7]. OME is associated with behavioral, developmental, and cognitive difficulties in some children, with a risk of difficulties persisting into late childhood and early teens [8]. The median hearing loss in children with OME was found to be 25 dB, and a similar level of hearing loss would result from putting plugs in the ears of a normally hearing child [9,10]. The total annual cost of treating children under 5 years of age for OME is over $5000 million annually in the United States [11]. The insertion of grommets (ventilation or tympanostomy tubes) is the second most common surgical procedure on children, costing $1200 million annually in the United States [11]. In England and Wales, expenditure by the National Health Service on surgical treatment for OME is around £47.8 million annually [12]. OME is therefore an important and common condition. This review aims to synthesize recent research in the field of OME with a major focus on developments with direct clinical relevance.

Epidemiology

Otitis media with effusion has a prevalence of about 20% at around 2 years of age [13]. It remains common up to the age of 7 years at which time the prevalence is between 3% and 8% [14–16]. OME often resolves spontaneously with a median duration of about 3 months [17]. However, about 50% of those recovering will have a further episode of OME [14,17]. About one fifth of UK children had either unilateral or bilateral OME for more than half of their first 3 years of life [18]. Children referred by general practitioners to 16 ear, nose, and throat departments in the United Kingdom were recently observed as part of a lead into a treatment trial. Some children recovered during this period, while others had persistent OME. The factors that predicted persistence, after adjustment for possible confounders, were referral between July and December, having a mother who smokes 10 or more cigarettes per day, multiple upper airway symptoms, and siblings with a history of OME [19••,20]. Additional risk factors for persistence were source of referral (community clinic with previous audiometry), and hearing level worse than 30 dB in the better hearing ear [20].

Etiology

It is not clear why OME develops. Low-grade infection, poor clearance due to poor eustachian tube function, local inflammatory reactions, and adenoidal infection or hypertrophy have all been implicated [21].

Bacteria

Viral and bacterial microorganisms have been found in children with OME. *Streptococcus pneumoniae* accounted for 38% of positive cultures and *Haemophilus influenzae* accounted for 27% of positive cultures in a large series of bacterial cultures of middle ear fluids in 2807 children [22]. A smaller study found culture-positive aspirates were more common in younger children (56% of children under 2 years of age compared with 35% of children over 2 years of age), and found an increase in isolation of anaerobic bacteria in effusions over 6 months duration [23]. In a more recent study of middle ear samples from 123 patients with OME, bacterial culture and polymerase chain reaction (PCR) were used to detect *Alloiococcus otitidis*, *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis* [24]. Bacteria were cultured in 45%, and major pathogens (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*) were found in 33%. *A. otitidis* was not found at all in cultures. However, PCR of the effusions yielded positive results for one or more of the four tested pathogens in 88%, with 20% positive for *A. otitidis*. Effusions that persisted for 3 months or longer had a higher prevalence of *A. otitidis* than those with shorter durations, and PCR for *A. otitidis* was more often positive in mucoid effusions compared with mucoserous effusions. In a smaller study of 54 samples of effusions from 32 children, PCR evidence of *A. otitidis* was found more often (10 samples) than any other bacteria [25].

Viruses

In a recent study, 100 samples of middle ear effusions collected at the time of ventilation tube replacement were analyzed and viral RNA was detected by reverse transcriptase (RT)-PCR in 19 children and by virus isolation in five children [26]. Respiratory syncytial virus RNA accounted for eight cases. Bacterial pathogens were isolated from 35 samples and were associated with viral RNA in 11 cases, nine of them human rhinovirus. Rhinovirus infection may therefore be present in more effusions than previously suspected, but further research is needed to determine whether viral RNA found in OME represents old, ongoing, or recurrent infection [27]. Researchers examined the promontory mucosa and adenoidal tissue of 18 children with OME for evidence of rhinovirus infection. Seven of eight adenoid biopsies were positive for rhinovirus but rhinovirus RNA was not found in any of the 18 middle ear biopsies [28].

Gastroesophageal reflux

Reflux of gastric contents into the nasopharynx and the eustachian tubes has been implicated in OME. A study of 65 samples of middle ear fluid found evidence of pepsin protein in 59 cases. This suggests that antireflux therapy may come to play a part in treatment of OME [29]. Indeed, a case series of 19 adults with refractory OME or ear discomfort were found to have reflux, and their ear problems resolved on proton pump inhibitor therapy [30,31].

Environmental smoke

A systematic review of five studies found an odds ratio for parental smoking on referral for middle ear effusion of 1.21 (95% confidence interval [CI], 0.95–1.53) [32]. The odds ratio for persistence of OME from having a mother who smokes 10 or more cigarettes a day is 1.7 (95% CI, 1.1–2.8) [19••].

Day care attendance

Children attending day care outside the home are exposed to more pathogens, so frequently suffer acute respiratory infections that are associated with OME [33]. A prospective cohort of 252 Australian children attending day care found that OME was detected 4.4 times in 12, 2-week periods [34]. A US prospective cohort study of 2253 infants found that repeated exposure to large numbers of other children, either in the home or at day care, was the most significant sociodemographic risk factor for OME [35]. A meta-analysis of studies involving children aged 0 to 4 years confirmed the finding that day care is a risk factor for OME [36].

Breast feeding

A prospective cohort of 306 infants in two suburban practices in the United States found that the incidence of OME was inversely related to rates of breast feeding beyond 3 months of age [37]. A twofold elevated risk of first episode of OME was observed in exclusively formula-fed infants compared with infants breast fed for 6 months. Logistic regression found that formula feeding was the most significant predictor of OME episodes. Age of colonization with middle ear pathogens and day care attendance outside the home were less significant predictors. A cohort of 1439 preschool children aged 2 years in the Netherlands were followed at 3-month intervals to their fourth birthday [38]. Once again it was found that breast feeding protected against OME. Preventing early colonization may be important in reducing the risk of persistent OME. One study found that the only significant determinant for persistent OME was an episode of acute otitis media in the first year of life [33].

Family history

The odds ratio for OME persisting among children with a sibling with a history of OME is 1.6 [19••]. The risk relates to environmental and genetic factors that are difficult to separate, but studies indicate a strong genetic component in twins with otitis media [39].

Pathophysiology

The chronic inflammation of OME usually follows from episodes of acute otitis media, and it has been hypothesized that this results from an imbalance in the ratio of proinflammatory cytokines and inhibitors [40].

Cytokines and mucin

The chronic inflammation of OME usually follows from episodes of acute otitis media. This suggests that bacteria

stimulate a mucin-rich effusion by activating mucin-producing genes [41,42]. The activation of inflammatory cells within the middle ear is a consistent feature in OME, and it has been hypothesized that this results from an imbalance in the ratio of proinflammatory cytokines and inhibitors [40]. This imbalance seems to be concurrent with the upregulation of mucin genes, and both processes are likely to influence each other [43]. There is also a relationship between the quantum of inflammatory activity and the disease progress, with one study showing a reduction in the interleukin-6 concentration within middle ear fluid as the condition improved, and this reduction appeared to be influenced by antibiotic treatment [44]. Highly elevated levels of C3a have been found in middle ear effusion fluid, indicating complement activation. Significantly higher levels of C3a were found in children with prolonged effusions and those who had previously undergone surgery to insert ventilation tubes [45]. The trigger for the activation of the complement system in OME has not been clearly identified, but the alternative C pathway is activated in normal human serum by middle ear effusion fluid. This implies a self-perpetuating inflammatory process [46]. Immune modulation and upregulation of mucin genes increases mucous secreting goblet cell density. Animal studies indicate that the increase in mucous gland density and mucin production may be more likely with some types of bacterial infection than others, with pneumococcus and *Haemophilus* species seeming to have a greater effect than *M. catarrhalis* [41,47,48].

Adenoidal hypertrophy

The belief that eustachian tube obstruction underpins the development of middle ear effusion is likely to be true for a minority of patients with OME. Eustachian tube function varies over time in children with chronic OME, and consequently eustachian tube function tests are of limited prognostic value [49]. Although adenoidal hypertrophy with secondary eustachian tube obstruction is still thought to be a contributory cause of OME in many children, the relationship is unlikely to be simply mechanical. Changes in the lymphocyte subpopulation within the adenoids result in an increased population of natural killer lymphocytes in children over 10 years of age [50]. The T-cell phenotype of lymphocytes within the adenoids has been found to be similar to those found within the middle ear in OME, whereas the same phenotype is rare in peripheral blood [51]. The adenoids may provide a source of primed lymphocytes that eventually extravasate in the middle ear mucosa.

Allergy

Many studies continue to implicate an allergic process in OME. One recent study has shown a much higher prevalence of allergic rhinitis, asthma, and eczema in children with OME compared with the general population [52]. Biochemical analysis of middle ear mucosa has also shown a significantly greater likelihood of finding allergy-competent cells and cytokines in OME patients compared with patients with no mucosal disease [53].

Ciliary activity

A laboratory-based study of human cells showed that ciliary activity is not reduced by the constituents of middle ear fluid in chronic otitis media with effusion [54].

Diagnostic Maneuvers

The basis of diagnosis is pneumatic otoscopic examination of the ear. This has a fairly high sensitivity and specificity in the hands of experienced clinicians [55]. A review of five studies of pneumatic otoscopy using fluid found in the middle ear at the time of surgery as gold standard found a mean sensitivity of 89% and specificity of 80% [56]. Audiometric evaluation supports the diagnosis, and the key investigations are conventional pure tone audiometry and/or play audiometry, as well as tympanometry. These supportive investigations play an increasingly important role if the clinician is less experienced in otoscopy. In the age range of 3.5 to 7 years, accurate threshold measurement is possible in about 98% of cases to within 5 dB. Audiometric testing is more challenging in younger children [57]. Tympanometry has a high sensitivity (up to 99%) and specificity (up to 93%) in children with significant hearing impairment due to OME and can be used as a screening investigation [58]. Tympanometry, pneumatic otoscopy, and videotelescopy were performed 2 days before myringotomy or tympanostomy in 89 children [59]. Videotelescopy gave the highest sensitivity, specificity, and accuracy for finding fluid at operation, followed by pneumatic otoscopy, tympanometry, and acoustic reflectometry. Overall, therefore, the diagnosis of OME is based primarily on clinical examination in experienced hands, with additional information from tympanometry and audiometry. Examinations should ideally be performed using a pneumatic otoscope with halogen lighting.

Management

Screening

Evidence continues to accumulate against including OME in a screening program [17]. A US study enrolled 6350 healthy infants from 2 to 61 days of age and evaluated them regularly for OME [60••,61]. Before the age of 3 years, 429 children with persistent OME were randomized to have tympanostomy tubes inserted as soon as possible or after 9 months if OME persisted. Language, speech, cognition, and psychosocial development were assessed at the age of 3 years in 402 of these children. Prompt insertion of tympanostomy tubes was not associated with a significant improvement in developmental outcomes. In a study from the Netherlands, 187 children aged 1 to 2 years with persisting OME identified by screening were randomized to immediate treatment with ventilation tubes or a period of watchful waiting [62••]. No

differences were found in expressive or comprehensive language between the two treatment groups. Both groups improved on measures of quality of life, but there was no difference between groups. The mean costs per child during 1 year of follow-up were $454 in the ventilation tube group and $120 in the watchful waiting group. On average, an additional investment of $334 per patient was needed for ventilation tube treatment [63••].

Autoinflation

Increasing the pressure in the nasopharynx may cause the eustachian tube to open, allowing effusions in the middle ear to drain. Short-term resolution of OME has been observed in children using a middle ear autoinflation device [64]. However, a systematic review of autoinflation found that studies of autoinflation of the middle ear were of low quality and results varied [65]. There is insufficient evidence to promote its use in clinical practice.

Nondrug treatment and ventilation tube insertion

A systematic review from the early 1990s found that treating children with OME with ventilation tubes resulted in a mean hearing threshold improvement of 12 dB at 6 months and 6 dB at 1 year [12]. Adenoidectomy in addition to ventilation tube insertion gives little additional benefit over ventilation tube insertion alone [12,66]. A more recent trial found a 5.6 dB pure tone average advantage from treating OME with ventilation tubes at 6 months, but this advantage had disappeared by 1 year [67]. A recent trial comparing early surgery with watchful waiting found that early surgical intervention reduced behavioral problems and improved language development in children with OME at 9 months [68,69••]. However, after 18 months, differences were no longer statistically significant. Other trials in children identified with OME by screening found that initial improvements in language developmental outcomes from ventilation tube insertion compared with watchful waiting were lost by about 18 months [60••,67]. Ventilation tube insertion is commonly associated with adverse effects. A meta-analysis of sequelae from ventilation tube insertion showed that 16% of children experienced otorrhea in the postoperative period, 26% experienced otorrhea later, and 3.8% experienced chronic otorrhea [70]. Ventilation tubes were associated with more common incidence of obstruction (7% of ears) and granulation tissue (5%). Sequelae after extrusion included tympanosclerosis (32%), focal atrophy (25%), retraction pockets (3.1%), cholesteatoma (0.7%), and perforation (2.2% with short-term tubes, 16.6% with long-term tubes) [70].

Advising children with ventilation tubes about ear protection when swimming

A meta-analysis to determine whether children with ventilation tubes would benefit from ear protection when swimming included 11 studies [71]. There was no evidence to suggest that protection with earplugs, swimming caps, or antibiotic ear drops in children with ventilation tubes reduces the risk of acute otitis media. In fact, there was some evidence that ear drops may even increase this risk.

Topical decongestants

Eighty children with persistent OME and ventilation tubes in situ were randomized to treatment with 0.05% xylometazoline hydrochloride nose drops or placebo and had their eustachian tube function assessed. Treatment with xylometazoline nose drops had no effect on the ventilatory or the protective function of the eustachian tube [72].

Surgical treatment: adenoidectomy and tonsillectomy

Adenoidectomy and adenotonsillectomy may reduce eustachian tube dysfunction and congestion and thus improve OME. However, 461 children aged 3 to 15 years with recurrent acute otitis media were randomized to adenoidectomy, adenotonsillectomy, or control, and 410 were observed for up to 3 years [73]. The efficacy of surgery in preventing otitis media was modest and mainly limited to the first year of follow-up. Interestingly, baseline presence of nasal obstruction attributable to large adenoids, probable presence of upper airway allergy, and parents' socioeconomic status had no notable associations with outcomes.

The most appropriate timing of surgical intervention and the selection of children for surgery continue to be debated. The benefits of surgery have to be balanced against the possible risks. As a result, there are no uncontroversial guidelines as to when to operate and which operation should be performed. Surgery should be considered in children with problems that can be directly attributed to OME. In those children with identified risk factors for persistence, namely season, passive smoking, and sibling with OME, it would seem reasonable to offer ventilation tubes. Adenoidectomy may provide sustained benefits in hearing and behavior, as well as improvements in nasal and upper respiratory health, but has not been shown to reduce the symptoms of ear infection. Adenoidectomy appears to be most effective in children between the ages of 3 and 7 years [66], and is likely to be appropriate in children within this age range who have a history of snoring and mouth breathing.

Hearing aids

Hearing aids may be an effective alternative to surgery in the treatment of hearing impairment in approximately two out of three children studied [74,75]. They should be considered in children in whom the only problem is hearing impairment associated with OME and also for those at higher risk of complications from surgery (including increased anesthetic risk and chronic tympanic membrane or middle ear disease). However, few studies have evaluated hearing aids for treating OME. To our knowledge, no randomized controlled studies have yet been published. Study numbers have been small and outcomes have been subjective improvements in hearing and behavior.

Antibiotics

Since the seminal meta-analysis of trials on the effects of antibiotic treatment in OME [76], further studies have confirmed the finding from the meta-analysis that there is short-term benefit in terms of resolution of effusions from antibiotic treatment [77,78]. This benefit rapidly disappears. None of the studies included in the meta-analysis or published subsequently have demonstrated long-term benefit on language and other developmental assessments from antibiotic treatment for refractory OME.

Steroids

A systematic review has shown that systemic steroids may enhance the resolution of effusions in the short term but longer-term benefit has not been demonstrated [79]. A new trial has been reported evaluating oral steroid treatment in conjunction with an antibiotic [80]. Prednisolone was given with amoxicillin and compared with amoxicillin alone either for 2 or 4 weeks. No advantage was found for adding an oral steroid to amoxicillin treatment for 2 or 4 weeks at 4 months follow-up. Intranasal steroids in addition to an antibiotic showed initial benefit over placebo, but by 3 months of treatment this benefit had largely disappeared [81].

Mucoactive drugs

A meta-analysis has found benefit from treatment with carboxymethylcysteine. For every five or six children treated with s-carboxymethylcysteine over 1 to 3 months, one child will not have to undergo ventilation tube insertion as they would have had they been treated with placebo [82]. However, despite these findings, this treatment remains controversial since the trials in the meta-analyses were small and generally of poor quality [83].

Vaccination

Two large studies of conjugate vaccine against pneumococci have been reported. A before and after (interrupted time series) US study evaluating the effect of a conjugate vaccine against pneumococcus involved 37,000 children and found an 8.9% reduction in all visits for otitis media and a 20.3% reduction in ventilation tube placement [84]. A Finnish randomized, controlled trial enrolled 1662 infants at age 2 months and found a 6% reduction in acute otitis media from the conjugate vaccine, but the CIs included zero [85]. Effect on OME was not studied. A systematic review of studies of pneumococcal vaccines in the prevention of otitis media (in addition to the above two studies of conjugate vaccine) identified eight trials of pneumococcal polysaccharide vaccine [86]. The authors concluded that the pneumococcal polysaccharide vaccine has little effect on the prevention of acute otitis media in children without documented prior episodes of acute otitis media and only moderate effect on children with a documented history of acute otitis media prior to vaccination. The authors agree that pneumococcal vaccination of the general population to prevent OME is not warranted. Another study has identified a subgroup of children who fail to respond to a 23-valent pneumococcal polysaccharide vaccine and have low immunoglobulin (Ig)G2 and IgA antibody levels [87]. Experimental research suggests that a nasal vaccine based on *Haemophilus* membrane protein may modulate local immune responses within the ear. Further research is needed before drawing any conclusions about its efficacy in preventing OME [88].

The effect of influenza vaccine on prevention of acute otitis media has been studied. A 2-year placebo-controlled trial (1602 children in year one and 1358 children in year two) found that the overall vaccine efficacy was 96% against acute otitis media associated with culture-confirmed influenza [89]. In another study, 288 children were vaccinated with a live, attenuated vaccine or placebo given by intranasal spray [90]. The vaccinated children had 30% (95% CI, 18%–45%) fewer episodes of acute otitis media. An efficacy trial (n = 133) of inactivated virosomal subunit influenza vaccine in children with recurrent otitis media found a positive effect for the vaccine in preventing recurrent acute otitis media [91]. In a 6-month period, 24 vaccine recipients had 32 episodes of acute otitis media while 42 control subjects had 64 episodes. Studies of the effect of influenza vaccination on OME are awaited.

Guidelines

Referral

The decision whether or not to treat an episode of OME is based on the effect on the child and the duration of the condition. Spontaneous resolution is common, with approximately 50% resolving within 3 months and 95% within a year [17]. A 3-month period of watchful waiting is therefore appropriate in most cases. Exceptional cases are those children who seem to have significant disability and those with pre-existing conditions such as Down syndrome and cleft palate. The National Institute for Clinical Excellence recommends that in those patients with a proven hearing loss, a referral to a specialist should be considered for the following reasons [92]: 1) persistent foul-smelling discharge and unusual otoscopic features suggestive of cholesteatoma; 2) excessive hearing loss suggestive of sensorineural deafness; 3) difficulties with language, cognition, or behavior; 4) a second disability such as Down syndrome; 5) frequent episodes of acute otitis media; and 6) persistent hearing loss in excess of 3 months.

Treatment

The American Academy of Pediatrics, the American Academy of Family Physicians, and the American Academy of Otolaryngology-Head and Neck Surgery with the review and approval of the Agency for Health Care Policy and Research of the Department of Health and Human Services produced an influential guideline in 1994 [2]. The target child for this guideline was aged 1 through 3 years without craniofacial

abnormalities and who was healthy apart from OME. The guideline recommended at least 3 months of watchful waiting in children with confirmed OME, and a hearing test before surgery is considered. Oral antibiotics, steroids, and decongestants and/or antihistamines were mentioned as possible treatment options. However, our literature review suggests there is insufficient evidence to support the use of medical treatments or autoinflation. We believe the best option for treatment is surgery (and possibly hearing aids). The recently published guidelines on the diagnosis and management of childhood otitis media in primary care from the Scottish Intercollegiate Guideline Network also stress the importance of hearing evaluation before watchful waiting or considering active treatment, given the fluctuating nature of the condition [93••]. They recommend watchful waiting for children under 3 years of age with persistent OME and hearing loss of 25 dB or less, but no speech, language, developmental, or behavior problems ("A" recommendation). Referral to an otolaryngologist is recommended for children with persistent bilateral OME who are over 3 years of age or who have speech, language, developmental, or behavioral problems ("B" recommendation).

Conclusions

Regarding etiology of OME, new work suggests that the role of rhinoviruses, *A. otitidis*, and gastroesophageal reflux deserve heightened research attention. Major new studies involving large samples of children have contributed to our thinking about management of OME. Ventilation tube insertion can be far more expensive and invasive than watchful waiting, and advantages tend to disappear by 18 months for most children. Better targeted treatment is therefore indicated, and epidemiologic factors that predict slower resolution of OME have been identified that may help to guide selection of children for surgery. These factors include family history, environmental smoke, history of upper respiratory tract infections, severity of hearing loss, and month of referral. Breast feeding and care outside the home are related and contribute. These large studies have also added to the body of evidence that screening programs for the early detection of OME are not worthwhile. Oral steroids have again been shown to have a short-term benefit that is not sustained. The role of mucoactive drugs should be further clarified in new, well-conducted, and larger studies. The clinical and cost effectiveness and acceptability of treatment with hearing aids should be assessed using a randomized, controlled trial design. The search for effective, nonsurgical treatment continues, as does the search for better ways of targeting treatment to those children who will benefit from it in important ways.

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