

What is new in otitis media?

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Abstract The “wait and see” approach in acute otitis media (AOM), consisting of postponing the antibiotic administration for a few days, has been advocated mainly to counteract the increased bacterial resistance in respiratory infections. This approach is not justified in children less than 2 years of age and this for several reasons. First, AOM is an acute inflammation of the middle ear caused in about 70% of cases by bacteria. Redness and bulging of the tympanic membrane are characteristic findings in bacterial AOM. Second, AOM is associated with long-term dysfunction of the inflamed eustachian tube (ET), particularly in children less than 2 years of age. In this age group, the small calibre of the ET together with its horizontal direction result in impaired clearance, ventilation and protection of the middle ear. Third, recent prospective studies have shown poor long-term prognosis of AOM in children below 2 years with at least 50% of recurrences and persisting otitis media with effusion (OME) in about 35% 6 months after AOM. Viruses elicit AOM in about 30% of children. A prolonged course of AOM has been observed when bacterial and viral infections are combined because viral infection is also associated with ET dysfunction in young children. Bacterial and viral testing of the nasopharyngeal aspirate is an excellent tool both for initial treatment and recurrence of AOM. Antibiotic treatment of AOM is mandatory in children less than 2 years of age to decrease inflammation in the middle ear but also of the ET particularly during the first episode. The best choice is amoxicillin because of its superior penetration in the middle ear. Streptococci pneumoniae with intermediary bacterial

resistance to penicillin are particularly associated with recurrent AOM. Therefore the dosage of amoxicillin should be 90 mg/kg per day in three doses. In recurrent AOM with β -lactamase-producing bacilli, amoxicillin should be associated with clavulanic acid at a dose of 6.4 mg/kg per day. The duration of the treatment is not established yet but 10 days is reasonable for a first episode of AOM. OME may be a precursor initiating AOM but also a complication thereof. OME needs a watchful waiting approach. When associated with deafness for 2–3 months in children over 2 years of age, an antibiotic should be given according to the results of the bacterial resistance in the nasopharyngeal aspirate. The high rate of complications of tympanostomy tube insertion outweighs the beneficial effect on hearing loss. The poor results of this procedure are due to the absence of effects on ET dysfunction. Pneumococcal vaccination has little beneficial effects on recurrent AOM and its use in infants needs further studies. Treatment with amoxicillin is indicated in all children younger than 2 years with a first episode of AOM presenting with redness and bulging of the tympanic membrane. Combined amoxicillin and clavulanic acid should be given in patients with β -lactamase-producing bacteria. The duration of treatment is estimated to be at least 10 days depending on the findings by pneumo-otoscopy and tympanometry. Bacterial and viral testing of the nasopharyngeal aspirate is highly recommended particularly in children in day care centres as well as for regular follow-up. The high recurrence rate is due to the long-lasting dysfunction of the eustachian tube and the immune immaturity of children less than 2 years of age.

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Abbreviations

- AOM acute otitis media
- OME otitis media with effusion
- ET eustachian tube
- MEF middle ear effusion
- RSV respiratory syncytial virus
- SMZ sulfamethoxazole
- TMP trimethoprim

Introduction

The number of publications relating to acute otitis media (AOM) and otitis media with effusion (OME) has been increasing markedly within the last 2 years [40–49]. It points to the difficulties in giving generally accepted guidelines for treatment. The confusion can be partially explained by the absence of uniform definitions and inhomogeneous groups of patients being included in clinical studies.

AOM is an acute inflammation of the middle ear, frequently elicited by viral infections and characterized by redness and bulging of the tympanum. Infections with bacteria can be identified in at least 70% of the cases by

culture of the middle ear purulent fluid containing mainly polymorphonuclear cells [35].

OME is an effusion of the middle ear without symptoms of acute inflammations such as pain and fever, with frequently an amber or opaque aspect of the tympanum, the effusion containing mainly macrophages. Retraction of the tympanum with the light reflex still present may render the diagnosis difficult. Cultures for bacteria are positive in about 50% of cases whereas viruses have been identified in about 30% [35]. OME may be a precursor event initiating suppurate AOM but it can be the continuum of AOM as well. OME is the direct consequence of impaired middle ear ventilation.

Tympanometry (Fig. 1) shows a flat curve type b in both AOM and OME. In contrast, in OME associated with incomplete obstruction of the eustachian tube (ET) a curve c with a peak in the negative pressure zone is observed. Moreover, lower peak height and greater width in the negative pressure zone are frequent findings in OME [54].

This overview summarizes the main new findings about AOM and OME which are in accordance with some basic well-known but sometimes forgotten data and facts, with particular emphasis on the vulnerability of young children below the age of 2 years.

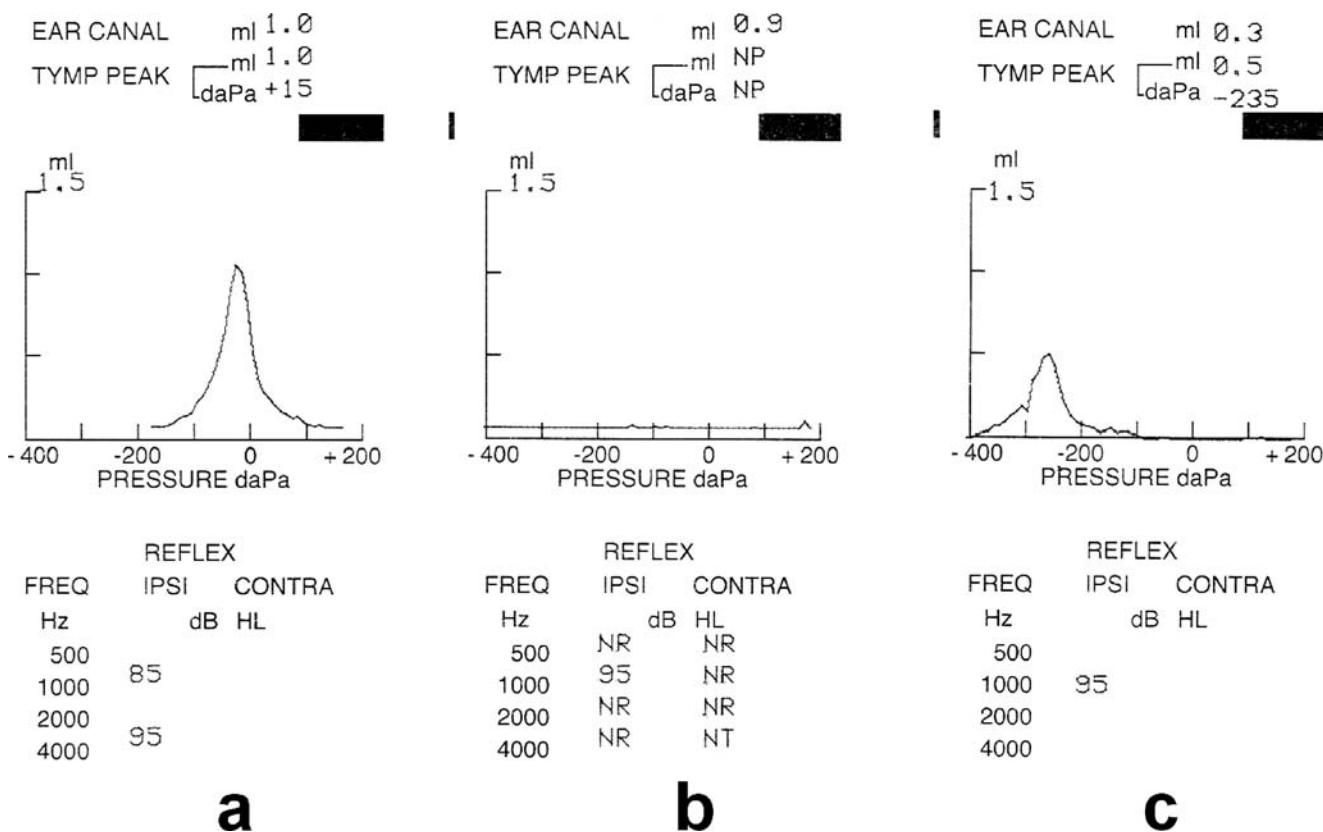


Fig. 1 The three main types of tympanograms showing: **a** a peak near atmospheric pressure expressed in daPa with stapedius reflex for different Hz frequencies, **b** a flat curve without stapedius reflex for 500, 2000, 4000 Hz pointing to presence of middle ear exudate: AOM

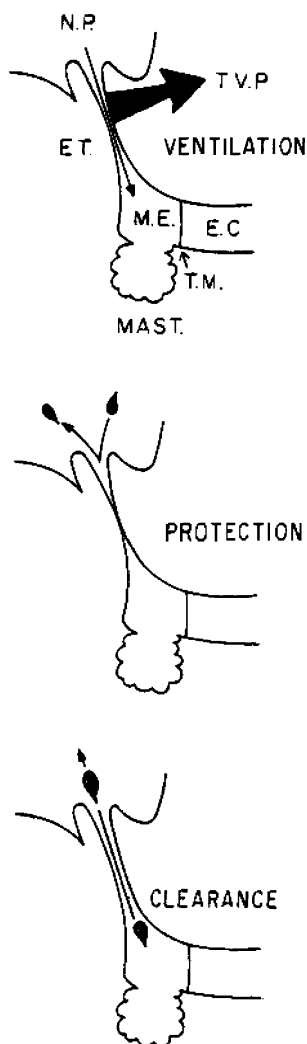
or OME, **c** a lower peak in the negative pressure zone (–235 daPa) with an enlarged width pointing to OME with partial permeability of ET to air entrance and still a stapedius reflex

Aetiopathogenesis

Role of the eustachian tube

The great importance of the first attack of AOM in young children lies in the subsequent long-lasting dysfunction of the ET. Indeed, the main functions of the ET are ventilation, protection and clearance of the middle ears (Fig. 2) [5, 35] and play a determining role in the recurrence of AOM. Ventilation of the middle ear occurs by each deglutition by action of the tensor velum palatinum muscle leading to air equilibration with the atmospheric pressure. By obstruction of the ET, a negative pressure develops inside the middle ear resulting in effusion and aspiration of nasopharyngeal secretions. Poor ventilation leads to decreased PO_2 which results in decreased bactericide power of polymorphonuclear cells. Impaired clearance results in proliferation not only of aerobic but also anaerobic bacteria in the middle ear. Conversely, reflux otitis occurs with decreased compliance of the ET due to abnormal flaccidity.

Fig. 2 Three physiologic functions of the eustachian tube in relation to the middle ear. *NP* nasopharynx, *ET* eustachian tube, *TVP* tensor velum palatinum muscle, *ME* middle ear, *MAST* mastoid, *TM* tympanic membrane, *EC* external canal



ET dysfunction is a major problem in the young child: the small calibre of the ET as well as its horizontal direction [5] (Figs. 3 and 4) are responsible for both the high incidence of AOM and the frequent relapses by each viral infection. This explains the poor long-term prognosis evidenced in a prospective study comprising 210 AOM patients of less than 2 years of age by Damoiseaux et al. [16]. At least 50% of the patients had recurrences of AOM and persistence of OME was observed in 47% of them after 3 months and in 35% after 6 months. Yet, only 50% of these patients were treated with amoxicillin. Unfortunately, the authors do not mention either the delay of treatment or the dosage of the antibiotic.

In other words, the first episode of AOM determines the evolution and the recurrences because of the associated acute inflammation involving also the ET.

Role of viruses and bacteria

Viruses

Most children are infected with respiratory syncytial virus (RSV) in their first year of life. A prospective study [2] in 42 children aged 2–24 months with bronchiolitis showed that 26 of them had AOM at entry or within 10 days and an additional 10 developed OME; only 6 patients remained free of both AOM and OME during a 3-week observation period. These findings were confirmed in a recent study showing that in patients with persistent RSV antigen in the middle ear effusion, 31% relapsed despite a favourable outcome of the first AOM episode [50].

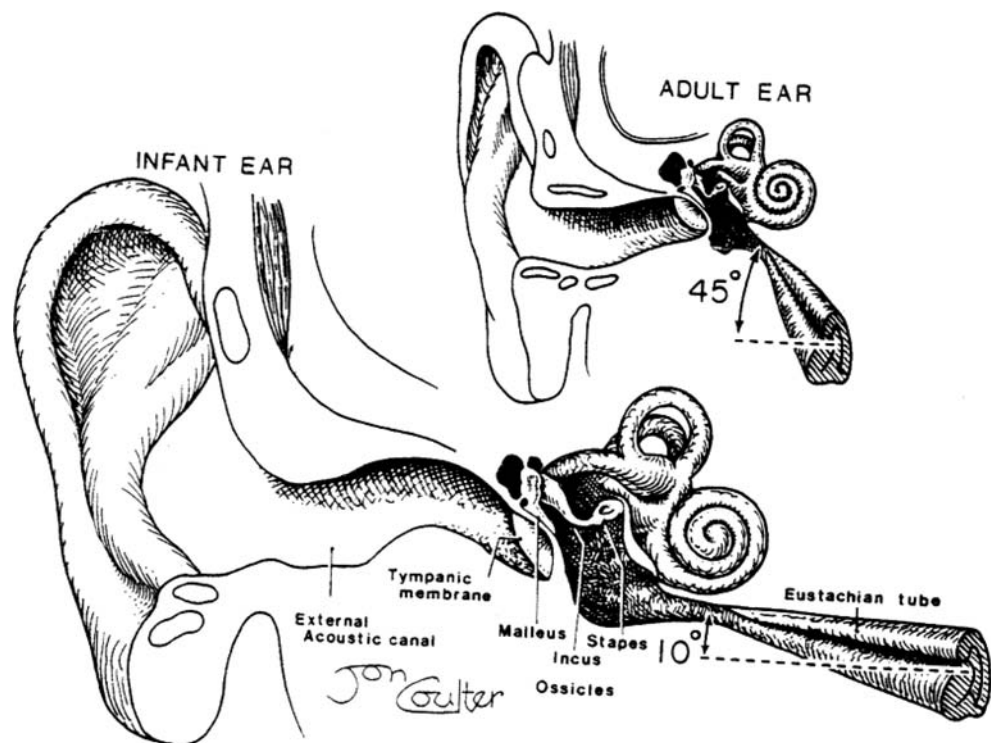
The association of AOM with several viral infections has been largely documented. The prevalence of respiratory viruses in the middle ear fluid of 456 children, aged 7 months to 7 years, with AOM was 41% [21]. RSV was the most frequent virus isolated followed by parainfluenza, influenza, enteroviruses and adenoviruses. These findings have been confirmed by others [18, 32, 33, 41, 50] and rhinovirus, coronavirus and metapneumovirus should be added to the above-mentioned list [53]. Even the measles virus has recently been isolated from the middle ear fluid in two patients [64].

Bacteria

In 70% of patients with AOM, bacteria can be found by culturing the middle ear fluid [35]. The most frequent species isolated are *Haemophilus influenzae* and *Streptococcus pneumoniae* [27]. Nasopharyngeal aspirate culture may give valuable information on the bacteria involved in AOM [28, 51, 55, 58]. The presence of conjunctivitis points to *Haemophilus influenzae* infection [4].

Heikkinen et al. found *Streptococcus pneumoniae* in 25% of their patients, *Haemophilus influenzae* in 23% and

Fig. 3 The difference in the angle of the eustachian tube between infants and adults [5]



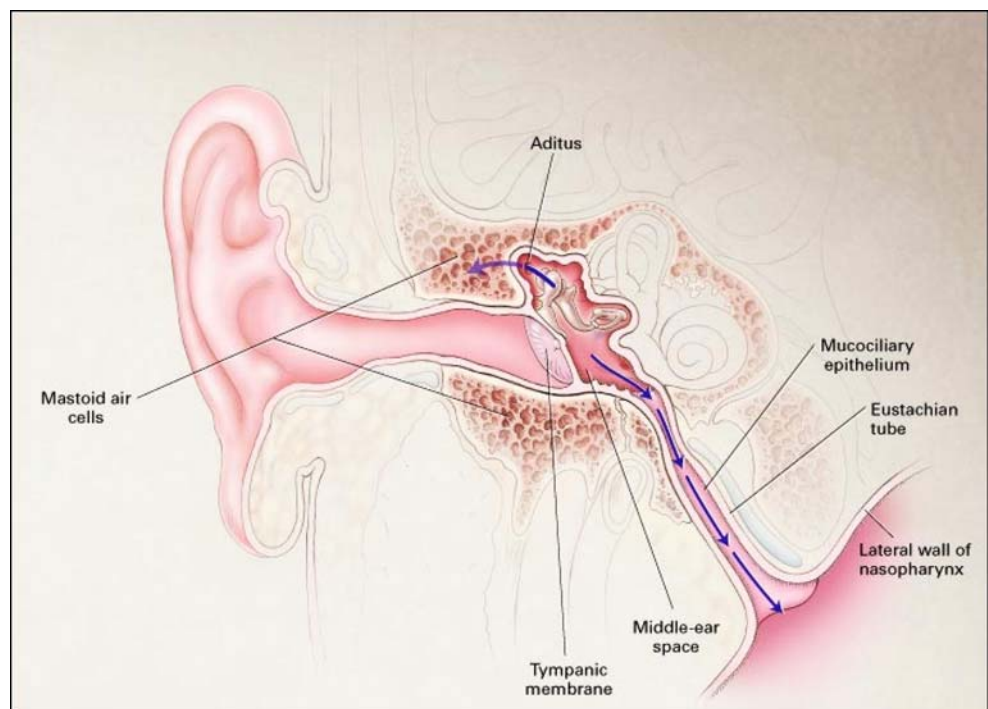
Moraxella catarrhalis in 15% [21]. It has been demonstrated that recurrences of AOM are associated with positive bacterial culture in the nasopharynx [23], even at the end of the antibiotic treatment [28] and in most cases the pathogen was *Streptococcus pneumoniae* [58]. However, recurrence more than 14 days after an initial AOM episode is mostly due to a new infection, i.e. not a true relapse [27]. In a most

recent prospective study on purulent meningitis [11], the association of AOM was found in half of the patients [14].

Bacteria and viruses

Bulut et al. performed both bacterial and viral testing in 120 children with AOM [8]. These patients, aged between

Fig. 4 The tympanic membrane forms the lateral wall of the box-shaped middle ear. The function of the eustachian tube is to equilibrate middle ear pressure with that in the nasopharynx. Bacteria and viruses resident in the nasopharynx may reach the middle ear during pressure equilibration. One-third of the middle ear mucosa and the entire eustachian tube are lined with mucociliary epithelium to transport bacteria from the middle ear back to the nasopharynx. Air from the middle ear enters the mastoid air cells by way of the aditus



6 months and 12 years, did not receive an antibiotic for 2 weeks prior to the study. A positive bacterial culture was obtained in 54% of the children and respiratory viruses were identified in 32% of them; combined viral and bacterial infection was demonstrated in 12% of the samples.

Persistent otitis was documented in about 50% of the children with combined viral and bacterial infection in a prospective study of 271 children because viral infections contribute to the ET dysfunction [12].

Other risk factors

The immaturity of the immune system of young children makes them incapable of killing encapsulated bacteria. This, along with the ET dysfunction, explains the long-lasting course of AOM as well as the high recurrence rate.

This is particularly important for infants attending day care centres [37, 38]. It is sometimes necessary to withdraw these infants from these institutions during the winter to avoid recurrences. Additional risk factors are passive smoking, young siblings going to school and siblings with previous AOM episodes.

These factors were identified in a prospective study on 2,253 children aged 2 months to 2 years published in 1997 [37]. The proportion of patients developing at least one episode of OME was 79% at 12 months and 91% at 24 months. Breast feeding and exposure to tobacco smoke contributed little to the outcome, but a lower socioeconomic status and repeated exposure to other children at home or in day care centres were the most important risk factors.

Children with cleft palate are particularly prone to otitis and should be treated by early tympanostomy tube insertion [60].

Complications: mastoiditis

Mastoiditis should be treated by antibiotics according to the bacterial resistance and by temporarily inserting tympanostomy tubes to improve drainage [65] because of the narrow calibre of the aditus ad antrum. [22] (Fig. 4).

Treatment

General considerations

A “wait and see” approach has been advocated in the treatment of AOM in children mainly because of the increased antimicrobial resistance of bacteria causing respiratory infections [13]. Indeed, a meta-analysis of 5,400 children, aged 6 months to 18 years, and collected from 33 randomized trials concluded that there was a significant but modest impact of antibiotics on the primary control of AOM [45]. Similar results emerged from a subsequent study published by Damoiseaux et al. in 2000 [15]. This randomized double-blind prospective trial carried out by general practitioners in 240 children, aged 6 months to 2 years, showed that only 7 and maybe 8 of them needed antibiotics. Both studies, however, suffer from major flaws; the absence of long-term data, in particular the recurrence rate of AOM, and OME not being considered an end point. Moreover, the former study included patients with a very large age range and therefore blunted the effect of the critical age group of the patients below the age of 2 years. Indeed, over 70% of AOM patients present their first attack during the first year of life and over 90% within 2 years of age [35]. The visualisation of the tympanum in this age group is not always easy especially when cerumen obstructs the narrow external ear channel. Yet, as already mentioned above, bulging and redness of the tympanic membrane are important diagnostic signs of bacterial AOM [27, 39].

Treatment of AOM

The crucial role of the first attack of AOM makes the immediate administration of antibiotics mandatory in all patients with AOM with redness and a bulging tympanum (Table 1) [26]. A “wait and see” approach can only increase the inflammation and hence the ET dysfunction. The choice of the antibiotic must take into account the penetration in the middle ear and the type of bacteria involved. The

Table 1 Guidelines for treatment of AOM

Episode	Signs or symptoms	Treatment or approach
Children <2 years of age		
First episode		Amoxicillin 90 mg/kg per day for at least 10 days according to the bacterial resistance Weekly follow-up by tympanometry and pneumo-otoscopy
Recurrent episode	With redness and bulging tympanum	Amoxicillin or amoxicillin 90 mg/kg per day + clavulanic acid 6.4 mg/kg per day according to bacterial resistance
	Without bulging	“Wait and see” approach
Children >2 years of age		
	With redness and bulging tympanum or otorrhoea	Same treatment as “recurrent episode”
	Without evident bulging tympanum	“Wait and see” approach

penetration for amoxicillin—about 40% of the blood concentration—is much higher than for cephalosporins (about 20%) and macrolides (about 10%) but lower than for cotrimoxazole (60%) [31]. The penetration of amoxicillin is not changed by the addition of clavulanate to amoxicillin [10, 52].

Because of the increased incidence of *Streptococcus pneumoniae* with intermediary resistance [57, 61], the dosage of amoxicillin should be doubled, i.e. 90 mg/kg per day given in three administrations as recommended by the Centers for Disease Control and Prevention [3].

Haemophilus influenzae is more likely to become β -lactamase positive after previous antibiotic administration [9]. Therefore, the addition of clavulanate—at a dose of 6.4 mg/kg per day—to amoxicillin makes sense. Most *Moraxella catarrhalis* strains are nowadays also β -lactamase positive [42].

The duration of the antibiotic treatment is a matter of discussion. For children less than 2 years of age, a 10-day course is reasonable. Pneumo-otoscopy and tympanometry can help to appreciate the permeability of the ET. Careful follow-up is necessary.

Nasopharyngeal aspirate cultures may give valuable results and are highly recommended in children remaining in day care centres or with a history of previous AOM episodes [28, 51].

For children more than 2 years of age the previously watchful guidelines can be maintained but some flexibility is recommended [22, 36].

Treatment of OME: tympanostomy tubes?

The approach to OME must take into account the natural history of spontaneous healing and the main complication which is temporary hearing impairment [1]. The absence of spontaneous healing after 6 weeks to 2 months in children over 2 years of age is an indication for a 10-day antibiotic course according to the results of the nasopharyngeal

aspirate cultures. It is our experience that this approach has several advantages. First, the effect even temporarily on the hearing defect is frequently successful. Second, it decreases the recurrence of AOM by improving the ET functions and third, it allows postponement or avoidance of tympanostomy tube insertion, because improved hearing points to improved permeability of the ET.

The delay of 6 weeks or 2 months before treatment of OME (Table 2) is based on the duration of OME. Indeed, in a prospective study by Renko et al. [43] of 90 children with AOM, 0.6–7 years of age, treated with amoxicillin or cefuroxime axetil for 10 days, the mean duration of OME was 10.2 days (range: 1–58 days); only 10 of 90 still had OME after 29–43 days.

In a long-term prospective study in 6,350 healthy infants treated according to specified guidelines, Paradise et al. [38] observed bilateral OME in only 5.6% of the 161 children who had not received tympanostomy tubes at the age of 4.

The indication to insert tubes is equivocal. The large prospective studies on 3,686 infants and young children by the Paradise group have shown the absence of or negligible effects of tympanostomies on developmental outcomes at 3–4 years [34, 37]. On the other hand, insertion of tympanostomy tubes during the first 3 years of life is associated with complications in at least 80% of the patients [63]. Tympanostomy can be a source of bacterial infections [24] and of tympanosclerosis.

Extensive reviews by Kubba et al. [25], Rosenfeld et al. [46], Rovers et al. [48] and the recent Cochrane Database by Lous et al. [30] concluded that there was only a small benefit of the conventional ventilation tube. The main reason for the poor results of tympanostomy tubes is the absence of effects on the ET dysfunction. It has never been demonstrated that tympanostomy tubes improve the functions of the ET.

The recommendations by the American Academy of Pediatrics [1] are to insert tubes in conditions with persisting hearing loss of more than 40 dB particularly

Table 2 Guidelines for treatment of OME. *SMZ* sulfamethoxazole, *TMP* trimethoprim

Indication	Approach	Treatment
Without deafness	“Watchful waiting” approach	
With deafness	After 6 weeks-2 months in children ≥ 2 years	Amoxicillin 90 mg/kg per day or amoxicillin 90 mg/kg per day + clavulanic acid 6.4 mg/kg per day for 10 days according to the results of the bacterial resistance
Recurrent OME or OME of long duration		No swimming Azithromycin 10 mg/kg per day, 3 days/week for 4 weeks Cotrimoxazole 30 mg SMZ + 6 mg TMP/kg per day according to the results of the bacterial resistance Adenoidectomy in children ≥ 3 years of age with nasopharyngeal obstruction and recurrent adenoiditis No swimming

with posterosuperior retraction pockets, ossicular erosions and adhesive atelectasis because of the increase of structural damage with effusion duration.

Watchful waiting for 3–6 months in the winter period seems advisable in children with mild hearing deficit.

Adenoidectomy should be considered in children ≥ 3 years of age with nasopharyngeal obstruction and recurrent adenoiditis [45].

Vaccination

The effects of pneumococcal vaccination on recurrent AOM have been studied extensively. In a randomized controlled trial by Brouwer et al. [6] in 383 children, aged 1–7 years, with recurrent AOM, the effects in 190 children treated with heptavalent pneumococcal vaccine were compared with 193 children receiving hepatitis A or B vaccines. The study concluded that there was no beneficial effect. A similar conclusion was drawn from a study by Van Kempen et al. [62] in 74 children aged 1–7 years and in the Cochrane Database by Straetemans et al. [56].

A shift of the causative pathogen has been observed from *Streptococcus pneumoniae* to *Haemophilus influenzae* or to other strains of pneumococci than the ones included in the vaccine [20, 59]. A slight reduction of the incidence of AOM of 6–8% was observed in the USA [7].

Infants and prematures

A high incidence of OME has been observed in neonatal intensive care units due to the nasally placed tubes for ventilatory assistance. It has been suggested that immune immaturity with impaired neuromotor function predisposes to this complication [17]. Vaccination with the heptavalent pneumococcal vaccine has been advocated in premature babies and neonates [19], but this study does not provide information on the actual AOM prevalence in a control group receiving only hepatitis B vaccine. It should be remembered that meconium aspiration into the entry of the middle ear is associated with increased risk of AOM and therefore early nasopharyngeal suction is mandatory [29].

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