Management of Otitis Media with Effusion and Recurrent Acute Otitis Media

Abstract

Otitis media with effusion (OME) and recurrent acute otitis media (RAOM) are both extremely common, with a significant impact on the child’s and parents’ quality of life. Various treatment options have therefore been investigated to prevent their occurrence. A literature search was carried out on Medline, EMBASE and Cochrane databases for relevant randomised controlled trials and meta-analyses. We sought to summarise the current evidence on the management of these common conditions.

Keywords

otitis media with effusion, recurrent acute otitis media, randomised controlled trial, evidence based management

Introduction

OME is characterised by the presence of a middle ear effusion in the absence of symptoms and signs of acute infection, while AOM is the presence of a middle ear effusion accompanied by signs and symptoms of an acute infection. RAOM is defined as three or more episodes of AOM within six months, or at least four episodes within a year, with complete resolution of symptoms in between episodes.

Both OME and RAOM are common conditions. Up to 80% of children will have been affected by OME by the age of 10, while 83% of children will have had at least one episode of acute otitis media by the age of 3. The conditions can have a significant impact on children and their parents, and may affect speech, language, cognition and school performance. They are commonly encountered in primary care practice, by otolaryngologists and by audiologists. A variety of treatment interventions have been proposed, and this review aims to summarise the therapeutic options for these conditions.

Otitis Media with Effusion

OME is the commonest cause of deafness in children in the developed world. Prevalence is in the region of 20% and up to 80% of children are affected at least temporarily by the age of 10. OME gives rise to a conductive hearing loss (CHL) which is usually transient, but can persist, possibly leading to educational, language and behavioural problems.

In most instances of uncomplicated OME, no intervention is required as the fluid clears spontaneously and hearing recovers. However, once bilateral OME has persisted over 3 months, the chance of it being cleared spontaneously a year later is only 32%. If bilateral OME persists in a symptomatic child, intervention may be required to remove the effusion and improve hearing.

Much quality research on the management of OME has been performed, but this research is made difficult by the fluctuating and often self-resolving nature of OME; this makes the inclusion of control groups essential and both researchers and clinicians can erroneously believe that treatment is effective where in fact spontaneous resolution would be just as likely. Equally important is the choice of study population (children with temporary unilateral OME may be very different to those with bilateral effusions persisting 3 months, whilst children with existing communication difficulties or developmental delay may be particularly at risk if they develop concomitant hearing difficulties), and outcome measures which could include hearing level, OME resolution, requirement for surgery, or quality of life measures. Furthermore subjects can be analysed in terms of the child or individual ears. In the context of a condition that for many children is minor or temporary, the risks of any intervention also need to be carefully examined.
Formal guidelines on the management of OME are published, although they may not always be followed. The current UK treatment strategy, based on NICE guidelines on the surgical management of OME, is ventilation tube (VT) insertion in children with symptomatic persistent bilateral OME documented over a period of 3 months with a hearing level in the better ear of 25-30dB HL or worse; exceptionally, surgery may be considered in children with persistent bilateral OME with a hearing loss less than 25-30dB HL where the impact of the hearing loss on a child’s developmental, social or educational status is judged to be significant.

Methods
A literature search using the terms “Otitis Media with Effusion, management, treatment” was performed using MEDLINE and EMBASE databases from Jan 1980 to October 2012. English language meta-analysis and randomised controlled trials (RCTs) were reviewed. The reference lists of identified articles were also screened for additional studies. The outcome of interest was the effect of interventions on the management of OME in otherwise healthy children. Studies not including children were excluded, as were studies of children with other known medical problems such as Down’s syndrome or cleft palate.

Studies and results
The electronic search resulted in the initial identification of 5397 publications. Subsequently only RCTs and meta-analyses were used. Titles and abstracts were examined by one reviewer and checked by a second. Fifty-six manuscripts were identified to provide data to answer the research question identified. The following interventions were reviewed: VTs, adenoidecctomy, autoinflation, antibiotics, antihistamines, decongestants, steroids and mucolytics.

Ventilation Tubes in OME
The beneficial effects from short term VTs have been shown in an individual patient meta-analysis and Cochrane systematic review, with VTs also being recommended by NICE guidelines on the surgical management of OME. Browning et al. reviewed 10 RCTs to analyse the effectiveness of treatment with VTs compared to non-surgical treatment. Compared to controls, the benefit of VTs to hearing was demonstrated over the first six months, with greatest benefit at 3 months (in the region of 12 dB HL), and then decreasing to 4 dB HL at six to nine months. Another meta-analysis of three high quality trials showed a benefit of 4 dB at 6-9 months but at 12-18 months no difference was found. Additionally, no difference was found on language or developmental outcomes. VTs may not provide entirely normal hearing, with this thought to be due to mucosal oedema around the ossicular chain, which remains despite middle ear ventilation.

Rovers et al. tried to identify subgroups of children with OME that might benefit more than others from treatment with VTs. There was significant interaction between day-care and surgery, concluding that VTs may be used in young children that grow up in an environment with a high infection load such as attending a nursery, or in older children with a hearing level of 25dB HL or greater in both ears persisting for at least 12 weeks. Causal association between speech and language problems and a history of OME in early childhood has been surrounded by considerable controversy. Roberts et al. performed meta-analyses to show that OME during early childhood did not adversely affect receptive or expressive language during the preschool years in correlation studies. However, Hall et al. showed those aged 4 ½ years undergoing a watchful wait (WW) period had a significantly poorer performance in language and writing, and teachers reported significantly more emotional problems for WW children; in this study the WW time period was on average 9 months, which is longer than the current recommended period of 3 months.

Studies with less stringent trial entry criteria typically show less benefit from VTs. For example, the Paradise study in 2007 showed that, in otherwise healthy young children (n=391), delaying the insertion of VTs does not improve the developmental outcomes. However this study included children with unilateral effusions (only 20% of children had continuously-present bilateral OME), and analysed largely children that were treated under 2 years of age.

VTs are not free from adverse effects. Complications tend to increase with the length of time VTs are in situ, for example with Shah grommets a persistent perforation rate of 5.6 is reported, but this rises to 10% in long term ventilation tubes. Other complications of VTs include myringosclerosis, atrophy and retraction; these may or may not be significant, and they may also occur as a consequence of OME itself. Schilder in 1999 reported the differences in tympanic membrane changes comparing the effects of VTs with the effect on OME itself. In both observational and experimental studies tympanosclerosis is reported to occur in 39-65% of ears treated with VTs and 0-10% of untreated ears, while for segmental atrophy the corresponding rates are 16-73% and 5-31%. Regarding the prevalence of atelectasis and attic retraction, the difference between ventilated and untreated ears, respectively is less: 10-37% as opposed to 1-20% for atelectasis, and 10-52% as opposed to 29-40% for attic retraction. The average hearing loss associated with these tympanic membrane abnormalities is less than 5 dB. A cohort study by de Beer et al. found a persistent small conductive hearing impairment in non-surgically managed OME children compared with non-OME children. A further study compared 27 subjects who never received VTs with 38 who had received one set of VTs. Pathological abnormalities of the tympanic membrane were present in 81% of those treated with VTs and 19% of those that had not had VTs, with hearing thresholds also 2.1-8.1 dB worse in the treated group.

Adenoidecctomy for OME
Following VT insertion a quarter of children will require further surgical treatment within 2 years. In order to reduce recurrence of OME, adenoidecctomy as an adjunct to VT insertion has been investigated. NICE guidelines recommend adenoidecctomy only in children with co-present severe or persistent upper respiratory tract infection. The beneficial effects of adenoidecctomy on OME have been shown by Cochrane systematic review and RCTs, with adenoidecctomy having a significant benefit on the resolution of middle ear effusion in OME, but only a small benefit to hearing. Not all studies agree, for example, Casselbrant et al. found, in children aged 2-3 years, that adenoidecctomy conferred no advantage in terms of time with effusion over VTs alone. However, another trial comparing VTs plus adenoidecctomy with myringotomy and adenoidecctomy in 3-7 year old children...
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concluded that hearing in both groups improved, but using VTs instead of a myringotomy showed no additional advantage, implying that the hearing improvement is the result of adenoidectomy.23 The TARGET (Trial of Alternative Regimes in Glue Ear Treatment) randomised study investigated the role of adjuvant adenoidectomy in addition to VTs in persistent bilateral OME in children aged 3.25-6.75 with at least a 20dB hearing loss in both ears. They found that adding adenoidectomy to VTs doubles benefit from short stay VTs by extending better hearing through to the second year; it also halved the numbers meeting an actual reduction in re-insertion surgery. There was, however, a 0.6% rate of post-operative haemorrhage severe enough to warrant return to theatre.24

In the UK, adjuvant adenoidectomy is not recommended in the absence of persistent frequent upper respiratory tract symptoms. American guidelines agree with this in the case of primary surgery, however they recommend adenoidectomy is undertaken in conjunction with any revision surgery.2 There is a great variation in the number of children receiving adenoidectomy in different countries, but generally the number of children having adenoidectomy appears to be reducing.25 Although adenoidectomy does appear to help OME resolution, the fact that many children do not require a second set of VTs is used to argue against routinely performing adenoidectomy in all children.

**Autoinflation**

Autoinflation refers to the opening of and forcing of air through the Eustachian tube by raising intranasal pressure and introducing air into the middle ear. Evidence remains limited following meta-analysis listed on the Cochrane database. The studies included were small, of limited treatment duration and short follow up. Overall, pooled analysis showed no benefit to tympanometry or audiometry, but subgroup analysis suggested that the Politzer device appeared to be beneficial. The review concludes that, because of the low cost and absence of adverse effects, it is reasonable to consider autoinflation whilst awaiting resolution of OME.26 NICE guidelines on OME management also agree with this strategy. However, evidence of efficacy remains limited, while the frequency and duration of autoinflation also remain unknown.8

**Antibiotics in OME**

Currently, antibiotics are not a recommended treatment in the UK.8 The rationale for using antibiotics is the involvement of bacteria and biofilms in the aetiopathogenesis of OME.27 A recent Cochrane review28 found that antibiotics increased the OME resolution in individual studies by between 1-45% at 2-3 months. Meta-analysis was only possible for OME resolution at 6 months after treatment: this demonstrated that antibiotic treatment increased resolution rate by 13%, and 8 children would have to be treated in order to resolve OME in an extra one child. The most favourable outcomes were seen when antibiotics were used for 4 weeks or 3 months, when the increased resolution rates were 32% to 34%, respectively. Antibiotics also increased the risk of adverse effects. Therefore, any possible modest effect on OME needs to be balanced against the risk of side effects, emergence of bacterial resistance and replacement with new bacterial strains or species in the context of a condition that for many children is mild and self-resolving;28-30 the review therefore does not recommend antibiotic use in OME.

**Antihistamines or Decongestants for OME**

Effectiveness of antihistamines, decongestants and antihistamine/decongestant combinations for the resolution of effusions have been reviewed in a Cochrane database publication by Griffin & Flynn.31 They reviewed 16 studies (1880 participants), which showed no statistical or clinical benefit. Pooled data showed no benefit and some harm from use of antihistamines or decongestants alone or in combination in the management of OME. Evaluating the side effects found a rate of 17% in the treated group versus 6% in the placebo group.

Montelukast appears to be no more effective than placebo in eliminating persistent middle ear effusion. A prospective randomised, placebo controlled, double blind study of montelukast effect on persistent middle ear effusion was abandoned because it was having no effect on effusion clearance.32

**Steroids in OME**

A meta-analysis of the use of oral and intranasal steroids has been published by the Cochrane collaboration. Following review of 12 RCTs including 945 children with OME, no beneficial effect from systemic or topical steroids on hearing loss was seen. When analysing OME resolution in the short term (<1 month), pooled data showed that oral steroids did have a beneficial effect compared to controls (RR 4.48; 95% CI 1.52 to 13.23); combining oral steroids with antibiotics also resulted in improved OME resolution compared to placebo plus antibiotic at less than one month follow up (RR 1.99; 95% CI 1.14 to 3.49). Additionally, no benefit was seen beyond one month, these studies were limited by heterogeneity, and the significant possibility of adverse reactions should not be underestimated.33

Several studies of topical nasal steroids for OME have not demonstrated any benefit.34 Gluth et al.35 studied 91 patients assigned to treatment or control in a randomised double blinded controlled trial. They found no statistical difference in the normalization of abnormal tympanometric signs on a per-patient basis (19% steroid vs. 32% placebo; p = 0.18) or a per-ear basis (22% steroid vs. 35% placebo, p = 0.15). Additionally there was no statistical difference in overall symptom study score between the control and treatment group (P = 0.27).

**Mucolytics**

A meta-analysis in 1996,36 on placebo-controlled studies of medical treatment with S-carboxymethylcysteine (SCMC) suggested that it is an effective treatment for OME. Four hundred and thirty participants were included. Those receiving oral SCMC avoided surgical intervention approximately 2.31 times more often than similar patients receiving placebo (ratio of active drug to placebo-effect on overall clinical improvement: 2.31; C.I. 1.28-4.20, p < 0.01); the odds ratio for achieving normal tympanometry also favoured SCMC, but this was not statistically significant (odds ratio: 2.25, C.I. 0.97-5.22, p = 0.058).

In 2001 a systematic quantitative review of double blind comparisons of placebo and SCMC by Moore et al.37 (n=283 children and 146 ears) showed that the number of children that needed to be treated in order to prevent one VT insertion was 5.5 (95% confidence interval 3.8 to 9.8). In 2000, Commins et al.38 carried out a double blind RCT, in which 78 patients were
randomised to Mucodyne and 88 to placebo. The main outcome measure was surgical or non-surgical intervention. There were 28 patients with resolved OME, 17 in the Mucodyne group and 11 in the placebo group. Patients treated with mucodyne were 1.68 times more likely to undergo resolution of OME rather than placebo, but this was non-significant (risk ratio 1.68, 95% confidence interval 0.74-3.37, p = 0.13).

Evidence based management of OME: Summary
This systematic review found that high quality evidence on the treatment of OME is available, in the form of numerous controlled trials and Cochrane reviews (table 1). VTs improve hearing (in the short term), whilst adenoidectomy increases OME resolution particularly once VTs extrude. Current high quality evidence does not support the use of antibiotics, antihistamines, decongestants and oral or topical steroids, whilst autoinflation may be beneficial with minimal associated risks. There is some evidence that mucolytics may be beneficial, but the existing meta-analysis is made difficult by study heterogeneity.

Clinical trials of existing technologies and procedures may in the future provide evidence for the use (or non-use) of interventions such as autoinflation or surgery to the Eustachian tube, whilst further research may refine criteria for adenoidectomy and VTs. Novel methods of drug delivery may prove to be useful treatments, and advances in our understanding of the genetics and aetipathogenesis of OME may lead to developments of new treatments in the future.

Recurrent Acute Otitis Media
AOM is one of the most common illnesses of childhood with a peak incidence between six to twelve months of life. It has a significant impact on healthcare costs, which have been estimated at US $3-5 billion per year. Epidemiological studies have shown that by the age of one, 62% of children will have at least one episode of AOM. This rises to 83% by the age of three. RAOM is therefore not uncommon in children, and frequently encountered by ENT surgeons and audiologists.

Several studies have shown that RAOM during the first 3 years of life can have adverse long-term consequences on school performance, cognition, and speech and language development. Furthermore, the quality of life of these children and their caregivers are significantly worse compared to their counterparts. Therefore, there is a need for strategies to prevent RAOM. Currently, they include prophylactic antibiotics, VT insertion and adenoidectomy. The use of pacifiers, pneumococcal vaccine (PCV), xylitol and zinc supplements are amongst other strategies that have also been investigated. Here we review the evidence for each of these management options.

Methods
A literature search using the term “recurrent acute otitis media” was performed using MEDLINE and EMBASE search engines in September 2012. We included studies that were RCTs with RAOM as defined by Goycoolea et al. comparing intervention with control (placebo/other intervention), and a follow-up period of at least 6 months. We excluded studies where patients had a history of Down’s syndrome, cleft palate, or immunodeficiency. The search was limited to the English language and studies published between January 1980 to September 2012. The reference lists of identified articles were also screened for additional studies. We also included relevant reviews from the Cochrane database. The measured outcome was the effect of interventions on the recurrence of AOM.

Studies and results
The literature search yielded 32 articles. We excluded 16 studies because they did not meet the inclusion criteria. The 16 studies used in this review are summarised in Table 1. Additionally, 6 papers were identified from the Cochrane library and included in this review.

Prophylactic versus episodic antibiotics
Persico et al. compared prophylactic antibiotics with episodic antibiotics prescribed during an episode of AOM, with 111 children between the ages of 3 to 30 months randomised to receive phenoxymethylpenicillin V at 25mg/kg/day for 3

Table 1. Cochrane reviews on the management of OME (Abx = antibiotics, vs = versus, VT = ventilation tube)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>RCTs</th>
<th>Outcome</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics (Van zon et al.24)</td>
<td>3027</td>
<td>23</td>
<td>OME resolution, hearing, VT rates</td>
<td>Oral Abx vs placebo</td>
<td>Do not support the use of antibiotics</td>
</tr>
<tr>
<td>Antihistamines and/or decongestants (Griffin &amp; Flynn11)</td>
<td>1880</td>
<td>16</td>
<td>Resolution of symptoms or signs</td>
<td>Oral or nasal decongestant and/or antihistamine vs placebo</td>
<td>Do not support use of antihistamines and decongestants</td>
</tr>
<tr>
<td>Oral or topical nasal steroids (Simpson et al.33)</td>
<td>945</td>
<td>12</td>
<td>Differences in hearing level and degree of conductive hearing loss</td>
<td>Systemic or topical steroid vs control</td>
<td>No evidence of beneficial effect from steroids (oral or topical)</td>
</tr>
<tr>
<td>Grommets (ventilation tubes) (Browning et al. 201011)</td>
<td>1728</td>
<td>10</td>
<td>Differences in hearing level</td>
<td>Grommet vs non surgical treatment</td>
<td>Grommets mainly beneficial in the first six months</td>
</tr>
<tr>
<td>Adenoidectomy (van den Aardweg et al 201021)</td>
<td>2712</td>
<td>14</td>
<td>Resolution of signs and hearing loss</td>
<td>Adenoidectomy with and without VTs</td>
<td>Significant benefit with adenoidectomy</td>
</tr>
<tr>
<td>Autoinflation for hearing loss (Perera et al 200624)</td>
<td>6</td>
<td></td>
<td></td>
<td>Any form of autoinflation vs no autoinflation</td>
<td>Improvement in tympanometry and audiometry at less and greater than 1 month</td>
</tr>
</tbody>
</table>
months, or ampicillin at 50mg/kg/day for 7-10 days for each new episode of AOM. In the prophylactic group, 26/60 (43%) patients did not have a further episode of AOM compared to 7/48 (15%) in the episodic group at 6 months follow-up (p <0.04), indicating that prophylactic antibiotics are more effective at preventing recurrence of AOM than episodic antibiotics.

**Prophylactic antibiotics versus placebo**

Five studies compared prophylactic antibiotics with placebo. The studies used different antibiotics with differing doses, frequencies or durations, making direct comparison difficult.

Roark & Berman included 158 patients (aged 3 months to 6 years) in a double blind RCT. Subjects received placebo twice daily, amoxicillin 20mg/kg once daily plus placebo once daily, or amoxicillin 10mg/kg twice daily for 90 days. Children who developed AOM during the study were treated with a different antibiotic for 10 days. Compliance was assessed by urine antibiotic activity, which was 89% in the amoxicillin groups and 31% in the placebo group; the authors attributed the latter finding to residual antibiotics from a recently treated episode of AOM. During the study, the number of children who developed AOM was 22/59 (37%), 20/55 (36%) and 17/44 (39%) in each group respectively. A statistically significant benefit was not observed between amoxicillin and placebo, and between once daily and twice daily dosing of amoxicillin in preventing RAOM.

Similarly, Koivunen et al. randomised 120 children (aged 10 to 24 months) to sulfafurazole 50mg/kg once daily or placebo for 6 months. The study failed to show a significant benefit between the two groups. Intervention failure (defined as 2 episodes of AOM in 2 months, 3 episodes in 6 months, or persistent middle ear effusion for 2 months) occurred in 17/46 (37%) and 26/46 (55%) children respectively. However, compliance was lower in the sulfafurazole group and was attributed to one child being given sulfafurazole irregularly.

Gonzalez et al. compared sulfisoxazole prophylaxis 500mg twice daily with placebo in 41 subjects under the age of 4, for six months. The authors were unable to ascertain compliance in the study. Treatment failure (defined as two or more episodes of AOM in 3 months) occurred in 8/21 (38%) and 12/60 (60%) children in each group respectively (p>0.05).

On the other hand, Principi et al. compared amoxicillin 20mg/kg once daily, sulfamethoxazole and trimethoprim 12mg/kg once daily, and placebo in 96 children (age 9 months to 5 years) taken for 6 months in a single blind RCT. Compliance ascertained by measurement of medication at each follow up visit was good at 94-97% in each group. The number of children who developed AOM were 9/33 (27%), 9/33 (27%) and 19/30 (63%) respectively (p<0.01). Overall, a two-fold increase in episodes of AOM was observed with placebo compared to the antibiotic groups.

Likewise, Casselbrant et al. randomised 166 patients (age 7 to 35 months) to receive amoxicillin 20mg/kg once daily or placebo for 4 weeks. Compliance was good at 90% and 91% respectively. The outcome was the rate of new episodes of AOM.

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**Table 2.** Studies included in the review for RAOM (Ad = adenoidectomy, AdT = adenotonsillectomy, AOM = acute otitis media, RAOM = recurrent acute otitis media, VT = ventilation tube, vs = versus)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Diego et al. 2001</td>
<td>69</td>
<td>6 months</td>
<td>Amoxicillin vs azithromycin</td>
<td>RAOM (≥2 episodes/6 month)</td>
</tr>
<tr>
<td>Roark &amp; Berman 1997</td>
<td>158</td>
<td>Monthly until 2 episodes AOM</td>
<td>Amoxicillin vs placebo</td>
<td>RAOM (≥2 episodes/6 month)</td>
</tr>
<tr>
<td>Marchisio et al. 1996</td>
<td>159</td>
<td>12 months</td>
<td>Amoxicillin vs azithromycin</td>
<td>RAOM (≥3 episodes/month)</td>
</tr>
<tr>
<td>Principi et al. 1989</td>
<td>96</td>
<td>6 months</td>
<td>Amoxicillin vs sulfamethozoxazole/trimethoprim vs placebo</td>
<td>RAOM (≥2 episodes/6 month)</td>
</tr>
<tr>
<td>Persico et al. 1985</td>
<td>111</td>
<td>6 months</td>
<td>Phenoxymethylpenicillin V vs ampicillin</td>
<td>RAOM (≥1 episodes/month for 3 months)</td>
</tr>
<tr>
<td>Kujala et al. 2012</td>
<td>300</td>
<td>12 months</td>
<td>VT vs VT + Ad vs control</td>
<td>RAOM (≥2 episodes/6 month)</td>
</tr>
<tr>
<td>Hammarén-Malmi et al. 2005</td>
<td>217</td>
<td>12 months</td>
<td>Ad + VT vs VT</td>
<td>RAOM (≥2 episodes/6 month)</td>
</tr>
<tr>
<td>El Sayed 1996</td>
<td>53</td>
<td>6 months</td>
<td>VT vs sulfamethoxazole/trimethoprim</td>
<td>RAOM (≥3 episodes/6 month)</td>
</tr>
<tr>
<td>Casselbrant et al. 1992</td>
<td>264</td>
<td>2 years</td>
<td>VT vs amoxicillin vs placebo</td>
<td>RAOM (≥3 episodes/6 month)</td>
</tr>
<tr>
<td>Le et al. 1991</td>
<td>44</td>
<td>24 months</td>
<td>VT vs myringotomy/no surgery</td>
<td>RAOM (Age 0-1 years, ≥4 episodes/12 months and Age 1-6 years, 26 episodes/12 months)</td>
</tr>
<tr>
<td>Gonzalez et al. 1986</td>
<td>65</td>
<td>6 months</td>
<td>VT vs sulfisoxazole vs placebo</td>
<td>RAOM (≥2 episodes/6 month)</td>
</tr>
<tr>
<td>Koivunen et al. 2004</td>
<td>180</td>
<td>24 months</td>
<td>Ad vs sulfafurazole vs placebo</td>
<td>RAOM (≥2 episodes/6 month)</td>
</tr>
<tr>
<td>Paradise et al. 1999</td>
<td>304</td>
<td>3 years</td>
<td>Ad vs AdT vs control</td>
<td>RAOM (≥3 episodes/6 months or ≥4 episodes/12 months)</td>
</tr>
<tr>
<td>Mattila et al. 2003</td>
<td>137</td>
<td>7 months</td>
<td>Ad + VT vs VT</td>
<td>RAOM (≥3 episodes/6 months or ≥4 episodes/12 months)</td>
</tr>
<tr>
<td>Gebhart 1981</td>
<td>95</td>
<td>6 months</td>
<td>Control vs VT</td>
<td>RAOM (≥3 episodes/6 month)</td>
</tr>
<tr>
<td>Paradise et al. 1990</td>
<td>99</td>
<td>3 years</td>
<td>Ad vs control</td>
<td>RAOM (≥3 episodes/6 months or ≥4 episodes/12 months)</td>
</tr>
</tbody>
</table>
A Cochrane review, which included 17 high-quality studies (of which 7 were of children with RAOM), showed that long-term antibiotics given once or twice daily for at least 6 weeks, can reduce the number of episodes of AOM per year from 3 to 1.5. The NNT to prevent one child from developing AOM when on treatment was 5.51

On the whole, there is evidence to support the use of prophylactic antibiotics in RAOM. The use of long-term antibiotics needs to be carefully balanced against the possibility of adverse effects and emergence of bacterial resistance. Compliance with treatment is also important and must be fully discussed with parents.

**Amoxicillin versus azithromycin prophylaxis**

Two studies compared once-daily amoxicillin to once-weekly azithromycin in the prevention of RAOM. De Diego et al.52 randomised 69 patients (age 9 to 120 months) to receive azithromycin at 10mg/kg once a week or amoxicillin at a third of the therapeutic dose of 20mg/kg once daily for 3 months. Otoscopic findings prior to commencement of the study were not reported and compliance was measured by asking parents directly. In the amoxicillin group, 34/38 (89.5%) patients had a 50% or more reduction in the episodes of AOM compared to 25/31 (80.6%) in the azithromycin group (p=0.30).

Marchisio et al.53 randomised 148 children to receive once-weekly azithromycin at 5-10mg/kg or amoxicillin 20mg/kg once daily for 6 months. Children were free of AOM at the start of the study but OME was not an exclusion criteria. Nine children assigned to the azithromycin 5mg/kg once-weekly arm were prematurely terminated from the study due to a high rate of recurrence. Compliance was assessed by the amount of medication left at subsequent visits and was 93.4% and 100% in the amoxicillin and azithromycin groups respectively. The occurrence of AOM was 25/74 (33.8%) in amoxicillin group and 11/74 (14.9%) in the azithromycin group (p=0.03). At the 6-month post prophylaxis follow-up, 30/70 (42.8%) children in the amoxicillin group and 27/69 (39.1%) in the azithromycin group experienced further episodes of AOM and most of these children were under the age of 2 (p>0.05).

Both studies suggest that azithromycin at a dose of 10mg/kg once a week for 3 to 6 months is comparable to once-daily amoxicillin in the prevention of RAOM. The study by Marchisio et al.53 indicated that azithromycin is superior to amoxicillin. These findings have important implications for young children who are more likely to be compliant with a once-weekly regimen. However this effect is only short lived with recurrence occurring within 6 months of stopping prophylaxis particularly in children aged under 2 years.

**Ventilation tubes versus placebo**

Five RCTs compared the use of VTs and placebo/no treatment in RAOM. Kujala et al.54 randomised children under the age of 2 years to VTs or no treatment. The outcome was intervention failure (defined as 2 episodes of AOM in 2 months, 3 episodes in 6 months or persistent effusion for 2 months). At 1-year follow-up, intervention failure had occurred in 21/100 (21%) children in the VT group and 34/100 (34%) in the control group (p=0.04).

Gonzalez and colleagues55 assessed VTs and placebo medication comparing the rate of treatment failure (2 or more episodes of AOM in less than 3 months) in children under the age of 4. At 6 months follow-up, treatment failure occurred in 5/22 (23%) and 12/20 (60%) children in each group respectively (p=0.02). In a similar study, Casselbrant et al.56 assigned children to VTs or placebo medication. At 2 years follow-up, the rate of new episodes of acute otitis media per child year were 1.02 in the VT group and 1.08 in the placebo group (p=0.25), and the proportion of time with AOM during the 2-year period were 6.6% and 15% respectively (p<0.001). Persistent tympanic membrane perforation occurred in 3.9% of children but all cases eventually healed spontaneously, although this took up to 21 months.

Gebhart57 randomised children under the age of 3 to VTs or conservative management (antibiotics for each episode of AOM) and followed up patients for 2.5 years. At 6 months follow up, 36 episodes of AOM were observed in the VT group and 25/54 (46%) children had no further infections. In comparison, 89 episodes of AOM were observed in the conservative group and only 2/41 (5%) children had no further infections (p<0.001). During the follow-up period, the VT re-insertion rate was 31% indicating ongoing ear problems post extrusion.

In another study that examined individual ears,58 44 children (age 9 to 82 months) received VT insertion in one ear and either myringotomy or no surgery in the contralateral ear. All children had a history of RAOM in both ears and had failed antibiotic prophylaxis. The outcome was the mean number of AOM episodes per ear assessed at 6 monthly intervals. Prior to the study this was 5.7 in the VT ear and 3.8 in the contralateral ear (p=0.5). VTs remained in situ for a mean duration of 10 months and there was no significant difference in the episodes of AOM in the ears that received myringotomy alone or no surgery. At 6 months post-intervention, episodes of AOM per ear were 0.6 and 1.8 in the VT and contralateral ears (p=0.0001) and at 12 months 0.7 and 1.1 respectively (p=0.02). This reduction of AOM episodes in the VT ear became less evident after 12 months and indeed was not significant beyond this. The sequelae of VT insertion included tympanosclerosis, atrophy, retraction and permanent perforation, which were significantly greater in ears with VT than myringotomy.

A Cochrane review consisting of 2 RCTs concluded that VTs have a role to play in preventing RAOM. VT insertion reduces the occurrence of AOM in the first 6 months with a mean reduction of 1.5 episodes.57 There is thus strong evidence to support the use of VTs in the prevention of RAOM. The reduction in episodes of AOM occurs in the first 6-12 months of insertion. Myringotomy alone does not have any benefit. The use of VTs should consider the potential adverse effects and the possibility of re-insertion at a future date.

**Ventilation tubes versus antibiotics**

Three studies compared the efficacy of VTs with antibiotic prophylaxis. Casselbrant and colleagues58 compared VTs with amoxicillin (20mg/kg once daily for 4 weeks) in 163 children, and found that the results favoured antibiotics, with the rate of AOM per child year being 1.02 and 0.6 respectively (p=0.001).
Gonzalez et al. randomised patients under the age of 4 years to VTs or sulfisoxazole 500mg twice a day for 6 months. VTs were favoured, with treatment failure rates of 5/22 (23%) and 8/21 (38%) in the two groups respectively, but the difference was not statistically significant. El-Sayed et al. randomised children under the age of 3 years to VTs or sulfamethoxazole and trimethoprim syrup 12mg/kg once daily for 6 months. The number of children with no further episodes of AOM at 6 months was 20/31 (65%) in the VT group and 10/22 (45%) in the antibiotic group, again not significant (p = 0.37).

The study by Casselbrant et al. indicates that antibiotic prophylaxis is favourable to VT insertion. On the other hand, the two latter studies suggest a relatively large benefit in favour of VT over antibiotics, but this was not statistically significant and may be due to the fact that these studies were relatively small. Nonetheless both VTs and prophylactic antibiotics appear to be beneficial in preventing RAOM. However, both treatments have potential adverse effects, so the choice of treatment has to be based on individual patients.

**Adenoidectomy**

Three studies compared adenoidectomy to placebo in preventing RAOM. Koivunen et al. randomised children under the age of 2 to receive adenoidectomy or oral placebo medication. Twelve children in the adenoidectomy group also received concurrent VTs due to the presence of middle ear effusion. At 6 months follow-up, the rate of intervention failure was 25/59 (42%) and 26/47 (55%) respectively, and at 24 months, 42/58 (72%) and 35/45 (78%) respectively; the differences in this small study were not statistically significant.

In an initial study by Paradise et al., 99 children (aged 1 to 15 years) previously treated with VTs for RAOM who subsequently developed AOM after VT extrusion were randomly assigned to adenoidectomy or control. Although the VTs had extruded in some children, most children still had at least one VT in situ at the start of the study. During the first year of follow-up, the adenoidectomy group had 47% less time with AOM than children who had not previously undergone VT (odds ratio 1.11, 95% confidence interval 0.94-1.32), and adenoidectomy did not further reduce the risk of AOM (odds ratio 1.66, 95% confidence interval 0.80-3.46). In a similar study of children under the age of 2, 54 RAOM occurred in 16/100 (16%) children in the VT and adenoidectomy group, and 21/100 (21%) in the VT group (p = 0.37). Marttila et al. randomised 137 children between the age of 1 and 2 years. The rate of otitis media per person-year was 2.05 in the VT and adenoidectomy group and 2.40 in the VT group. The difference did not reach significance.

A Cochrane review of 14 RCTs on adenoidectomy in otitis media concluded that although a benefit is seen with adenoidectomy in children with OME, the benefit of adenoidectomy in AOM is small and non-significant. Although there may be small benefits associated with adenoidectomy for AOM, this has not been conclusively shown to date. Adding adenoidectomy to VT insertion does not appear to further reduce the recurrence rate of RAOM in children under the age of 4 years. Given the associated risks and costs of adenoidectomy, the procedure should not be considered as first line surgical treatment.

**Pacifiers in RAOM**

Current literature suggests that pacifier use is a risk factor for RAOM. Various hypotheses have been proposed including the reflux of nasopharyngeal secretions into the middle ear, dental deformities and Eustachian tube dysfunction with pacifier use. A recent study showed that children who do not use a pacifier continuously have 33% fewer AOM episodes than children who do.

**Pneumococcal conjugate vaccines**

A Cochrane review on the effect of PCV in the prevention of AOM identified seven RCTs. However due to the large heterogeneity of the studies a meta-analysis was not possible. The 7-valent PCV was shown to reduce the risk of AOM by 6-7%. This benefit was not observed in older children with RAOM when immunised outside of infancy. Unfortunately, it has been shown that in a number of other conditions the benefits of pneumococcal vaccination tend to be short-lived, so vaccination may not prove to be a long term solution to AOM.

**Xylitol**

Xylitol is a naturally occurring sugar substitute that has been shown to reduce the adherence of bacteria to nasopharyngeal cells. A recent meta-analysis of four RCTs in healthy Finnish children under the age of 12 showed that prophylactic xylitol (chewing gum, syrup or lozenges) at a dose of 8.4g per day can reduce the occurrence of AOM by 25%. Furthermore, there were no significant adverse effects, and xylitol can prevent tooth decay.

**Zinc supplements**

Zinc has an important role in the functioning of the immune system and resisting infection. A recently published Cochrane review of 10 randomised placebo controlled trials on healthy children showed no evidence to support the use of zinc supplements in reducing the occurrence of AOM.
Management of Otitis Media with Effusion and Recurrent Acute Otitis Media

Evidence base management of RAOM: Summary

This review included 16 RCT and 6 Cochrane reviews on the management of RAOM. There is strong evidence to support the use of prophylactic antibiotics in preventing RAOM and amoxicillin at 20mg/kg once daily for at least 4 weeks in children under the age of 5 is beneficial. However a once-daily amoxicillin regimen may pose compliance issues particularly with young children and two RCTs showed once-weekly azithromycin at 10mg/kg for at least 3 months is comparable to once-daily amoxicillin. However, the effect of antibiotic prophylaxis is only short lived. Up to 40% of children will have recurrence of AOM at 6 months after stopping antibiotics especially in children under the age of 2. There are also additional concerns about side effects and emergence of resistant bacteria.

There is good evidence for the use of VTs in the prevention of RAOM. This is in agreement with a recent Cochrane review which showed VTs to have a significant role in reducing the episodes of AOM, and increasing the number of children disease-free in the first 6 months. Three RCTs have compared antibiotic prophylaxis to VT insertion. Neither of the two treatment options is superior to the other. Clinicians must consider the adverse effects of both treatment options when deciding the appropriate management. An initial conservative approach is often the preferred strategy. There is some evidence for the use of adenoidectomy with benefits seen in the first 6 to 12 months. However, concurrent adenoidectomy with VT insertion appears not to further reduce the recurrence rate of RAOM in children under the age of 4 years.

Current literature suggests that children who use a pacifier are at increased risk of AOM. PCV given as part of the UK childhood vaccination programme has a modest effect reducing the risk of RAOM by 6-7% while xylitol can reduce the risk of RAOM by 25%. Zinc supplements have no role in the prevention of RAOM.

Conclusion

This review on the evidence based management of OME and RAOM has found a significant number of high quality RCTs and Cochrane reviews. The use of VTs in OME can improve hearing in the first 12 months and there is evidence that adenoidectomy can increase OME resolution. Some evidence exists to support the use of mucolytics and autoinflation; but antibiotics, antihistamines, decongestants and oral/topical steroids have no role in the management of OME.

There is good evidence to support the use of prophylactic antibiotics and VTs in the management of RAOM. However it is prudent to consider the risk of side effects, antibiotic resistance, and adverse effects of surgical intervention before embarking on a treatment option. There is some evidence that adenoidectomy, reducing pacifier use, pneumococcal vaccination and xylitol can reduce the occurrence of RAOM, but there is no evidence to support the use of zinc supplements.

Declaration of competing interests

Nothing to declare.

References

15. Current literature suggests that children who use a pacifier are at increased risk of AOM. PCV given as part of the UK childhood vaccination programme has a modest effect reducing the risk of RAOM by 6-7% while xylitol can reduce the risk of RAOM by 25%. Zinc supplements have no role in the prevention of RAOM.
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