PANEL 7 OTITIS MEDIA: TREATMENT AND COMPLICATIONS

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ABSTRACT

OBJECTIVE: We aimed to summarize key articles published between 2011 and 2015 on the treatment of (recurrent) acute otitis media, otitis media with effusion, tympanostomy tube otorrhea, chronic suppurative otitis media and complications of otitis media, and their implications for clinical practice.

DATA SOURCES: PubMed, Ovid Medline, the Cochrane Library, and Clinical Evidence (BMJ Publishing)**.**

REVIEW METHODS: All types of articles related to otitis media treatment and complications between January 2011 and March 2015 were identified. A total of 1122 potential related articles were reviewed by the panel members; 118 relevant articles were ultimately included in this summary.

CONCLUSIONS: Recent literature and guidelines emphasize accurate diagnosis of acute otitis media and optimal management of ear pain. Watchful waiting is optional in mild to moderate acute otitis media; antibiotics do shorten symptoms and duration of middle ear effusion. The additive benefit of adenoidectomy to tympanostomy tubes in recurrent acute otitis media and otitis media with effusion is controversial and age-dependent. Topical antibiotic is the treatment of choice in acute tube otorrhea. Symptomatic hearing loss due to persistent otitis media with effusion is best treated with tympanostomy tubes. Novel molecular and biomaterial treatments as adjuvants to surgical closure of eardrum perforations seem promising. There is insufficient evidence to support the use of complementary and alternative treatments.

IMPLICATIONS FOR PRACTICE: Emphasis on accurate diagnosis of otitis media, in its various forms, is important to reduce over-diagnosis, over-treatment and

antibiotic resistance. Children at risk for otitis media and its complications deserve special attention.

INTRODUCTION

Otitis media (OM) is a leading cause of health care visits, antibiotic prescriptions and surgery[1,2]. Its complications and sequelae are important causes of preventable hearing loss, particularly in developing countries. Reducing OM burden is warranted, and decision making should be based on the best available evidence.

Our 'Treatment and Complications' Panel consisted of 11 clinician scientists in the field of OM who convened at the 2015 Post-Symposium Research Conference, following the 18th International Symposium on Recent Advances in Otitis Media, National Harbor, MD. We focused on articles on the treatment of OM and its complications which were published since the last Panel report[3], and reviewed their implications for clinical practice. This paper summarizes our main findings.

METHODS

Panel members were assigned to review the literature on the management of one of the following disease entities: acute otitis media (AOM), recurrent AOM (rAOM), otitis media with effusion (OME), tympanostomy tube (TT) otorrhea, chronic suppurative otitis media (CSOM), and OM-related complications.

Each panel member designed a topic-specific key-word search strategy for the various electronic databases, including PubMed, Ovid Medline, the Cochrane Library and Clinical Evidence (BMJ Publishing). Databases were searched from 6/1/2011 through 3/31/2015, restricted to articles with at least an abstract published in the English language. Publications cited in the previous review[3] were excluded. Searches were supplemented by additional relevant articles (including evidence-based practice guidelines) identified by members during discussion at the panel meeting.

We retrieved a total of 1935 records from the initial electronic database searches, of which 813 were excluded because of irrelevant title. Of 1122 articles retrieved for more detailed evaluation, 116 articles remained after excluding duplicates, irrelevant articles, narrative (non-systematic) review articles, commentaries and letters to the editor. Finally, after adding two more articles from reference lists, 118 articles were included in this manuscript after final discussion.

DISCUSSION

Acute Otitis Media (Table 1)

A high-quality placebo-controlled trial performed by Tapiainen[4], found that oral antibiotics shortened the period with middle ear effusion (MEE) after AOM. This trial was included in a 2015 Cochrane review update[5], which showed that oral antibiotics for AOM reduce the proportion of children with abnormal tympanograms at 2-4 and 6-8 weeks, but not at 3 months. Both this review[5] and a 2014 BMJ Clinical Evidence review[6] concluded that "antibiotic treatment reduces AOM symptoms more quickly than placebo, but this benefit needs to be weighed against the increased risk of adverse events such as vomiting, diarrhea or rash".

Type of Antibiotic Treatment

The 2014 BMJ review[6] summarized the evidence on antibiotic choice in children with AOM and concluded that, "we do not know whether any one antibiotic regimen should be used in preference to another, although amoxicillin may be more effective than macrolides and cephalosporin, and should be considered as first-line treatment".

The randomized clinical trial (RCT) performed by Casey[7], which was included in the BMJ review[6], showed that children treated with amoxicillin/clavulanate for 10 days reached "clinical cure" at 11-14 days more frequently than those treated with cefdinir for 5 days.

The RCT performed by Arguedas[8], which was not included in the BMJ review, focused on children with tympanocentesis positive bacteriological cultures at baseline (54% of children), and found no differences in "clinical cure" rates at 12-14 days between a single dose of azithromycin extended release and amoxicillin/clavulanate for 10 days.

A 2013 Cochrane review update[9] comparing 1-2 versus 3-4 daily doses of amoxicillin (with or without clavulanate) found no new studies on this topic, and a firm conclusion could not be drawn due to limited evidence.

Ototopical Symptomatic Agents

The 2014 BMJ review[6] found two low quality trials suggesting that topical analgesics may be more effective than placebo at reducing ear pain 10-30 minutes after administration. Another systematic review[10] included the same two trials and two additional trials comparing anesthetic drops and herbal extracts drops. Again, quality of evidence was judged low, and the authors concluded that "further studies with more rigorous methodology are needed to demonstrate the utility of ototopical agents".

Systemic Steroids

A 2013 systematic review[11] identified a 2003 RCT comparing one intramuscular dose of ceftriaxone combined with 5 days of either oral prednisolone (and/or anti-histamine) or placebo for children with AOM. There was no significant benefit of systemic steroids.

Complementary and Alternative Medicine (CAM) Treatments

An RCT performed by Sinha[12], at high risk of bias, compared homeopathy versus conventional treatment and found similar numbers of patients cured at 21 days follow-up.

At-risk Populations

No new studies were found on this topic.

Recurrent Acute Otitis Media (Table 2)

Culture-Specific Antibiotic Treatment

Pichichero[13] conducted a prospective cohort study to determine whether strict AOM diagnostic criteria, tympanocentesis and culture-specific antibiotic treatment of early life AOM episodes (individualized care) reduced the incidence of rAOM and TT placement. During 24 months follow-up, rAOM incidence and TT placement were lower in children receiving individualized care than in legacy and community controls.

Surgical Treatment

Kujala[14] randomized children aged 10 months to 2 years with rAOM, with and without MEE at baseline, into three groups: TTs only, TTs and adenoidectomy or neither (control). Although there was a benefit of surgery over no surgery, the two surgical groups did not significantly differ with regard to number of failures for AOM recurrence and proportion of children with MEE for more than 2 months.

Lous[15] systematically reviewed the effectiveness of TTs in children with rAOM and included five RCTs published during 1981-1996. Because of heterogeneity, no meta-analysis was performed. Based on these trials, it was concluded that “both TT and long-term treatment with antibiotics seems to prevent one attack of AOM, or keep one child out of three free from AOM in six months”.

Cheong[16] conducted a systematic review of studies comparing the effect of prophylactic antibiotics, TTs and adenoidectomy on rAOM. Eighteen studies were identified, of which seven met the inclusion criteria. The authors concluded that all three treatments strategies had some benefits in preventing AOM recurrence, frequency of AOM episodes and total time spent with AOM. Based on 2 studies in children aged 1-15 years, the authors concluded that adenoidectomy was beneficial only in children over the age of 2.

Boonacker[17] performed an individual patient data meta-analysis (IPDMA) of adenoidectomy for OM in children less than12 years. The authors included 15 RCTs

of adenoidectomy alone or as an adjuvant to TTs in 1761 children, and used a composite outcome including elements of both AOM and OME to summarize results. Analyzing different studies than those reviewed by Cheong[16], they found that children aged less than2 years with rAOM may benefit from adenoidectomy, whereas in older children no benefit was found.

CAM Treatments

Marchisio[18] performed an RCT evaluating the risk of rAOM in relation to Vitamin D deficiency, and whether supplementation is effective in reducing AOM recurrences in otitis-prone children. Daily administration of 1000 IU of Vitamin D for 4 months during the coldest months of the year was found to reduce AOM incidence.

Another RCT by Cohen[19] studied the effects of pro/prebiotic-supplemented formula in infants 7-13 months old at high risk for AOM. Nasopharyngeal carriage of bacterial pathogens and AOM incidence was the same in the pro/prebiotic group and in infants who received a placebo formula.

A placebo-controlled trial by Vernacchio[20] found viscous xylitol solution three times daily for 12 weeks did not reduce AOM recurrences in otitis-prone infants and young children.

Otitis Media with Effusion (Table 3)

Oral Antibiotics

A 2012 Cochrane review and meta-analysis of RCTs of antibiotics in children with OME[21] included 23 studies. The results of the review did not support routine use of antibiotics in children with OME; however, an effect on MEE clearance was seen at 1-3 months. There was no evidence of an effect of antibiotics on hearing, and none of the trials reported on speech, language, cognitive development or quality of life (QoL) outcomes. The authors emphasized that the benefits must be weighed

against the adverse effects of antibiotics for the individual and for society. One RCT of antibiotics for OME[22] has been published since the Cochrane review, showing some benefit of macrolides as an adjuvant to nasal steroids over nasal steroids alone in clearing MEE, as assessed by repeated tympanometry measurements.

Steroids

Since the 2011 Cochrane review on oral or topical steroids in OME cited in the previous Treatment Panel[3], one additional placebo-controlled trial examined the effect of nasal steroids on OME in children with adenoid hypertrophy[23]; tympanometry and audiometry outcomes were better in the steroid group. One trial evaluated the effect of intra-tympanic steroid injections in adults and older children with OME[24], and found some benefit on subjective symptoms and MEE. Neither of these studies reported on speech and language or other developmental outcomes.

Antihistamines and Decongestants

A Cochrane review of antihistamines, decongestants and their combinations for OME was updated in 2011[25]. While no clinical benefit was found for any of these treatments, adverse effects were more frequent than in those treated with placebo. A subsequent RCT[26] of montelukast and levocetirizine for OME found improvement in otoscopic sign scores after 1 month.

CAM Treatments

Fixsen[27] conducted a systematic review of homeopathy in AOM and OME and found only one small study in children with OME. The author concluded that the evidence was incomplete and larger well-designed studies of CAM treatments for OM are needed.

One RCT evaluated the effect of thermal therapy in children with OME[28]. The treatment group had better tympanometry outcomes at some of the follow-up visits.

Hearing Aids

The psychosocial impact and parental attitude to hearing aids were compared between parents of children with OME treated by TTs and those treated with hearing aids; children treated with hearing aids did not suffer the bullying nor lower self-esteem anticipated by parents of children treated with TTs[29].

Auto-inflation

A Cochrane review of the effects of auto-inflation on OME-associated hearing loss was updated in 2013[30]. Eight studies were included; meta-analysis showed small but positive effects of auto-inflation. The authors recommended auto-inflation during watchful waiting for OME resolution, in light of the absence of adverse effects and low cost. Since this Cochrane review, a new device for auto-inflation was tested in a small cross-over study[31] on children waiting to receive TTs. Middle ear pressures continually improved, and after 8 weeks, only 4 of the 45 children received TTs.

Balloon Dilatation of the Eustachian tube

Miller[32] reviewed the literature on balloon dilatation of the Eustachian tube; only uncontrolled case series in adults with OME were identified, with heterogeneous data collection methods and no long-term follow-up.

Tympanostomy Tubes

No new trials of TTs for OME have been published since 2011, but there were new analyses based upon existing data. Hellström[33] performed a systematic review and included 63 studies. They found high level evidence of benefit of tubes for hearing and QoL for up to 9 months after treatment.

Berkman[34] reviewed the literature on treatment for OME and included 59 studies. They found that TTs are beneficial for clearing MEE for up to 2 years and for

improving hearing for 6 months, but found no evidence of a beneficial effect on language development.

Baik[35] applied utility-based Markov decision theory modelling to the question of optimum duration of intubation with TTs. They found that intermediate-type TTs provide the greatest benefit compared to short-term TTs or permanent tubes, but this was influenced by the probability of needing a further set of TTs. Children not developing recurrent OME after a single set of TTs would be better treated with short-term tubes, but the challenge is to identify these children at first insertion.

Khodaverdi[36] reported long-term outcomes of TTs in children treated with a unilateral tube for bilateral OME 25 years earlier. They found no difference in hearing thresholds between the treated and untreated ear. In contrast, a retrospective study in children diagnosed with OME 5 years earlier found that hearing was poorer in those treated with TTs compared to children who did not receive TTs[37].

Adenoidectomy

The previously cited IPDMA by Boonacker[17] included patients with persistent OME. They found benefit of adenoidectomy in children with OME aged over 4 years, but not in younger children.

Mikals[38] reviewed the literature on adenoidectomy as an adjuvant to primary TT insertion. Five RCTs met the inclusion criteria; the pooled estimate of the rate of repeat TT surgeries for children undergoing primary adenoidectomy in addition to TTs was 20.4% vs 34.1% for children undergoing primary TTs only.

In the TARGET RCT[39], children with OME were randomized to either TTs only, adenoidectomy and TTs or watchful waiting. Adenoidectomy with TTs extended the benefit to hearing through the second year of follow-up without evident

diminution; the magnitude of this benefit was 4.2 dB HL over TTs alone. Adjuvant adenoidectomy reduced audiometric eligibility for revision surgery.

In a retrospective case series of children treated with TTs, Gleinser[40] found a repeat TT insertion rate of 20%. Adenoidectomy performed at the first TT insertion for OME decreased the risk of repeat TT placement, especially for children aged 4-10 years.

At-risk Groups

Children with cleft palate (CP) and Down syndrome (DS) are both more prone to developing OM, as well as to its complications and developmental sequelae[41], yet they are excluded from most RCTs. Children with CP and DS are more likely to undergo treatment for OME, as are children with autistic spectrum disorder[42]. The systematic review on the effectiveness of OME treatments by Berkman[34] concluded that additional research is needed to support treatment decisions in these at-risk groups.

Kuo[43] undertook a systematic review of TTs for OME in children with CP. They identified 9 studies of high- or moderate-quality and found short-term benefit of TTs on hearing. Tierney[44] carried out a qualitative study of parents' experiences of OME treatment in CP children and found that TTs were seen as a simple fix with some worries about complications. Hearing aids were associated with social stigma, but were well tolerated by those who wore them.

Mohiuddin[45] evaluated the economic impact of TT insertion in children with OME and showed that in children with CP and bilateral OME, treatment with TTs is likely to be cost-effective. In a retrospective case series of more than 100 children with DS treated with TTs, Paulson[46] found hearing did not normalize after TTs in 14% of ears, signifying another underlying conductive cause or sensorineural

hearing loss. Most children (64%) had a second set of TTs, and sequelae such as chronic perforations, atelectasis and cholesteatoma were common.

Tympanostomy Tube Otorrhea and Complications of Tubes (Table 4)

Incidence of Tympanostomy Tube Otorrhea (TTO)

Van Dongen[47] used a parental web-based questionnaire to collect retrospective data on TTO incidence. In 1184 children treated with TTs aged below 10 years, 52% had at least one TTO episode, 12% had recurrent TTO and 4% had prolonged TTO. Independent predictive factors for TTO were young age, rAOM as the indication for TTs, recent history of recurrent URIs and having older siblings.

Treatment of TTO

In an RCT, van Dongen[48] compared 3 treatment modalities in children with acute TTO: hydrocortisone-bacitracin-colistin eardrops, oral amoxicillin-clavulanate suspension or initial observation. At 2 weeks, antibiotic-steroid eardrops were more effective than oral antibiotics and initial observation in resolving otorrhea, and were most cost-effective[49].

Cheng[50] retrospectively reviewed the management of children with methicillin-resistant *Staphylococcus aureus* (MRSA) TTO. Of medical treatments, fluoroquinolone eardrops were most successful. In 54% of patients, TTO resolved only after TT extrusion and/or removal, with or without TT replacement.

Prevention of Early Postoperative TTO

A Cochrane review[51] of prevention of post-operative TTO found 15 eligible RCTs, of which 7 were considered at low risk of bias. Four treatments were found to reduce the rate of otorrhea up to two weeks after surgery: multiple saline washouts during surgery, single application of topical antibiotic/steroid drops during surgery, prolonged application of topical antibiotic/steroid drops and prolonged application of

oral antibacterial agents/steroids. The authors concluded that if a surgeon has a high rate of postoperative otorrhea, either saline irrigation or single application of topical antibiotic drops during surgery could be an option to reduce that rate.

Park[52] followed 67 adult patients who received a mupirocin-coated TT and found early postoperative TTO occurred in only one patient, leading the authors to conclude that their product could be effective at preventing this problem.

Complications of TTs

Barati[53] reviewed the medical records of all children aged 2-4 years who had TTs for OME in two hospitals. Eighty-two had otomicroscopy 10-11 years later; myringosclerosis was the most common sequela. Of note, none had developed cholesteatoma.

Erdoglija[54] retrospectively studied complications within 18 months after TT insertion for OME in 487 children. Common complications included transient TTO, TT obstruction and premature TT extrusion.

Saki[55] reviewed the medical records of 208 children followed for 12-18 months after TTs insertion for OME. “Transient” and “delayed” otorrhea occurred in 13% and 8% of children, respectively. Complications after TT extrusion included atrophy, myringosclerosis and persistent perforation.

Smillie[56] studied complication rates after TT insertion in 60 children with cleft lip and/or palate (CLP) and in 60 matched children without. TTO episodes were not more frequent in CLP children than in the control children. Other TT complications were more frequent in the control group.

Chronic Suppurative Otitis Media (Table 5)

Topical Antibiotics

Morris[57] reviewed the literature on treatments for CSOM and cholesteatoma in adults and children. Although topical antibiotics seemed more effective than topical antiseptics in resolving otorrhea, the benefits of their use versus placebo in children is yet unclear.

A longitudinal cohort study in Greenland looked at evolution of CSOM[58]. Of 591 Inuit children originally examined in 1993-1994, 226 were followed up in 2009. Of 37 ears with CSOM at the initial examination, 39% had healed spontaneously. Fourteen ears not diagnosed originally with CSOM had CSOM at follow-up. One-third of children had CSOM, had undergone ear surgery or had sequelae from CSOM at the follow-up visit.

An RCT comparing the effects of swimming versus no-swimming in chlorinated pools in children with tympanic membrane (TM) perforations showed neither differences in proportion with discharge nor in nasopharyngeal or middle-ear microbiology of children who did or did not swim[59].

CAM

A Cochrane review[60] on the effects of zinc supplementation in preventing OM found mixed results in otherwise healthy children under 5 years living in low- and middle-income countries.

Surgical Treatment

Two systematic literature reviews compared temporalis muscle fascia (TMF) to cartilage tympanoplasty[61,62]. Both reviews reported better structural outcomes (fewer post-operative TM perforations) with a cartilage graft, but no better functional outcomes (similar hearing).

Novel Adjuvant Therapies

Hong[63] reviewed various adjuvant treatments for enhancing TM perforation repair, including biomolecules to stimulate the growth of perforation edges and bioengineered scaffolds. The majority of the scaffold materials tested were safe and improved TM perforation healing rates.

Kanemaru[64] performed an RCT (included in Hong[63]) in 53 patients with chronic perforations comparing a gelatin sponge scaffold soaked in fibroblast growth factor (b-FGF) vs a gelatin sponge only following freshening of the perforation edge. They found significantly higher closure rate in the b-FGF group with no adverse events.

Guidelines for Treatment of Otitis Media

Acute Otitis Media and Recurrent Acute Otitis Media (Table 6)

Since 2011, guidelines on the diagnosis and management of AOM have been published across the world, including the US[65], Japan[66,67], Korea[68], the Netherlands[69] and Spain[70]. All guidelines emphasize the need for accurate diagnosis. Pain relief is considered paramount, and watchful waiting has continued to be an option in children with “non-severe” AOM. Immediate antibiotics are reserved for children at high risk for an unfavorable outcome, with minor differences regarding definitions of “at risk” between guidelines.

For rAOM, reduction of risk factors (including day care attendance and tobacco smoke exposure) is encouraged[65-67], active immunoprophylaxis with pneumococcal conjugate vaccines (PCVs)[65-68] and influenza vaccine[65] is recommended, while long-term prophylactic antibiotics are discouraged[65].

Otitis Media with Effusion

Guidelines on OME were published in Korea[68], the US[71], the Netherlands[72] and Denmark[73]. All guidelines emphasize the importance of age-appropriate hearing

testing when the diagnosis of OME is made. Watchful waiting is recommended initially, unless the child belongs to a high-risk group or has TM morphological findings that require surgical treatment. Follow-up is recommended at 3 months with repeated hearing testing. Medical treatment is discouraged, whereas surgical intervention, TTs initially, is recommended in selected cases, considering laterality (bilateral) and duration of the disease (>3 months), hearing status (varies across guidelines from >25 to >40dB HL in the better ear), effect on the child's wellbeing, behavior and development. The importance of involving parents in the decision-making process is emphasized in all guidelines. Concomitant adenoidectomy and/or tonsillectomy are recommended only if there is concomitant upper airway disease. Audiometric surveillance every 3-6 months is recommended whenever TTs are not inserted.

Impact of Guidelines

A range of studies have looked at the impact of local, national and international guidelines on the treatment of AOM and URIs on clinical practice, and in particular antibiotic prescribing rates. The studies vary in their design (ranging from a survey of private physicians to analysis of regional electronic databases), study population (at-risk groups vs general population) and outcomes (ranging from diagnosis to antibiotic prescribing). Overall, adherence to published guidelines seems sub-optimal (e.g. in the UK, Italy, Sweden, Turkey, Serbia, Greece, Israel, the US)[74-82]. In France[83], guidelines have been effective in changing the antibiotic prescribing habits of pediatricians, and in Denmark[84], GPs to a large degree prescribe antibiotics appropriately. In the UK, the proportion of AOM episodes for which an antibiotic was prescribed was largely unchanged[74], and the use of a

broader spectrum antibiotic (amoxicillin plus clavulanic acid instead of amoxicillin) was the reason for diverging from recommendations in Hungary[78].

In a small UK audit[75], adherence to OM guidelines seems independent of medical specialty: GPs, pediatricians and otolaryngologists were equally non-compliant with antibiotic guidance. In contrast, Italian pediatricians were less likely to prescribe symptom-relieving drugs, such as decongestants and mucolytics, other than antibiotics[76], and Greek physicians aged below 40 years seem to adhere better to guidelines than those aged 60 years or higher[79].

All studies advocated continuing medical education as a means to improve the implementation of guidelines on antibiotic use; yet, the optimal method to achieve this goal is unclear. Information alone seems ineffective, which could be attributed to either the insufficient educational power of these educational interventions or other barriers to their implementation (e.g. cultural/social beliefs about the benefits and harms of antibiotics)[77]. Targeting specific scenarios associated with immediate vs delayed or no antibiotics prescribing for AOM, e.g. diagnosis on weekends vs weekdays, urgent care vs clinical setting, family care vs specialist care, may be effective in reducing unnecessary prescribing[81]. Electronic health record-based clinical decision support and performance feedback systems were found effective in improving adherence to OM guidelines; combining these two interventions, however, was no better than either delivered alone[85].

Complications of Otitis Media

Acute mastoiditis

Differing trends in acute mastoiditis (AM) incidence have recently been reported, with small series suggesting an increase[86,87], while larger series suggesting no change or even a decline[88-93]. Many of these studies have methodological

limitations. A large US insurance claims database of children less than 6 years suggested that AM incidence has declined following the introduction of PCVs, especially PCV-13[93]. Nevertheless, *S. pneumoniae* remains the most common cause of AM across the globe[86,89,91,94-104]. Country-wide hospital data from Denmark and Sweden show that there has been no increase in the incidence of AM[95, 102] since the introduction of guidelines to reduce antibiotic use for AOM, released a few years earlier.

Several case series show that 33-81% of patients diagnosed with AM had been treated with antibiotics prior to admission, suggesting that antibiotics administered for AOM treatment do not eliminate the risk of developing this complication[86,89,91,95,97-99,101,102].

While AM treatment traditionally involved cortical mastoidectomy, there is a recent trend towards non-surgical management with intravenous antibiotics, either alone or combined with myringotomy and TT insertion and/or needle aspiration of the subperiosteal abscess. Contemporary case series report mastoidectomy rates between 29-93% of mastoiditis patients; this variation may represent differences in clinical practice rather than disease severity[89,90,94,95,98,99,101,102,104-106]. In a review of 577 cases of AM from across Sweden, 10% of patients were successfully treated with antibiotics alone, 68% with antibiotics and myringotomy, and 22% with antibiotics and mastoidectomy[102]. In Eastern Denmark[95], 183/214 (86%) pediatric AM cases were treated with myringotomy and antibiotics, and 31% of them also received TT. Sixty-eight children had a subperiosteal abscess and all of these, except one, were treated by mastoidectomy. In a smaller case-series from Greece, 13/24 (57%) children with a subperiosteal abscess were successfully treated with needle aspiration and myringotomy, and did not require mastoidectomy[106,107].

Chesney[108] developed an algorithm whereby in uncomplicated AM cases (without neurologic deficits or sepsis), computerized tomography (CT) scanning is postponed and treatment is initiated with intravenous antibiotics, with or without myringotomy and/or drainage or aspiration of any subperiosteal abscess. Failure to improve after 48 hours or clinical deterioration should prompt a CT scan to assess coexistent intracranial pathology, followed by mastoidectomy.

Intracranial Complications

Retrospective reviews show that brain abscess is the most common intracranial complication of OM[104,109,110], with an estimated incidence of 1 per million per annum[111]. A small Israeli case-series found no reliable clinical signs or symptoms to distinguish children presenting with AM and coexistent intracranial complications from those without, confirming that imaging is warranted in cases not resolving promptly with conservative measures[112].

The role of anticoagulation in otogenic sigmoid sinus thrombosis remains controversial. Au[113] reviewed the literature, and found that anticoagulation was employed in 39/68 (57%) cases; 84% achieved partial or complete recanalization. However, 3/4 (75%) patients not treated with anticoagulation also achieved partial or complete recanalization. Reviews by Cochrane[114] and by the European Pediatric Neurology Society[115] found no RCTs of treatments of cerebral venous sinus thrombosis; both concluded that in the absence of contraindications, anticoagulation seems a safe and reasonable treatment[114,115]. Several retrospective reviews report no complications of anticoagulation in patients with otogenic sinus thrombosis[116-121].

IMPLICATIONS FOR PRACTICE

While there were no studies that revolutionized treatment of OM in its various forms, the recent literature refines our knowledge of the effectiveness, and lack thereof, of various treatments. Accurate diagnosis of OM, in its various forms, and optimal management of ear pain is key to reducing over-diagnosis and over-treatment of this common condition in children. While antibiotics do shorten symptoms and duration of middle ear effusion, it is important to weigh their benefits and harms in OM. Watchful waiting is optional in mild to moderate AOM. Symptomatic hearing loss with OME is best treated with tympanostomy tubes. The benefit from adenoidectomy in OM is controversial and age-dependent. Topical antibiotics are the treatment of choice in acute tube otorrhea. Novel molecular and biomaterial treatments as adjuvants to surgical closure of eardrum perforations are promising. There is insufficient evidence to support the use of CAM.

From this review of the literature, it was apparent to the panel members that high quality studies of OM treatments are needed in children particularly at risk for OM and its complications, as such children have so far been excluded from most research.

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Table 1: AOM Studies (Antibiotic Treatments)

Author, Year	Type	No. of Participants, Setting	Intervention (participants)	Comparator (participants)	Main Outcomes	Effect Estimates (95%CI)
Tapiainen, 2014[1]	RCT	84 (1), primary care	Amox-clav, 7d (42)	Placebo (42)	Time to MEE disappearance	18.9d vs 32.6d; p=.02.
					Normal tympanometry at 14d	29/42 vs 16/42; p<.01; NNTB: 4.
Venekamp, 2015[2]	SR	3401 (12), primary + secondary care	Oral antibiotics	Placebo	Pain at 2-3d	RR 0.7 (0.6-0.9); NNTB: 20.
					Adverse effects	RR 1.3 (1.2-1.6); NNTH: 14.
Casey, 2012[3]	RCT	330 (1), secondary care	Amox-clav, 10d (165)	Cefdinir, 5d (165)	Clinical cure at 11-14d	141/165 vs 115/165; p<.01.
Arguedas, 2011[4]	RCT	923 (1), secondary care	Azithromycin ER, single dose (462)	Amox-clav, 10d (461)	Clinical cure at 12-14d	207/258 vs 202/239; p=.24.
					Clinical cure at 41-64d	74/79 vs 60/66; p=.55.

Amox-clav: amoxicillin-clavulanate; CI: confidence interval; d: days; ER: extended release; MEE; middle ear effusion; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm; RCT: randomized controlled trial; RR: relative risk; SR: systematic review

[1]Amox-clav: 40 mg/kg/d amoxicillin.

[2]Reported results for pain at 2-3d correspond to 138/1186 and 180/1134 children (7 studies) in the oral antibiotics and placebo groups, respectively, and for adverse events to 283/1044 and 208/1063 children (8 studies) in the oral antibiotics and placebo groups, respectively.

[3]Amox-clav: 80 mg/kg/d amoxicillin; cefdinir: 14 mg/kg/d.

[4]Azithromycin ER: 60mg/kg; amox-clav 90mg/kg/d amoxicillin. Reported results are for 258 and 239 children with available bacteriological studies in the azithromycin ER and amox-clav groups on the test-of-cure days (12-14d), respectively, and for 79 and 66 children with available bacteriological studies in the azithromycin ER and amox-clav groups in the end of the study period (41-64d), respectively.

Table 2: RAOM Studies

Author, Year	Type	No. of Participants	Intervention	Comparator	Main Outcome(s)	Effect Estimate(s)
Pichichero 2013	Cohort	1482	Individualized care (254)	Legacy controls (208); Community controls (1024)	rAOM incidence	6% vs 14% vs 27%; p<.0001.
					TTs incidence	2% vs 6% vs 15; p<.0001.
Kujala 2012	RCT	300	TTs+Ad (100), TTs (100)	Controls (100)	Treatment Failure: 2 AOMs in 2 mos, 3 AOMs in 6 mos or MEE >2 mos	TTs 21%,TTs+Ad 16%, controls 34%. TTs vs controls: -13% [95%CI:-25%-(-1%), p=.04].TTs+Ad vs controls: -18% [95%CI: -30%-(-6%), p=.004].
					Treatment Failure reduction	TTs 38%, TTs+Ad 53%.
Lous 2011	SR	5 studies, 519	TTs (235)	Observation, ABx, placebo (284)	Prevention of AOM in 6 mos	2-5 children need to be tubed to prevent 1 child from AOM attacks.

					Prevention of AOM during 6 mos after TTs placement	TTs prevent 1 AOM attack.
Cheong 2012	SR	7 studies, >1300	Prophylactic ABx, TTs, Ad	Observation, placebo, ABx	AOM recurrence Frequency of AOM Total time with AOM	Prop. ABx TT Ad + - + + + + + + -
Boonacker 2014[1]	Meta-analysis	10 studies, 1761	Ad (with or without TTs)	TTs, observation	Failure at 12 mos, stratified according to age, baseline disease	Ad 56%. 16% of children <2 years with rAOM and had Ad failed, vs 27% of those who did not have Ad failed. RD -12%, 95%CI: 6% to 18%. 51% of children ≥4 years with OME and had Ad failed, vs 70% of those who did not have Ad. RD -19%, 95%CI: 12%-26%.
Marchisio	RCT	116	Vitamin D,	Placebo (58)	≥ 1 AOM(s) in 7 mos	26 vs 38, p=.03.

2013			1000 IU/d (58)		Mean AOM episode(s) in 7 mos	0.7±0.8 vs 1.4±1.4, (p=.003).
Cohen 2013	RCT	224	Pro/Prebiotic enriched formula (112)	Follow-up formula (112)	No. of AOM episode(s) in 12 mos	IRR 1.0; 95%CI: 0.8-1.2 (p=.797).
					rAOM	OR =1.0; 95%CI: 0.5-1.7 (p=.889).
Vernacchio 2014	RCT	326	Xylitol (160)	Controls (166)	AOM incidence/90d	0.53 vs 0.59, 95%CI: -0.25-0.13.
					Time to first AOM in 90d	HR: 0.93, 95% CI: 0.56-1.57.
					Total days with ABx in 90d	6.8d vs 6.4d, 95%CI: -1.8-2.7.

ABx, antibiotic therapy; Ad: adenoidectomy; AOM, acute otitis media; CI: confidence interval; d: day; HR: hazards ratio; IRR: incidence rate ratio; IU: international units; MEE: middle ear with effusion; mos, months; OR: odds ratio; rAOM, recurrent acute otitis media; RCT: randomized controlled trial; RD: rate difference; SR: systematic review; TT: tympanostomy tube

[1]In this trial, eligible studies for inclusion in this meta-analysis were randomized controlled trials in children up to 12 years of age diagnosed with recurrent AOM and/or persistent OME in which adenoidectomy (with or without tympanostomy tubes) was compared to non-surgical treatment or grommets alone.

Table 3: OME Studies

Author, Year	Study Type	No. of Participants	Intervention	Primary Outcome	Results (95%CI)
Van Zon 2012[1]	Cochrane/ meta-analysis	23 studies, 3027	ABx vs no treatment or placebo	MEE complete resolution at 2-3 mos	Improvement in 1% (-0.11-0.12) to 45% (0.25-0.65) of children receiving ABx.
Chen, 2013[2]	RCT	84 (73 completed)	Macrolides (36) vs nasal steroids (37)	MEE clearance at 8-12 weeks (%)	38 vs 19, 70 vs 25, and 80 vs 26, after 8, 10 and 12 weeks, respectively.
Bhargava 2014	RCT	62	Mometasone (30) vs saline (32)	MEE resolution at 24 weeks	93% vs 50%, p=.0004.
Yang 2014	RCT	90 (112 ears)	Intra-tympanic injection with budesonide (30), dexamethasone (31) or saline (29)	Improvement of subjective symptoms, on a 10-point visual scale	Budesonide vs saline, RR 0.139 (0.054-0.358); Dexamethose vs saline, RR 0.485 (0.240-0.979)
				Efficacy at 8 and 16 weeks	Budesonide: 95%, 90%; Dexamethasone: 75%, 55%; Saline: 40%, 20%.

Griffin 2011	Cochrane/ meta-analysis	16 studies, 1880	Anti-histamines, decongestants, combinations	Resolution of MEE at 1 mo	RR 0.99 (0.92-1.05) for all interventions.
Ertugay 2013	RCT	120	Montelukast vs levocetirizine vs both vs placebo	Otoscopic scores improvement, at 1 mo	Both montelukast and levocetirizine: greater improvement in scores than all other groups, p<.05. Multiple risk differences, 0.6-10.0.
Fixsen 2013	SR	-	Homeopathy	MEE improvement	Insufficient evidence.
Califano 2014	RCT	80	Oral steroids vs thermal therapy (sulphur water)	Tympanogram type improvement at various time points	Thermal therapy group had better tympanograms, sometimes reaching statistical significance.
Qureishi 2014[3]	Cross-sectional	97	HAs vs TTs	Psychosocial impact difference of HAs	Families with HAs rating higher marks than families without HAs (p<.05).
Perera 2013	Cochrane review / meta-analysis	8 studies, 702	Auto-inflation vs no treatment	Tympanogram improvement; >10dB improvement in hearing level; both	No effect on individual measures. For composite measure >1 mo., RR 1.74 (1.22 2.50).

Bidarian-Moniri 2014	Cross-over study	45	New device for auto-inflation vs no treatment for 4 weeks, then treatments cross-over between 4th-8th weeks	Middle ear pressure improvement at 4 and 8 weeks	At 4 weeks: improvement by 166 daPa (treatment) and 19 daPa (control), p<.0001. At 8 weeks: improvement by 187 daPa (in group having received treatment, p<.0001.
				Improvement in hearing at 4 and 8 weeks.	At 4 weeks: mean hearing levels improved by 6dB (p<.0001) vs 1dB, p<0.0001. At 8 weeks: unchanged and improved by 7 dB.
Miller 2013[4]	SR	5 studies, 375	Balloon dilatation of the Eustachian tube (surgery)	Normalization of tympanometry	69/89 (78%) abnormal tympanograms (type B/C) normalized to post-operative type A.
				Normalization of otoscopic findings	40/46 (87%) pre-operative abnormal findings normalized post-operatively.
Hellström 2011	SR	63 studies, 11 on OME (1756); QoL studies	Bilateral TTs vs WW; unilateral TT vs no treatment	TTs effectiveness, assessed by QoL, hearing, language, and rAOM frequency	Hearing levels improved significantly with TTs, no clear effects on language, some evidence of TTs improving QoL.
Berkman 2013	Meta-analysis	59 studies	WW, TTs, Ad, myringotomy, auto-inflation, oral or nasal steroids,	OME improvement, hearing improvement, complications,	Length of TT retention corresponded to TT type. TT type was not related to improved OME and hearing outcomes. TT decreased OME for 2 years compared to WW or

			complementary medicine		myringotomy, and improved hearing for 6 months compared to WW. OME resolution was more likely with Ad.
Baik 2015	Markov decision analysis	Hypothetical cohort	Short-, intermediate- and long-term TTs	Complications of TTs in 2, 4 and 6 yrs (total utility)	Intermediate-term TTs: 2.48, 3.96, 5.27, superior to short-term TTs (2.32, 3.82, 5.18) and long-term TTs (2.42, 3.86, 5.18).
Khodaverdi 2013	LFS	104	TT-treated ear to non-treated ear in the same patient	Difference in hearing thresholds	No significant difference.
MRC Otitis Media Study Group 2012	RCT	376	WW vs TTs only vs TTs+Ad	Hearing thresholds, revision surgery, otoscopic sequelae and Ad complications	Ad did not add to the benefit of TTs before 6 mos: 8.8 dB (7.1-10.5); for longer observation, it conferred 4.2 dB benefit (2.6-5.7), compared to none for TTs. For re-TT, RR=3.2 (1.8-5.9).
Gleinser 2011	RS	904	TTs+Ad vs TTs	Re-TTs rate	Re-TTs rate: 7% vs 20%, p=.0001.
Hong 2015	RS follow-up	89	Children with OME who had no	Hearing thresholds differences (dB)	No surgery: 10±6.5, TTs once: 15.9±11.2; >1 set of TTs: 17.8±7.6. No surgery vs rest, p<.005.

			surgery, 1 set of TTs, and TTs>1		
Kuo 2014	SR	9 studies, 702	TTs vs observation in children with CP	Effectiveness of TTs on hearing and speech	TTs have a beneficial effect on hearing in the short term; long-term effects are still unknown. Positive effect on speech.
Tierney 2013	Qualitative study	37 parents of CP children	Interviews with parents on TTs vs HAs	Parents' experiences	TTs: “quick-fix”, but some had concerns about complications. HAs: possible social stigma, but tolerated them well if worn.
Paulson 2014	RS	102	Children with DS receiving TTs	Hearing results, no. of TT operations, long-term complications	Most patients had normal post-operative hearing. Most had ≥2 TT sets. Long-term complications increased with the number of TT sets.
Wang 2014	RS	1755	TTs+Ad vs TTs	Re-TTs rate	Re-TT rate: 5.1% vs 9%, p=.002. Ad effect more obvious >4 years. Controlled for age, RR: 0.60 (0.41–0.89).

ABG: air-bone gap; ABx, antibiotic therapy; Ad: adenoidectomy; amox-clav: amoxicillin-clavulanate; CI: confidence interval; CP: cleft palate; DS: Down's children; HA: hearing aids; LFS: Longitudinal follow-up study; MEE: middle ear effusion; mo: month; OME: otitis media with effusion; QoL: quality of life; RAOM: recurrent acute otitis media; RCT: randomized controlled trial; RR: relative risk; RS: retrospective; SR: systematic review; TT: tympanostomy tube; WW: watchful waiting; yrs; years.

[1]Numbers are shown for studies who tested normalization of tympanometry profiles and otoscopy findings.[2]Clarithromycin: 15 mg/kg/d bid daily in the first week, then changed to a low dose, 5-8 mg/kg/d qd, until the tympanogram was type "A". [3]Qualititive cross-sectional study. Parents of children with hearing aids filled the questionnaires. [4]Only 5 case-series studies fullfilled enrollment criteria for this systematic review.

Table 4: Otorrhea Studies

Author, Year	Type	Population, No. of Participants	Main Outcome(s)	Results (95%CI)
van Dongen 2013	RS	Children <10 yrs with TTs (1184)	TTO incidence	52% had ≥1 episode(s) of TTO: 12% had TTO within the calendar month of TT placement. 50% had ≥1 acute TTO episodes, 4% had ≥1 chronic TTO episode(s), and 12% had recurrent TTO episode(s).
van Dongen 2014, 2015	Open label RCT	230 Children aged 1-10 yrs with acute TTO: hydrocortisone-bacitracin-colistin eardrops (76), oral amox-clav suspension (77), observation (77)	TTO at 2 weeks	5% eardrops treated, 44% amox-clav treated, risk difference, -39% [-51-(-26)], 55% observed, risk difference, -49%; [-62-(-37)].
			Mean total cost/patient at 2 weeks and at 6 mos	2 weeks: US$42.43 for eardrops, US$70.60 for oral antibiotics, and US$82.03 for initial observation. At 6 mos: US$368.20, US$420.73, and US$640.44, respectively

Cheng 2012	RS	Children <18 yrs with MRSA-positive TTO (41)	ABx resistance patterns and treatment success rates	Fluoroquinolones and clindamycin resistance in 88% and 61% of cases. Ototopical fluoroquinolone and sulfacetamide were associated with successful TTO resolution, p=.005, p=.009.
Park 2012	RS	67 children with mupirocin-coated TTs (98 ears)	Post-operative TTO incidence (at 2 weeks)	1 (1.5%) case had post-operative TTO with experimental TT.
Barati 2012	LFS	10-11 yrs FU of children who underwent TTs at 2-4 yrs (82)	TT complication rate	Myringosclerosis, 17.1%; TM atrophy, 1.2%; permanent TM perforation, 0.6%; TM atelectasis 0.6%; cholesteatoma 0%.
Erdoglija 2012	RS	478 children who were treated with TTs (843 ears)	TTs complication rate at 12-18 mos FU	Transient TTO: 16.5%, TT obstruction: 9.5%, premature extrusion: 3.9%, chronic TTO: 3.1%, granulation tissue: 1.1%
Saki 2012	Prospective	Children aged 10 mos-6 years with TTs (208)	Post-operative TTO incidence, post-extrusion complications rate	At 12-18 mos FU: transient TTO: 12.5%; delayed TTO: 8.2%. Complications after TT extrusion: atrophy: 27.8%; myringosclerosis: 37.9%; persistent TM perforation: 2.4%.

Smillie 2014	Case-control	60 children with CLP who underwent TTs, vs age- and sex-matched controls	TTO incidence	Controls had 151 cases of TTO, compared to 121 in the CLP group (ratio 1.25:1). Difference was not significant (p = .52).

Amox-clav: amoxicillin-clavulanate; CLS: cleft lip and palate; FU: follow up; mos: months; LFS: longitudinal follow-up study; MRSA: methicillin-resistant *Staphylococcus aureus*; RS: retrospective study; TM: tympanic membrane; TT: tympanostomy tube; TTO: tympanostomy tube otorrhea; yrs: years

Table 5: CSOM Studies

Author, Year	**Type**	**Population, No. of Participants**	**Intervention**	**Comparator**	**Results (95%CI)**
Morris 2012	SR	Children and adults with CSOM, 51 studies	Topical ear cleansing, surgery for cholesteatoma, systemic ABx, topical ABx topical ABX plus topical corticosteroids, topical antiseptics, topical corticosteroids, tympanoplasty	Various	**Children**: topical antibiotics may improve Sx, compared to antiseptics. Other topical treatments are not superior to placebo. **Adults**: topical antibiotics alone/with topical corticosteroids may improve Sx, compared to placebo or either treatment alone.

Jensen 2012	LFS	226 children seen at 10-12 yrs FU	Spontaneous healing of the TM	-	591 children initially examined. TM spontaneous healing: 39%; Overall CSOM prevalence: 9%.
Stephen 2013	RCT	89 children with CSOM	Swam in chlorinated pool (41)	Did not swim (44)	No significant changes in the nasopharynx or middle ear microbiology.
Gulani 2014[1]	SR	10 studies, 6820 children	Zinc supplements, at any dose, given at least once a week, for at least one month	Placebo	One old trial found benefit in treating children with severe malnutrition, and correlated lower levels of minerals and vitamin D with CSOM severity.
Iacovou 2013	SR	12 studies, 1286 patients	CR	TMF	Mean graft integration rate: CR 92.4% vs TMF 84.3%. CR promoted better ABG closure ($p<.05$).
Mohamad 2012	SR	14 studies, 1475 patients	Tympanoplasty with CR	Tympanoplasty with TMF	Revision rate: CR: 10% vs TMF: 19%. Statistically significant better morphologic success with CR. No significant differences regarding hearing outcome.
Hong 2013	SR	26 studies	Tympanoplasty grafts made with biomolecules (platelet-derived growth factor, platelet-rich plasma, hyaluronic acid, epidermal growth factor and pentoxifylline,	TMF or no material	Several studies demonstrated positive results. Many questions still remain, such as the adequacy of animal models and long-term biocompatibility of adjuvant materials.

			b-FGF, combinations) and scaffolding materials (i.e., alloderm, silk patches)		
Kanemaru 2011	RCT	63 patients	TEM, b-FGF (53)	TEM, saline (10)	TM closure rate: 98.1% vs 10%. Average hearing was improved. No serious sequelae were reported.

ABG: air-bone gap; ABx: antibiotic therapy; b-FGF: basic fibroblast growth factor; CI: confidence interval; CSOM: chronic suppurative otitis media; CR: cartilage reconstruction; FU: follow up; LFS: Longitudinal follow-up study; OR: odds ratio; PTF: temporalis fascia; RCT: randomized controlled trial; RS: Retrospective study; SR: systematic review; Sx: symptoms; TEM: tissue engineered myringoplasty; TM: tympanic membrane; TMF: temporalis muscle fascia; vs: versus; Zn, zinc

Table 6: Selected National Guidelines for AOM

Country	Age	Diagnosis/Instruments	Management	First-line Antibiotics[1]
USA, 2013	6 mos-12 yrs	Stringent criteria. Key factors: TM bulging or new-onset otorrhea. Use of pneumatic otoscopy and tympanometry. Treat pain.	ABx: children ≥6 mos with severe AOM, non-severe bilateral AOM in children 6-23 mos. WW: non-severe unilateral AOM in children <23 mos, non-severe AOM in children >24 mos.	High dose amox; High dose amox-clav in children receiving amoxicillin in the previous 30 days or with otitis-conjunctivitis.
Japan, 2013	0-15 yrs	Accurate diagnosis. Otomicroscopy or otoscopic observation. Pneumatic otoscopy acceptable.	Mild AOM: 3 days WW, otherwise ABx. Moderate AOM: immediate ABx. Severe AOM: myringotomy and ABx.	Low dose amox→ high dose amox→ amox-clav or ceftidoren pivoxil.
South Korea, 2012	0-15 yrs	Definitive (Sx and TM findings) vs suspicious (Sx without objective findings) diagnosis	WW: possible, FU visit after 2-3 days. ABx: severe AOM, <6 mos, 6-24 mos with definite AOM, when FU is impossible, co-morbidities.	High dose amox; Severe AOM: high dose amox-clav.
The Netherlands, 2014	0-18 yrs	Patient's history, Sx and otoscopy findings. Treat pain.	Immediate ABx: infants <6 mos, severe AOM. Consider ABx: children <2 years & bilateral AOM, otorrhea, persisting Sx.	Low dose amox. Amox-clav if no improvement after 48 hours

ABx: antibiotic therapy; amox: amoxicillin; amox-clav: amoxicillin-clavulanic acid; AOM, acute otitis media; mos: months; FU: follow up; MEE: middle ear effusion; rAOM, recurrent otitis media; Sx: symptoms; TM: tympanic membrane; WW: watchful waiting; yrs, years

[1]High dose amoxicillin/amox-clav: 80-90mg/kg/d of amoxicillin; low dose amoxicillin: 40mg/kg/d of amoxicillin