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44 Keywords: otitis, otitis media, otorrhea, tympanostomy tube, adenoidectomy,  
45 perforation, guidelines, mastoiditis

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50 **ABSTRACT**

51 **OBJECTIVE:** We aimed to summarize key articles published between 2011 and  
52 2015 on the treatment of (recurrent) acute otitis media, otitis media with effusion,  
53 tympanostomy tube otorrhea, chronic suppurative otitis media and complications of  
54 otitis media, and their implications for clinical practice.

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

57 **REVIEW METHODS:** All types of articles related to otitis media treatment and  
58 complications between January 2011 and March 2015 were identified. A total of  
59 1122 potential related articles were reviewed by the panel members; 118 relevant  
60 articles were ultimately included in this summary.

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

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

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

76 **INTRODUCTION**

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

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

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## 91 **METHODS**

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

96 Each panel member designed a topic-specific key-word search strategy for  
97 the various electronic databases, including PubMed, Ovid Medline, the Cochrane  
98 Library and Clinical Evidence (BMJ Publishing). Databases were searched from  
99 6/1/2011 through 3/31/2015, restricted to articles with at least an abstract published  
100 in the English language. Publications cited in the previous review<sup>3</sup> were excluded.  
101 Searches were supplemented by additional relevant articles (including evidence-  
102 based practice guidelines) identified by members during discussion at the panel  
103 meeting.

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

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## 112 **DISCUSSION**

### 113 **Acute Otitis Media (Table 1)**

114 A high-quality placebo-controlled trial performed by Tapiainen<sup>4</sup>, found that oral  
115 antibiotics shortened the period with middle ear effusion (MEE) after AOM. This trial  
116 was included in a 2015 Cochrane review update<sup>5</sup>, which showed that oral antibiotics  
117 for AOM reduce the proportion of children with abnormal tympanograms at 2-4 and  
118 6-8 weeks, but not at 3 months. Both this review<sup>5</sup> and a 2014 BMJ Clinical Evidence  
119 review<sup>6</sup> concluded that “antibiotic treatment reduces AOM symptoms more quickly  
120 than placebo, but this benefit needs to be weighed against the increased risk of  
121 adverse events such as vomiting, diarrhea or rash”.

#### 122 Type of Antibiotic Treatment

123 The 2014 BMJ review<sup>6</sup> summarized the evidence on antibiotic choice in  
124 children with AOM and concluded that, “we do not know whether any one antibiotic  
125 regimen should be used in preference to another, although amoxicillin may be more  
126 effective than macrolides and cephalosporin, and should be considered as first-line  
127 treatment”.

128 The randomized clinical trial (RCT) performed by Casey<sup>7</sup>, which was included  
129 in the BMJ review<sup>6</sup>, showed that children treated with amoxicillin/clavulanate for 10  
130 days reached “clinical cure” at 11-14 days more frequently than those treated with  
131 cefdinir for 5 days.

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

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

#### 140 Otological Symptomatic Agents

141 The 2014 BMJ review<sup>6</sup> found two low quality trials suggesting that topical  
142 analgesics may be more effective than placebo at reducing ear pain 10-30 minutes  
143 after administration. Another systematic review<sup>10</sup> included the same two trials and  
144 two additional trials comparing anesthetic drops and herbal extracts drops. Again,  
145 quality of evidence was judged low, and the authors concluded that “further studies  
146 with more rigorous methodology are needed to demonstrate the utility of otological  
147 agents”.

#### 148 Systemic Steroids

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

#### 153 Complementary and Alternative Medicine (CAM) Treatments

154 An RCT performed by Sinha<sup>12</sup>, at high risk of bias, compared homeopathy  
155 versus conventional treatment and found similar numbers of patients cured at 21  
156 days follow-up.

#### 157 At-risk Populations

158 No new studies were found on this topic.

### 159 **Recurrent Acute Otitis Media (Table 2)**

#### 160 Culture-Specific Antibiotic Treatment



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

### 166 Surgical Treatment

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

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

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

184 Boonacker<sup>17</sup> performed an individual patient data meta-analysis (IPDMA) of  
185 adenoidectomy for OM in children less than 12 years. The authors included 15 RCTs

186 of adenoidectomy alone or as an adjuvant to TTs in 1761 children, and used a  
187 composite outcome including elements of both AOM and OME to summarize results.  
188 Analyzing different studies than those reviewed by Cheong<sup>16</sup>, they found that  
189 children aged less than 2 years with rAOM may benefit from adenoidectomy,  
190 whereas in older children no benefit was found.

### 191 CAM Treatments

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

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

200 A placebo-controlled trial by Vernacchio<sup>20</sup> found viscous xylitol solution three  
201 times daily for 12 weeks did not reduce AOM recurrences in otitis-prone infants and  
202 young children.

### 203 **Otitis Media with Effusion (Table 3)**

#### 204 Oral Antibiotics

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

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

### 215 Steroids

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

### 223 Antihistamines and Decongestants

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

### 229 CAM Treatments

230 Fixsen<sup>27</sup> conducted a systematic review of homeopathy in AOM and OME and  
231 found only one small study in children with OME. The author concluded that the  
232 evidence was incomplete and larger well-designed studies of CAM treatments for  
233 OM are needed.

234 One RCT evaluated the effect of thermal therapy in children with OME<sup>28</sup>. The  
235 treatment group had better tympanometry outcomes at some of the follow-up visits.

### 236 Hearing Aids

237           The psychosocial impact and parental attitude to hearing aids were compared  
238 between parents of children with OME treated by TTs and those treated with hearing  
239 aids; children treated with hearing aids did not suffer the bullying nor lower self-  
240 esteem anticipated by parents of children treated with TTs<sup>29</sup>.

### 241 Auto-inflation

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

### 250 Balloon Dilatation of the Eustachian tube

251           Miller<sup>32</sup> reviewed the literature on balloon dilatation of the Eustachian tube;  
252 only uncontrolled case series in adults with OME were identified, with heterogeneous  
253 data collection methods and no long-term follow-up.

### 254 Tympanostomy Tubes

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

259           Berkman<sup>34</sup> reviewed the literature on treatment for OME and included 59  
260 studies. They found that TTs are beneficial for clearing MEE for up to 2 years and for

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

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

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

#### 274 Adenoidectomy

275 The previously cited IPDMA by Boonacker<sup>17</sup> included patients with persistent  
276 OME. They found benefit of adenoidectomy in children with OME aged over 4 years,  
277 but not in younger children.

278 Mikals<sup>38</sup> reviewed the literature on adenoidectomy as an adjuvant to primary  
279 TT insertion. Five RCTs met the inclusion criteria; the pooled estimate of the rate of  
280 repeat TT surgeries for children undergoing primary adenoidectomy in addition to  
281 TTs was 20.4% vs 34.1% for children undergoing primary TTs only.

282 In the TARGET RCT<sup>39</sup>, children with OME were randomized to either TTs  
283 only, adenoidectomy and TTs or watchful waiting. Adenoidectomy with TTs extended  
284 the benefit to hearing through the second year of follow-up without evident

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

287 In a retrospective case series of children treated with TTs, Gleinser<sup>40</sup> found a  
288 repeat TT insertion rate of 20%. Adenoidectomy performed at the first TT insertion  
289 for OME decreased the risk of repeat TT placement, especially for children aged 4-  
290 10 years.

### 291 At-risk Groups

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

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

305 Mohiuddin<sup>45</sup> evaluated the economic impact of TT insertion in children with  
306 OME and showed that in children with CP and bilateral OME, treatment with TTs is  
307 likely to be cost-effective. In a retrospective case series of more than 100 children  
308 with DS treated with TTs, Paulson<sup>46</sup> found hearing did not normalize after TTs in  
309 14% of ears, signifying another underlying conductive cause or sensorineural

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

## 312 **Tympanostomy Tube Otorrhea and Complications of Tubes (Table 4)**

### 313 Incidence of Tympanostomy Tube Otorrhea (TTO)

314 Van Dongen<sup>47</sup> used a parental web-based questionnaire to collect  
315 retrospective data on TTO incidence. In 1184 children treated with TTs aged below  
316 10 years, 52% had at least one TTO episode, 12% had recurrent TTO and 4% had  
317 prolonged TTO. Independent predictive factors for TTO were young age, rAOM as  
318 the indication for TTs, recent history of recurrent URIs and having older siblings.

### 319 Treatment of TTO

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

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

### 329 Prevention of Early Postoperative TTO

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

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

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

#### 341 Complications of TTs

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

346 Erdogljija<sup>54</sup> retrospectively studied complications within 18 months after TT  
347 insertion for OME in 487 children. Common complications included transient TTO,  
348 TT obstruction and premature TT extrusion.

349 Saki<sup>55</sup> reviewed the medical records of 208 children followed for 12-18 months  
350 after TTs insertion for OME. "Transient" and "delayed" otorrhea occurred in 13% and  
351 8% of children, respectively. Complications after TT extrusion included atrophy,  
352 myringosclerosis and persistent perforation.

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

#### 357 **Chronic Suppurative Otitis Media (Table 5)**

#### 358 Topical Antibiotics



359 Morris<sup>57</sup> reviewed the literature on treatments for CSOM and cholesteatoma in  
360 adults and children. Although topical antibiotics seemed more effective than topical  
361 antiseptics in resolving otorrhea, the benefits of their use versus placebo in children  
362 is yet unclear.

363 A longitudinal cohort study in Greenland looked at evolution of CSOM<sup>58</sup>. Of  
364 591 Inuit children originally examined in 1993-1994, 226 were followed up in 2009.  
365 Of 37 ears with CSOM at the initial examination, 39% had healed spontaneously.  
366 Fourteen ears not diagnosed originally with CSOM had CSOM at follow-up. One-  
367 third of children had CSOM, had undergone ear surgery or had sequelae from  
368 CSOM at the follow-up visit.

369 An RCT comparing the effects of swimming versus no-swimming in  
370 chlorinated pools in children with tympanic membrane (TM) perforations showed  
371 neither differences in proportion with discharge nor in nasopharyngeal or middle-ear  
372 microbiology of children who did or did not swim<sup>59</sup>.

### 373 CAM

374 A Cochrane review<sup>60</sup> on the effects of zinc supplementation in preventing OM  
375 found mixed results in otherwise healthy children under 5 years living in low- and  
376 middle-income countries.

### 377 Surgical Treatment

378 Two systematic literature reviews compared temporalis muscle fascia (TMF)  
379 to cartilage tympanoplasty<sup>61,62</sup>. Both reviews reported better structural outcomes  
380 (fewer post-operative TM perforations) with a cartilage graft, but no better functional  
381 outcomes (similar hearing).

### 382 Novel Adjuvant Therapies

383 Hong<sup>63</sup> reviewed various adjuvant treatments for enhancing TM perforation  
384 repair, including biomolecules to stimulate the growth of perforation edges and  
385 bioengineered scaffolds. The majority of the scaffold materials tested were safe and  
386 improved TM perforation healing rates.

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

## 392 **Guidelines for Treatment of Otitis Media**

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

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

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

### 405 Otitis Media with Effusion

406 Guidelines on OME were published in Korea<sup>68</sup>, the US<sup>71</sup>, the Netherlands<sup>72</sup>  
407 and Denmark<sup>73</sup>. All guidelines emphasize the importance of age-appropriate hearing

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

#### 420 Impact of Guidelines

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

432 broader spectrum antibiotic (amoxicillin plus clavulanic acid instead of amoxicillin)  
433 was the reason for diverging from recommendations in Hungary<sup>78</sup>.

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

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

## 452 **Complications of Otitis Media**

### 453 Acute mastoiditis

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

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

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

468         While AM treatment traditionally involved cortical mastoidectomy, there is a  
469 recent trend towards non-surgical management with intravenous antibiotics, either  
470 alone or combined with myringotomy and TT insertion and/or needle aspiration of the  
471 subperiosteal abscess. Contemporary case series report mastoidectomy rates  
472 between 29-93% of mastoiditis patients; this variation may represent differences in  
473 clinical practice rather than disease severity<sup>89,90,94,95,98,99,101,102,104-106</sup>. In a review of  
474 577 cases of AM from across Sweden, 10% of patients were successfully treated  
475 with antibiotics alone, 68% with antibiotics and myringotomy, and 22% with  
476 antibiotics and mastoidectomy<sup>102</sup>. In Eastern Denmark<sup>95</sup>, 183/214 (86%) pediatric  
477 AM cases were treated with myringotomy and antibiotics, and 31% of them also  
478 received TT. Sixty-eight children had a subperiosteal abscess and all of these,  
479 except one, were treated by mastoidectomy. In a smaller case-series from Greece,  
480 13/24 (57%) children with a subperiosteal abscess were successfully treated with  
481 needle aspiration and myringotomy, and did not require mastoidectomy<sup>106,107</sup>.

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

#### 488 Intracranial Complications

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

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

504

**505 IMPLICATIONS FOR PRACTICE**

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

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

522

523

524 **REFERENCES**

- 525 1. Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis  
526 media: systematic review and global estimates. *PLoS One*. 2012;7(4):e36226.
- 527 2. Ahmed S, Shapiro NL, Bhattacharyya N. Incremental health care utilization  
528 and costs for acute otitis media in children. *Laryngoscope*. 2014;124(1):301-  
529 305.
- 530 3. Marchisio P, Chonmaitree T, Leibovitz E, et al. Panel 7: Treatment and  
531 comparative effectiveness research. *Otolaryngol Head Neck Surg*.  
532 2013;148(4 Suppl):E102-121.
- 533 4. Tapiainen T, Kujala T, Renko M, et al. Effect of antimicrobial treatment of  
534 acute otitis media on the daily disappearance of middle ear effusion: a  
535 placebo-controlled trial. *JAMA Pediatr*. 2014;168(7):635-641.
- 536 5. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM.  
537 Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*.  
538 2015;6:CD000219.
- 539 6. Venekamp RP, Damoiseaux RA, Schilder AG. Acute otitis media in children.  
540 *BMJ Clin Evid*. 2014;2014.
- 541 7. Casey JR, Block SL, Hedrick J, Almudevar A, Pichichero ME. Comparison of  
542 amoxicillin/clavulanic acid high dose with cefdinir in the treatment of acute  
543 otitis media. *Drugs*. 2012;72(15):1991-1997.
- 544 8. Arguedas A, Soley C, Kamicker BJ, Jorgensen DM. Single-dose extended-  
545 release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for  
546 the treatment of children with acute otitis media. *Int J Infect Dis*.  
547 2011;15(4):e240-248.



- 548 9. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily  
549 versus three times daily amoxicillin with or without clavulanate for the  
550 treatment of acute otitis media. *Cochrane Database Syst Rev*.  
551 2013;12:CD004975.
- 552 10. Wood DN, Nakas N, Gregory CW. Clinical trials assessing ototopical agents  
553 in the treatment of pain associated with acute otitis media in children. *Int J*  
554 *Pediatr Otorhinolaryngol*. 2012;76(9):1229-1235.
- 555 11. Principi N, Bianchini S, Baggi E, Esposito S. No evidence for the effectiveness  
556 of systemic corticosteroids in acute pharyngitis, community-acquired  
557 pneumonia and acute otitis media. *Eur J Clin Microbiol Infect Dis*.  
558 2013;32(2):151-160.
- 559 12. Sinha MN, Siddiqui VA, Nayak C, et al. Randomized controlled pilot study to  
560 compare Homeopathy and Conventional therapy in Acute Otitis Media.  
561 *Homeopathy*. 2012;101(1):5-12.
- 562 13. Pichichero ME, Casey JR, Almudevar A. Reducing the frequency of acute  
563 otitis media by individualized care. *Pediatr Infect Dis J*. 2013;32(5):473-478.
- 564 14. Kujala T, Alho OP, Luotonen J, et al. Tympanostomy with and without  
565 adenoidectomy for the prevention of recurrences of acute otitis media: a  
566 randomized controlled trial. *Pediatr Infect Dis J*. 2012;31(6):565-569.
- 567 15. Lous J, Ryborg CT, Thomsen JL. A systematic review of the effect of  
568 tympanostomy tubes in children with recurrent acute otitis media. *Int J Pediatr*  
569 *Otorhinolaryngol*. 2011;75(9):1058-1061.
- 570 16. Cheong KH, Hussain SS. Management of recurrent acute otitis media in  
571 children: systematic review of the effect of different interventions on otitis

- 572 media recurrence, recurrence frequency and total recurrence time. *J Laryngol*  
573 *Otol.* 2012;126(9):874-885.
- 574 17. Boonacker CW, Rovers MM, Browning GG, Hoes AW, Schilder AG, Burton  
575 MJ. Adenoidectomy with or without grommets for children with otitis media: an  
576 individual patient data meta-analysis. *Health Technol Assess.* 2014;18(5):1-  
577 118.
- 578 18. Marchisio P, Consonni D, Baggi E, et al. Vitamin D supplementation reduces  
579 the risk of acute otitis media in otitis-prone children. *Pediatr Infect Dis J.*  
580 2013;32(10):1055-1060.
- 581 19. Cohen R, Martin E, de La Rocque F, et al. Probiotics and prebiotics in  
582 preventing episodes of acute otitis media in high-risk children: a randomized,  
583 double-blind, placebo-controlled study. *Pediatr Infect Dis J.* 2013;32(8):810-  
584 814.
- 585 20. Vernacchio L, Corwin MJ, Vezina RM, et al. Xylitol syrup for the prevention of  
586 acute otitis media. *Pediatrics.* 2014;133(2):289-295.
- 587 21. van Zon A, van der Heijden GJ, van Dongen TM, Burton MJ, Schilder AG.  
588 Antibiotics for otitis media with effusion in children. *Cochrane Database Syst*  
589 *Rev.* 2012;9:CD009163.
- 590 22. Chen K, Wu X, Jiang G, Du J, Jiang H. Low dose macrolide administration for  
591 long term is effective for otitis media with effusion in children. *Auris Nasus*  
592 *Larynx.* 2013;40(1):46-50.
- 593 23. Bhargava R, Chakravarti A. A double-blind randomized placebo-controlled  
594 trial of topical intranasal mometasone furoate nasal spray in children of  
595 adenoidal hypertrophy with otitis media with effusion. *Am J Otolaryngol.*  
596 2014;35(6):766-770.

- 597 24. Yang F, Zhao Y, An P, et al. Longitudinal results of intratympanic injection of  
598 budesonide for otitis media with effusion in children over 12 years and adults.  
599 *Otol Neurotol.* 2014;35(4):629-634.
- 600 25. Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with  
601 effusion (OME) in children. *Cochrane Database Syst Rev.*  
602 2011(9):CD003423.
- 603 26. Ertugay CK, Cingi C, Yaz A, et al. Effect of combination of montelukast and  
604 levocetirizine on otitis media with effusion: a prospective, placebo-controlled  
605 trial. *Acta Otolaryngol.* 2013;133(12):1266-1272.
- 606 27. Fixsen A. Should homeopathy be considered as part of a treatment strategy  
607 for otitis media with effusion in children? *Homeopathy.* 2013;102(2):145-150.
- 608 28. Califano L, Salafia F, Mazzone S, D'Ambrosio G, Malafronte L, Vassallo A. A  
609 comparative randomized study on the efficacy of a systemic steroid therapy  
610 vs. a thermal therapy in Otitis media with effusion in children. *Minerva Pediatr.*  
611 2014 Nov 13 [E-pub ahead of print].
- 612 29. Qureishi A, Garas G, Mallick A, Parker D. The psychosocial impact of hearing  
613 aids in children with otitis media with effusion. *J Laryngol Otol.*  
614 2014;128(11):972-975.
- 615 30. Perera R, Glasziou PP, Heneghan CJ, McLellan J, Williamson I. Autoinflation  
616 for hearing loss associated with otitis media with effusion. *Cochrane Database*  
617 *Syst Rev.* 2013;5:CD006285.
- 618 31. Bidarian-Moniri A, Ramos MJ, Ejnell H. Autoinflation for treatment of  
619 persistent otitis media with effusion in children: a cross-over study with a 12-  
620 month follow-up. *Int J Pediatr Otorhinolaryngol.* 2014;78(8):1298-1305.

- 621 32. Miller BJ, Elhassan HA. Balloon dilatation of the Eustachian tube: an  
622 evidence-based review of case series for those considering its use. *Clin*  
623 *Otolaryngol*. 2013;38(6):525-532.
- 624 33. Hellström S, Groth A, Jörgensen F, et al. Ventilation tube treatment: a  
625 systematic review of the literature. *Otolaryngol Head Neck Surg*.  
626 2011;145(3):383-395.
- 627 34. Berkman ND, Wallace IF, Steiner MJ, et al. Otitis Media With Effusion:  
628 Comparative Effectiveness of Treatments. Comparative Effectiveness Review  
629 No. 101. (Prepared by the RTI-UNC Evidence-based Practice Center under  
630 Contract No. 290-2007-10056-I.) AHRQ Publication No. 13-EHC091-EF.  
631 Rockville, MD: Agency for Healthcare Research and Quality. May 2013.  
632 [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).
- 633 35. Baik G, Brietzke S. How much does the type of tympanostomy tube matter? A  
634 utility-based Markov decision analysis. *Otolaryngol Head Neck Surg*.  
635 2015;152(6):1000-1006.
- 636 36. Khodaverdi M, Jørgensen G, Lange T, et al. Hearing 25 years after surgical  
637 treatment of otitis media with effusion in early childhood. *Int J Pediatr*  
638 *Otorhinolaryngol*. 2013;77(2):241-247.
- 639 37. Hong HR, Kim TS, Chung JW. Long-term follow-up of otitis media with  
640 effusion in children: comparisons between a ventilation tube group and a non-  
641 ventilation tube group. *Int J Pediatr Otorhinolaryngol*. 2014;78(6):938-943.
- 642 38. Mikals SJ, Brigger MT. Adenoidectomy as an adjuvant to primary  
643 tympanostomy tube placement: a systematic review and meta-analysis. *JAMA*  
644 *Otolaryngol Head Neck Surg*. 2014;140(2):95-101.

- 645 39. MRC Multicentre Otitis Media Study Group. Adjuvant adenoidectomy in  
646 persistent bilateral otitis media with effusion: hearing and revision surgery  
647 outcomes through 2 years in the TARGET randomised trial. *Clin Otolaryngol.*  
648 2012;37(2):107-116.
- 649 40. Gleinser DM, Kriel HH, Mukerji S. The relationship between repeat  
650 tympanostomy tube insertion and adenoidectomy. *Int J Pediatr*  
651 *Otorhinolaryngol.* 2011;75(10):1247-1251.
- 652 41. Marchica CL, Pitaro J, Daniel SJ. Recurrent tube insertion for chronic otitis  
653 media with effusion in children over 6 years. *Int J Pediatr Otorhinolaryngol.*  
654 2013;77(2):252-255.
- 655 42. Ackerman S, Reilly B, Bernier R. Tympanostomy tube placement in children  
656 with autism. *J Dev Behav Pediatr.* 2012;33(3):252-258.
- 657 43. Kuo CL, Tsao YH, Cheng HM, et al. Grommets for otitis media with effusion in  
658 children with cleft palate: a systematic review. *Pediatrics.* 2014;134(5):983-  
659 994.
- 660 44. Tierney S, O'Brien K, Harman NL, Madden C, Sharma RK, Callery P. Risks  
661 and benefits of ventilation tubes and hearing aids from the perspective of  
662 parents of children with cleft palate. *Int J Pediatr Otorhinolaryngol.*  
663 2013;77(10):1742-1748.
- 664 45. Mohiuddin S, Payne K, Fenwick E, O'Brien K, Bruce I. A model-based cost-  
665 effectiveness analysis of a grommets-led care pathway for children with cleft  
666 palate affected by otitis media with effusion. *Eur J Health Econ.*  
667 2015;16(6):573-587.

- 668 46. Paulson LM, Weaver TS, Macarthur CJ. Outcomes of tympanostomy tube  
669 placement in children with Down syndrome--a retrospective review. *Int J*  
670 *Pediatr Otorhinolaryngol.* 2014;78(2):223-226.
- 671 47. van Dongen TM, van der Heijden GJ, Freling HG, Venekamp RP, Schilder  
672 AG. Parent-reported otorrhea in children with tympanostomy tubes: incidence  
673 and predictors. *PLoS One.* 2013;8(7):e69062.
- 674 48. van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder  
675 AG. A trial of treatment for acute otorrhea in children with tympanostomy  
676 tubes. *N Engl J Med.* 2014;370(8):723-733.
- 677 49. van Dongen TM, Schilder AG, Venekamp RP, de Wit GA, van der Heijden GJ.  
678 Cost-effectiveness of treatment of acute otorrhea in children with  
679 tympanostomy tubes. *Pediatrics.* 2015;135(5):e1182-1189.
- 680 50. Cheng J, Javia L. Methicillin-resistant Staphylococcus aureus (MRSA)  
681 pediatric tympanostomy tube otorrhea. *Int J Pediatr Otorhinolaryngol.*  
682 2012;76(12):1795-1798.
- 683 51. Syed MI, Suller S, Browning GG, Akeroyd MA. Interventions for the  
684 prevention of postoperative ear discharge after insertion of ventilation tubes  
685 (grommets) in children. *Cochrane Database of Systematic Reviews* 2013,  
686 4:CD008512. doi: 10.1002/14651858.CD008512.
- 687 52. Park KH, Lee CK. Mupirocin ointment prevents early post-tympanostomy tube  
688 otorrhea: a preliminary study. *Korean J Audiol.* 2012;16(3):130-133.
- 689 53. Barati B, Hashemi SM, Goljanian Tabrizi A. Otological findings ten years after  
690 myringotomy with tympanostomy tube insertion. *Iran J Otorhinolaryngol.*  
691 2012;24(69):181-186.

- 692 54. Erdogljija M, Sotirović J, Baletić N. Early postoperative complications in  
693 children with secretory otitis media after tympanostomy tube insertion in the  
694 Military Medical Academy during 2000-2009. *Vojnosanit Pregl.*  
695 2012;69(5):409-413.
- 696 55. Saki N, Nikakhlagh S, Salehe F, Darabifard A. Incidence of Complications  
697 Developed after the Insertion of Ventilation Tube in Children under 6 years old  
698 in 2008-2009. *Iran J Otorhinolaryngol.* 2012;24(66):15-18.
- 699 56. Smillie I, Robertson S, Yule A, Wynne DM, Russell CJ. Complications of  
700 ventilation tube insertion in children with and without cleft palate: a nested  
701 case-control comparison. *JAMA Otolaryngol Head Neck Surg.*  
702 2014;140(10):940-943.
- 703 57. Morris P. Chronic suppurative otitis media. *BMJ Clin Evid.* 2012;2012.
- 704 58. Jensen RG, Koch A, Homøe P. Long-term tympanic membrane pathology  
705 dynamics and spontaneous healing in chronic suppurative otitis media.  
706 *Pediatr Infect Dis J.* 2012;31(2):139-144.
- 707 59. Stephen AT, Leach AJ, Morris PS. Impact of swimming on chronic  
708 suppurative otitis media in Aboriginal children: a randomised controlled trial.  
709 *Med J Aust.* 2013;199(1):51-55.
- 710 60. Gulani A, Sachdev HS. Zinc supplements for preventing otitis media.  
711 *Cochrane Database Syst Rev.* 2014;6:CD006639.
- 712 61. Iacovou E, Vlastarakos PV, Papacharalampous G, Kyrodimos E, Nikolopoulos  
713 TP. Is cartilage better than temporalis muscle fascia in type I tympanoplasty?  
714 Implications for current surgical practice. *Eur Arch Otorhinolaryngol.*  
715 2013;270(11):2803-2813.

- 716 62. Mohamad SH, Khan I, Hussain SS. Is cartilage tympanoplasty more effective  
717 than fascia tympanoplasty? A systematic review. *Otol Neurotol*.  
718 2012;33(5):699-705.
- 719 63. Hong P, Bance M, Gratzner PF. Repair of tympanic membrane perforation  
720 using novel adjuvant therapies: a contemporary review of experimental and  
721 tissue engineering studies. *Int J Pediatr Otorhinolaryngol*. 2013;77(1):3-12.
- 722 64. Kanemaru S, Umeda H, Kitani Y, Nakamura T, Hirano S, Ito J. Regenerative  
723 treatment for tympanic membrane perforation. *Otol Neurotol*.  
724 2011;32(8):1218-1223.
- 725 65. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and  
726 management of acute otitis media. *Pediatrics*. 2013;131(3):e964-999.
- 727 66. Subcommittee of Clinical Practice Guideline for Diagnosis and Management  
728 of Acute Otitis Media in Children (Japan Otological Society JSfPO, Japan  
729 Society for Infectious Diseases in Otolaryngology). Clinical practice guidelines  
730 for the diagnosis and management of acute otitis media (AOM) in children in  
731 Japan. *Auris Nasus Larynx*. 2012;39(1):1-8.
- 732 67. Kitamura K, Iino Y, Kamide Y, et al. Clinical practice guidelines for the  
733 diagnosis and management of acute otitis media (AOM) in children in Japan -  
734 2013 update. *Auris Nasus Larynx*. 2015;42(2):99-106.
- 735 68. Lee HJ, Park SK, Choi KY, et al. Korean clinical practice guidelines: otitis  
736 media in children. *J Korean Med Sci*. 2012;27(8):835-848.
- 737 69. Damoiseaux RA. [Acute otitis media: do not change the Dutch practice  
738 guideline]. *Ned Tijdschr Geneeskd*. 2012;156(10):A3795.



- 739 70. Del Castillo Martín F, Baquero Artigao F, de la Calle Cabrera T, et al.  
740 [Consensus document on the aetiology, diagnosis and treatment of acute  
741 otitis media]. *An Pediatr (Barc)*. 2012;77(5):345.e341-348.
- 742 71. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline:  
743 Tympanostomy tubes in children. *Otolaryngol Head Neck Surg*. 2013;149(1  
744 Suppl):S1-35.
- 745 72. Venekamp RP, Damoiseux RAMJ, Schoch AG, et al. NHG-Guideline Otitis  
746 media with effusion in children (third revision). *Huisarts Wet* 2014;57(12):649.
- 747 73. National Clinical Guidelines for management of otitis media in preschool  
748 children. Danish Health and Medicines Authority. Sundhedsstyrelsen  
749 (available at [www.sst.dk](http://www.sst.dk), accessed August 13, 2015).
- 750 74. Hawker JI, Smith S, Smith GE, et al. Trends in antibiotic prescribing in primary  
751 care for clinical syndromes subject to national recommendations to reduce  
752 antibiotic resistance, UK 1995-2011: analysis of a large database of primary  
753 care consultations. *J Antimicrob Chemother*. 2014;69(12):3423-3430.
- 754 75. Smith NS. Antibiotic treatment for acute otitis media. *Int J Pediatr*  
755 *Otorhinolaryngol*. 2013;77(5):873-874.
- 756 76. Marchisio P, Tagliabue M, Klersy C, et al. Patterns in acute otitis media drug  
757 prescriptions: a survey of Italian pediatricians and otolaryngologists. *Expert*  
758 *Rev Anti Infect Ther*. 2014;12(9):1159-1163.
- 759 77. Cé Lind J, Södermark L, Hjalmarson O. Adherence to treatment guidelines for  
760 acute otitis media in children. The necessity of an effective strategy of  
761 guideline implementation. *Int J Pediatr Otorhinolaryngol*. 2014;78(7):1128-  
762 1132.

- 763 78. Lakić D, Tadić I, Odalović M, Tasić L, Sabo A, Mećava A. Analysis of  
764 antibiotic consumption for treating respiratory tract infections in children and  
765 compliance with the national clinical guidelines. *Med Pregl.* 2014;67(9-  
766 10):282-289.
- 767 79. Maltezou HC, Katerelos P, Asimaki H, Roilides E, Theodoridou M. Antibiotic  
768 prescription practices for common infections and knowledge about antibiotic  
769 costs by private-practice pediatricians in Greece. *Minerva Pediatr.*  
770 2014;66(3):209-216.
- 771 80. Dinleyici EC, Yuksel F, Yargic ZA, Unalacak M, Unluoglu I. Results of a  
772 national study on the awareness of and attitudes toward acute otitis media  
773 (AOM) among clinicians and the estimated direct healthcare costs in Turkey  
774 (TR-AOM Study). *Int J Pediatr Otorhinolaryngol.* 2013;77(5):756-761.
- 775 81. Grossman Z, Silverman BG, Miron D. Physician specialty is associated with  
776 adherence to treatment guidelines for acute otitis media in children. *Acta*  
777 *Paediatr.* 2013;102(1):e29-33.
- 778 82. Shviro-Roseman N, Reuveni H, Gazala E, Leibovitz E. Adherence to acute  
779 otitis media treatment guidelines among primary health care providers in  
780 Israel. *Braz J Infect Dis.* 2014;18(4):355-359.
- 781 83. Levy C, Pereira M, Guedj R, et al. Impact of 2011 French guidelines on  
782 antibiotic prescription for acute otitis media in infants. *Med Mal Infect.*  
783 2014;44(3):102-106.
- 784 84. Ryborg CT, Søndergaard J, Lous J, et al. Factors associated with antibiotic  
785 prescribing in children with otitis media. *ISRN Family Med.*  
786 2013;2013:587452.

- 787 85. Forrest CB, Fiks AG, Bailey LC, et al. Improving adherence to otitis media  
788 guidelines with clinical decision support and physician feedback. *Pediatrics*.  
789 2013;131(4):e1071-1081.
- 790 86. Amir AZ, Pomp R, Amir J. Changes in acute mastoiditis in a single pediatric  
791 tertiary medical center: our experience during 2008-2009 compared with data  
792 for 1983-2007. *Scand J Infect Dis*. 2014;46(1):9-13.
- 793 87. Marchisio P, Bianchini S, Villani A, et al. Diagnosis and management of acute  
794 mastoiditis in a cohort of Italian children. *Expert Rev Anti Infect Ther*.  
795 2014;12(12):1541-1548.
- 796 88. Pritchett CV, Thorne MC. Incidence of pediatric acute mastoiditis: 1997-2006.  
797 *Arch Otolaryngol Head Neck Surg*. 2012;138(5):451-455.
- 798 89. Kordeluk S, Orgad R, Kraus M, et al. Acute mastoiditis in children under 15  
799 years of age in Southern Israel following the introduction of pneumococcal  
800 conjugate vaccines: a 4-year retrospective study (2009-2012). *Int J Pediatr*  
801 *Otorhinolaryngol*. 2014;78(10):1599-1604.
- 802 90. Palma S, Bovo R, Benatti A, et al. Mastoiditis in adults: a 19-year  
803 retrospective study. *Eur Arch Otorhinolaryngol*. 2014;271(5):925-931.
- 804 91. Halgrimson WR, Chan KH, Abzug MJ, Perkins JN, Carosone-Link P, Simões  
805 EA. Incidence of acute mastoiditis in colorado children in the pneumococcal  
806 conjugate vaccine era. *Pediatr Infect Dis J*. 2014;33(5):453-457.
- 807 92. Walls A, Pierce M, Krishnan N, Steehler M, Harley EH. Pediatric head and  
808 neck complications of *Streptococcus pneumoniae* before and after PCV7  
809 vaccination. *Otolaryngol Head Neck Surg*. 2015;152(2):336-341.

- 810 93. Marom T, Tan A, Wilkinson GS, Pierson KS, Freeman JL, Chonmaitree T.  
811 Trends in otitis media-related health care use in the United States, 2001-  
812 2011. *JAMA Pediatr.* 2014;168(1):68-75.
- 813 94. Daniel M, Gautam S, Scrivener TA, Meller C, Levin B, Curotta J. What effect  
814 has pneumococcal vaccination had on acute mastoiditis? *J Laryngol Otol.*  
815 2013;127 Suppl 1:S30-34.
- 816 95. Anthonsen K, Høstmark K, Hansen S, et al. Acute Mastoiditis in Children: A  
817 10-year Retrospective and Validated Multicenter Study. *Pediatr Infect Dis J.*  
818 2013;32(5):436-440.
- 819 96. Glatstein M, Morag S, Scolnik D, Alper A, Reif S, Grisaru-Soen G. Acute  
820 mastoiditis before pneumococcal vaccination: the experience of a large  
821 tertiary care pediatric hospital. *Am J Ther.* 2014. (Epub ahead of print)  
822 doi 10.1097/MJT.0000000000000097
- 823 97. Tamir SO, Roth Y, Dalal I, Goldfarb A, Marom T. Acute mastoiditis in the  
824 pneumococcal conjugate vaccine era. *Clin Vaccine Immunol.*  
825 2014;21(8):1189-1191.
- 826 98. Laulajainen-Hongisto A, Saat R, Lempinen L, Markkola A, Aarnisalo AA, Jero  
827 J. Bacteriology in relation to clinical findings and treatment of acute mastoiditis  
828 in children. *Int J Pediatr Otorhinolaryngol.* 2014.
- 829 99. Gorphe P, de Barros A, Choussy O, Dehesdin D, Marie JP. Acute mastoiditis  
830 in children: 10 years experience in a French tertiary university referral center.  
831 *Eur Arch Otorhinolaryngol.* 2012;269(2):455-460.
- 832 100. Kontorinis G, Psarommatis I, Karabinos C, Iliodromiti Z, Tsakanikos M.  
833 Incidence of non-infectious 'acute mastoiditis' in children. *J Laryngol Otol.*  
834 2012;126(3):244-248.

- 835 101. Giannakopoulos P, Chrysovergis A, Xirogianni A, et al. Microbiology of acute  
836 mastoiditis and complicated or refractory acute otitis media among  
837 hospitalized children in the postvaccination era. *Pediatr Infect Dis J*.  
838 2014;33(1):111-113.
- 839 102. Groth A, Enoksson F, Hermansson A, Hultcrantz M, Stalfors J, Stenfeldt K.  
840 Acute mastoiditis in children in Sweden 1993-2007--no increase after new  
841 guidelines. *Int J Pediatr Otorhinolaryngol*. 2011;75(12):1496-1501.
- 842 103. Chien JH, Chen YS, Hung IF, Hsieh KS, Wu KS, Cheng MF. Mastoiditis  
843 diagnosed by clinical symptoms and imaging studies in children: disease  
844 spectrum and evolving diagnostic challenges. *J Microbiol Immunol Infect*.  
845 2012;45(5):377-381.
- 846 104. Mattos JL, Colman KL, Casselbrant ML, Chi DH. Intratemporal and  
847 intracranial complications of acute otitis media in a pediatric population. *Int J*  
848 *Pediatr Otorhinolaryngol*. 2014;78(12):2161-2164.
- 849 105. Stenfeldt K, Enoksson F, Stalfors J, Hultcrantz M, Hermansson A, Groth A.  
850 Infants under the age of six months with acute mastoiditis. A descriptive study  
851 of 15 years in Sweden. *Int J Pediatr Otorhinolaryngol*. 2014;78(7):1119-1122.
- 852 106. Psarommatis IM, Voudouris C, Douros K, Giannakopoulos P, Bairamis T,  
853 Carabinos C. Algorithmic management of pediatric acute mastoiditis. *Int J*  
854 *Pediatr Otorhinolaryngol*. 2012;76(6):791-796.
- 855 107. Psarommatis I, Giannakopoulos P, Theodorou E, Voudouris C, Carabinos C,  
856 Tsakanikos M. Mastoid subperiosteal abscess in children: drainage or  
857 mastoidectomy? *J Laryngol Otol*. 2012;126(12):1204-1208.
- 858 108. Chesney J, Black A, Choo D. What is the best practice for acute mastoiditis in  
859 children? *Laryngoscope*. 2014;124(5):1057-1058.

- 860 109. Wu JF, Jin Z, Yang JM, Liu YH, Duan ML. Extracranial and intracranial  
861 complications of otitis media: 22-year clinical experience and analysis. *Acta*  
862 *Otolaryngol.* 2012;132(3):261-265.
- 863 110. Sun J. Intracranial complications of chronic otitis media. *Eur Arch*  
864 *Otorhinolaryngol.* 2014;271(11):2923-2926.
- 865 111. Lildal TK, Korsholm J, Ovesen T. Diagnostic challenges in otogenic brain  
866 abscesses. *Dan Med J.* 2014;61(6):A4849.
- 867 112. Luntz M, Bartal K, Brodsky A, Shihada R. Acute mastoiditis: the role of  
868 imaging for identifying intracranial complications. *Laryngoscope.*  
869 2012;122(12):2813-2817.
- 870 113. Au JK, Adam SI, Michaelides EM. Contemporary management of pediatric  
871 lateral sinus thrombosis: a twenty year review. *Am J Otolaryngol.*  
872 2013;34(2):145-150.
- 873 114. Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral  
874 venous sinus thrombosis. *Cochrane Database Syst Rev.* 2011(8):CD002005.
- 875 115. Lebas A, Chabrier S, Fluss J, et al. EPNS/SFNP guideline on the  
876 anticoagulant treatment of cerebral sinovenous thrombosis in children and  
877 neonates. *Eur J Paediatr Neurol.* 2012;16(3):219-228.
- 878 116. Ulanovski D, Yacobovich J, Kornreich L, Shkalim V, Raveh E. Pediatric  
879 otogenic sigmoid sinus thrombosis: 12-Year experience. *Int J Pediatr*  
880 *Otorhinolaryngol.* 2014;78(6):930-933.
- 881 117. Ropposch T, Nemetz U, Braun EM, Lackner A, Walch C. Low molecular  
882 weight heparin therapy in pediatric otogenic sigmoid sinus thrombosis: a safe  
883 treatment option? *Int J Pediatr Otorhinolaryngol.* 2012;76(7):1023-1026.

- 884 118. Novoa E, Podvinec M, Angst R, Gürtler N. Paediatric otogenic lateral sinus  
885 thrombosis: therapeutic management, outcome and thrombophilic evaluation.  
886 *Int J Pediatr Otorhinolaryngol.* 2013;77(6):996-1001.
- 887 119. Csákányi Z, Rosdy B, Kollár K, Móser J, Kovács E, Katona G. Timely  
888 recanalization of lateral sinus thrombosis in children: should we consider  
889 hypoplasia of contralateral sinuses in treatment planning? *Eur Arch*  
890 *Otorhinolaryngol.* 2013;270(7):1991-1998.
- 891 120. Rosdy B, Csákányi Z, Kollár K, et al. Visual and neurologic deterioration in  
892 otogenic lateral sinus thrombosis: 15 year experience. *Int J Pediatr*  
893 *Otorhinolaryngol.* 2014;78(8):1253-1257.
- 894 121. Zangari P, Messia V, Viccaro M, et al. Genetic prothrombotic factors in  
895 children with otogenic lateral sinus thrombosis: five case reports. *Blood*  
896 *Coagul Fibrinolysis.* 2012;23(2):158-163.

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**Table 1: AOM Studies (Antibiotic Treatments)**

<b>Author, Year</b>	<b>Type</b>	<b>No. of Participants, Setting</b>	<b>Intervention (participants)</b>	<b>Comparator (participants)</b>	<b>Main Outcomes</b>	<b>Effect Estimates (95%CI)</b>
Tapiainen, 2014 <sup>1</sup>	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 <sup>2</sup>	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 <sup>3</sup>	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 <sup>4</sup>	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

<sup>1</sup>Amox-clav: 40 mg/kg/d amoxicillin.

<sup>2</sup>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.

<sup>3</sup>Amox-clav: 80 mg/kg/d amoxicillin; cefdinir: 14 mg/kg/d.

<sup>4</sup>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	<table border="1"> <thead> <tr> <th>Prop. ABx</th> <th>TT</th> <th>Ad</th> </tr> </thead> <tbody> <tr> <td>+</td> <td>-</td> <td>+</td> </tr> <tr> <td>+</td> <td>+</td> <td>+</td> </tr> <tr> <td>+</td> <td>+</td> <td>-</td> </tr> </tbody> </table>	Prop. ABx	TT	Ad	+	-	+	+	+	+	+	+	-
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Boonacker 2014 <sup>1</sup>	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

<sup>1</sup>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 <sup>1</sup>	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 <sup>2</sup>	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 <sup>3</sup>	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; $>10\text{dB}$ improvement in hearing level; both	No effect on individual measures. For composite measure $>1\text{ mo.}$ , 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 4 <sup>th</sup> -8 <sup>th</sup> 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 <sup>4</sup>	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 $\geq 2$ 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.

<sup>1</sup>Numbers are shown for studies who tested normalization of tympanometry profiles and otoscopy findings. <sup>2</sup>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". <sup>3</sup>Qualitative cross-sectional study. Parents of children with hearing aids filled the questionnaires. <sup>4</sup>Only 5 case-series studies fulfilled 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	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)].
	RCT		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. Otological 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%.
Erdogljaja 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).
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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	<b>Children:</b> topical antibiotics may improve Sx, compared to antiseptics. Other topical treatments are not superior to placebo. <b>Adults:</b> 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 <sup>1</sup>	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 <sup>1</sup>
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 $\geq$ 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 $\rightarrow$ high dose amox $\rightarrow$ 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

<sup>1</sup>High dose amoxicillin/amox-clav: 80-90mg/kg/d of amoxicillin; low dose amoxicillin: 40mg/kg/d of amoxicillin