AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2017, Vol. 156(4S) S88–S105

DOI: 10.1177/0194599816633697
http://otojournal.org
SAGE

Panel 7: Otitis Media: Treatment and Complications

Anne G. M. Schilder, MD, PhD[1,2], Tal Marom, MD[3], Mahmood F. Bhutta, DPhil, FRCS[4], Margaretha L. Casselbrant, MD, PhD[5], Harvey Coates, FRACS[6], Marie Gisselsson-Solén, MD, PhD[7], Amanda J. Hall, PhD[8], Paola Marchisio, MD[9], Aino Ruohola, MD, PhD[10], Roderick P. Venekamp, MD, PhD[2], and Ellen M. Mandel, MD[5]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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 June 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 overdiagnosis, overtreatment, and antibiotic resistance. Children at risk for otitis media and its complications deserve special attention.

Keywords

otitis, otitis media, otorrhea, tympanostomy tube, adenoidectomy, perforation, guidelines, mastoiditis

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, Maryland. We focused on articles on the treatment of OM and its complications that

[1]evidENT, Ear Institute, University College London, London, United Kingdom
[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[3]Department of Otolaryngology–Head and Neck Surgery, Assaf Harofeh Medical Center, Faculty of Medicine, Tel Aviv University, Zerifin, Israel
[4]Royal National Throat Nose and Ear Hospital, London, United Kingdom
[5]Division of Pediatric Otolaryngology, Children's Hospital of Pittsburgh of UPMC, Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[6]Department of Otolaryngology, School of Paediatrics and Child Health, The University of Western Australia, Nedlands, WA, Australia
[7]Department of Clinical Sciences, Division of Otorhinolaryngology, Head and Neck Surgery, Lund University Hospital, Lund, Sweden
[8]University Hospitals Bristol NHS Foundation Trust and School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom
[9]Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[10]Department of Pediatrics, University of Turku, Turku, Finland

Corresponding Author:
Ellen M. Mandel, MD, ENT Department, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Pittsburgh, PA 15224, USA.
Email: mandele@pitt.edu

Table 1. Acute Otitis Media Studies (Antibiotic Treatments).

Lead Author, Year	Type	No. of Participants (Centers), Setting	Intervention (Participants)	Comparator (Participants)	Main Outcomes	Effect Estimates (95% CI)
Tapiainen, 2014[4,a]	RCT	84 (1), primary care	Amox-clav, 7 d (42)	Placebo (42)	Time to MEE disappearance	18.9 d vs 32.6 d; $P = .02$
					Normal tympanometry at 14 d	29/42 vs 16/42; $P < .01$; NNTB: 4
Venekamp, 2015[5,b]	SR	3401 (12), primary + secondary care	Oral antibiotics	Placebo	Pain at 2-3 d	RR: 0.7 (0.6-0.9); NNTB: 20
					Adverse effects	RR: 1.3 (1.2-1.6); NNTH: 14
Casey, 2012[7,c]	RCT	330 (1), secondary care	Amox-clav, 10 d (165)	Cefdinir, 5 d (165)	Clinical cure at 11-14 d	141/165 vs 115/165; $P < .01$
Arguedas, 2011[8,d]	RCT	923 (1), secondary care	Azithromycin ER, single dose (462)	Amox-clav, 10 d (461)	Clinical cure at 12-14 d	207/258 vs 202/239; $P = .24$
					Clinical cure at 41-64 d	74/79 vs 60/66; $P = .55$

Abbreviations: Amox-clav, amoxicillin-clavulanate; CI, confidence interval; 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.
[a]Amox-clav: 40 mg/kg/d amoxicillin.
[b]Reported results for pain at 2 to 3 days correspond to 138 of 1186 and 180 of 1134 children (7 studies) in the oral antibiotics and placebo groups, respectively, and for adverse events to 283 of 1044 and 208 of 1063 children (8 studies) in the oral antibiotics and placebo groups, respectively.
[c]Amox-clav: 80 mg/kg/d amoxicillin; cefdinir: 14 mg/kg/d.
[d]Azithromycin ER: 60 mg/kg; amox-clav 90 mg/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 (12-14 days), respectively, and for 79 and 66 children with available bacteriological studies in the azithromycin ER and amox-clav groups at the end of the study period (41-64 days), respectively.

were published since the last panel report[3] and reviewed their implications for clinical practice. This article 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 keyword search strategy for the various electronic databases, including PubMed, Ovid Medline, the Cochrane Library, and Clinical Evidence (BMJ Publishing). Databases were searched from June 1, 2011, through March 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 (nonsystematic) review articles, commentaries, and letters to the editor. Finally, after adding 2 more articles from reference lists, 118 articles were included in this article after final discussion.

Discussion

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

A high-quality placebo-controlled trial performed by Tapiainen et al[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 to 4 and 6 to 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 et al,[7] which was included in the *BMJ* review,[6] showed that children treated with amoxicillin/clavulanate for 10 days

reached ''clinical cure'' at 11 to 14 days more frequently than those treated with cefdinir for 5 days.

The RCT performed by Arguedas et al,[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 to 14 days between a single dose of azithromycin extended release and amoxicillin/clavulanate for 10 days.

A 2013 Cochrane review update[9] comparing 1 to 2 vs 3 to 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 2 low-quality trials suggesting that topical analgesics may be more effective than placebo at reducing ear pain 10 to 30 minutes after administration. Another systematic review[10] included the same 2 trials and 2 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 1 intramuscular dose of ceftriaxone combined with 5 days of either oral prednisolone (and/or antihistamine) 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 et al,[12] at high risk of bias, compared homeopathy vs 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 et al[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 of follow-up, rAOM incidence and TT placement were lower in children receiving individualized care than in legacy and community controls.

Surgical treatment. Kujala et al[14] randomized children aged 10 months to 2 years with rAOM, with and without MEE at baseline, into 3 groups: TTs only, TTs and adenoidectomy, or neither (control). Although there was a benefit of surgery over no surgery, the 2 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 et al[15] systematically reviewed the effectiveness of TTs in children with rAOM and included 5 RCTs published during 1981 to 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 and Hussain[16] conducted a systematic review of studies comparing the effect of prophylactic antibiotics, TTs, and adenoidectomy on rAOM. Eighteen studies were identified, of which 7 met the inclusion criteria. The authors concluded that all 3 treatment 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 to 15 years, the authors concluded that adenoidectomy was beneficial only in children older than 2 years.

Boonacker et al[17] performed an individual patient data meta-analysis (IPDMA) of adenoidectomy for OM in children younger than 12 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 et al,[16] they found that children younger than 2 years with rAOM may benefit from adenoidectomy, whereas in older children, no benefit was found.

CAM treatments. Marchisio et al[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 et al[19] studied the effects of pro/prebiotic-supplemented formula in infants 7 to 13 months old at high risk for AOM. Nasopharyngeal carriage of bacterial pathogens and AOM incidence were the same in the pro/prebiotic group and in infants who received a placebo formula.

A placebo-controlled trial by Vernacchio et al[20] found viscous xylitol solution 3 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 to 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.

Table 2. Recurrent Acute Otitis Media Studies.

Lead Author, Year	Type	No. of Participants	Intervention	Comparator	Main Outcome(s)	Effect Estimate(s)
Pichichero, 2013[13]	Cohort	1482	Individualized care (254)	Legacy controls (208); community controls (1024)	rAOM incidence	6% vs 14% vs 27%; $P < .0001$
					TT incidence	2% vs 6% vs 15%; $P < .0001$
Kujala, 2012[14]	RCT	300	TTs + Ad (100), TTs (100)	Controls (100)	Treatment failure: 2 AOMs in 2 mo, 3 AOMs in 6 mo, or MEE >2 mo	TTs 21%, TTs + Ad 16%, controls 34%
						TTs vs controls: –13% (95% CI, –25% to –1%), $P = .04$
						TTs + Ad vs controls: –18% (95% CI, –30% to –6%), $P = .004$
					Treatment failure reduction	TTs 38%, TTs + Ad 53%
Lous, 2011[15]	SR	5 studies, 519	TTs (235)	Observation, ABx, placebo (284)	Prevention of AOM in 6 mo	2-5 children need to be tubed to prevent 1 child from AOM attacks.
					Prevention of AOM during 6 mo after TT placement	TTs prevent 1 AOM attack.
Cheong, 2012[16]	SR	7 studies, >1300	Prophylactic ABx, TTs, Ad	Observation, placebo, ABx	AOM recurrence	PrAbx (+), TT(–), Ad (+)
					Frequency of AOM	PrAbx (+), TT (+), Ad (+)
					Total time with AOM	PrAbx (+), TT (+), Ad (–)
Boonacker, 2014[17,a]	Meta-analysis	10 studies, 1761	Ad (with or without TTs)	TTs, observation	Failure at 12 mo, stratified according to age, baseline disease	Ad 56%; 16% of children aged <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 y with OME and had Ad failed, vs 70% of those who did not have Ad; RD –19% (95% CI, 12%-26%).
Marchisio, 2013[18]	RCT	116	Vitamin D, 1000 IU/d (58)	Placebo (58)	≥1 AOM(s) in 7 mo	26 vs 38, $P = .03$

(continued)

Table 2. (continued)

Lead Author, Year	Type	No. of Participants	Intervention	Comparator	Main Outcome(s)	Effect Estimate(s)
					Mean AOM episode(s) in 7 mo	0.7 ± 0.8 vs 1.4 ± 1.4 (*P* = .003)
Cohen, 2013[19]	RCT	224	Pro/prebiotic-enriched formula (112)	Follow-up formula (112)	No. of AOM episode(s) in 12 mo	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[20]	RCT	326	Xylitol (160)	Controls (166)	AOM incidence/ 90 d	0.53 vs 0.59 (95% CI, –0.25 to 0.13)
					Time to first AOM in 90 d	HR: 0.93 (95% CI, 0.56-1.57)
					Total days with ABx in 90 d	6.8 d vs 6.4 d (95% CI, –1.8 to 2.7)

Abbreviations: ABx, antibiotic therapy; Ad, adenoidectomy; AOM, acute otitis media; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; IU, international units; MEE, middle ear effusion; OR, odds ratio; PrAbx, prophylactic antibiotic; rAOM, recurrent acute otitis media; RCT, randomized controlled trial; RD, rate difference; SR, systematic review; TT, tympanostomy tube.

[a]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 otitis media with effusion in which adenoidectomy (with or without tympanostomy tubes) was compared with nonsurgical treatment or grommets alone.

Steroids. Since the 2011 Cochrane review on oral or topical steroids in OME cited in the previous Treatment Panel,[3] 1 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 intratympanic 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 1 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 crossover 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 and Elhassan[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 on existing data. Hellström et al[33] performed a systematic review and included 63 studies. They found high-level evidence of the benefit of tubes for hearing and QoL for up to 9 months after treatment.

Berkman et al[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.

Table 3. Otitis Media with Effusion Studies.

Lead Author, Year	Study Type	No. of Participants	Intervention	Primary Outcome	Results (95% CI)
van Zon, 2012[21,a]	Cochrane/ meta-analysis	23 studies, 3027	ABx vs no treatment or placebo	MEE complete resolution at 2-3 mo	Improvement in 1% (–0.11 to 0.12) to 45% (0.25 to 0.65) of children receiving ABx
Chen, 2013[22,b]	RCT	84 (73 completed)	Macrolides (36) vs nasal steroids (37)	MEE clearance at 8-12 wk (%)	38 vs 19, 70 vs 25, and 80 vs 26, after 8, 10, and 12 wk, respectively
Bhargava, 2014[23]	RCT	62	Mometasone (30) vs saline (32)	MEE resolution at 24 wk	93% vs 50%, $P = .0004$
Yang, 2014[24]	RCT	90 (112 ears)	Intratympanic 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); dexamethasone vs saline, RR 0.485 (0.240-0.979)
				Efficacy at 8 and 16 wk	Budesonide: 95%, 90%; dexamethasone: 75%, 55%; saline: 40%, 20%
Griffin, 2011[25]	Cochrane/ meta-analysis	16 studies, 1880	Antihistamines, decongestants, combinations	Resolution of MEE at 1 mo	RR 0.99 (0.92-1.05) for all interventions
Ertugay, 2013[26]	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[27]	SR	-	Homeopathy	MEE improvement	Insufficient evidence
Califano, 2014[28]	RCT	80	Oral steroids vs thermal therapy (sulfur water)	Tympanogram type improvement at various time points	Thermal therapy group had better tympanograms, sometimes reaching statistical significance.
Qureishi, 2014[29,c]	Cross-sectional	97	HAs vs TTs	Psychosocial impact of HAs	Families with HAs rating lower psychosocial impact than anticipated by families with TTs ($P < .05$).
Perera, 2013[30]	Cochrane review/ meta-analysis	8 studies, 702	Auto-inflation vs no treatment	Tympanogram improvement; >10 dB 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[31]	Crossover study	45	New device for auto-inflation vs no treatment for 4 wk, then treatments cross over between weeks 4 and 8	Middle ear pressure improvement at 4 and 8 wk	At 4 wk: improvement by 166 daPa (treatment) and 19 daPa (control), $P < .0001$
					At 8 wk: improvement by 187 daPa (in group having received treatment), $P < .0001$
				Improvement in hearing at 4 and 8 wk	At 4 wk: mean hearing levels improved by 6 dB ($P < .0001$) vs 1 dB, $P < .0001$

(continued)

Table 3. (continued)

Lead Author, Year	Study Type	No. of Participants	Intervention	Primary Outcome	Results (95% CI)
					At 8 wk: unchanged and improved by 7 dB
Miller, 2013[32,d]	SR	5 studies, 375	Balloon dilatation of the eustachian tube (surgery)	Normalization of tympanometry	69/89 (78%) abnormal tympanograms (type B/C) normalized to postoperative type A
				Normalization of otoscopic findings	40/46 (87%) preoperative abnormal findings normalized postoperatively
Hellström, 2011[33]	SR	63 studies, 11 on OME (1756); QoL studies	Bilateral TTs vs WW; unilateral TT vs no treatment	TT 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[34]	Meta-analysis	59 studies	WW, TTs, Ad, myringotomy, auto-inflation, oral or nasal steroids, complementary medicine	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 y compared with WW or myringotomy and improved hearing for 6 mo compared with WW. OME resolution was more likely with Ad.
Baik, 2015[35]	Markov decision analysis	Hypothetical cohort	Short-, intermediate-, and long-term TTs	Complications of TTs in 2, 4, and 6 y (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[36]	LFS	104	TT-treated ear to nontreated ear in the same patient	Difference in hearing thresholds	No significant difference
MRC Multicentre Otitis Media Study Group, 2012[39]	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 mo: 8.8 dB (7.1-10.5); for longer observation, it conferred a 4.2-dB benefit (2.6-5.7), compared with none for TTs. For re-TT, RR = 3.2 (1.8-5.9)
Gleinser, 2011[40]	RS	904	TTs + Ad vs TTs	Re-TT rate	Re-TT rate: 7% vs 20%, $P = .0001$
Hong, 2014[37]	RS follow-up	89	Children with OME who had no surgery,	Hearing thresholds differences (dB)	No surgery: 10 ± 6.5, TTs once: 15.9 ± 11.2;

(continued)

Table 3. (continued)

Lead Author, Year	Study Type	No. of Participants	Intervention	Primary Outcome	Results (95% CI)
			1 set of TTs, and TTs >1		>1 set of TTs: 17.8 ± 7.6 No surgery vs rest, $P < .005$
Kuo, 2014[43]	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[44]	Qualitative study	37 parents of children with CP	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[46]	RS	102	Children with DS receiving TTs	Hearing results, number of TT operations, long-term complications	Most patients had normal postoperative hearing. Most had ≥2 TT sets. Long-term complications increased with the number of TT sets.
Wang, 2014[47]	RS	1755	TTs + Ad vs TTs	Re-TT rate	Re-TT rate: 5.1% vs 9%, $P = .002$ Ad effect more obvious >4 y Controlled for age, RR: 0.60 (0.41-0.89)

Abbreviations: ABx, antibiotic therapy; Ad, adenoidectomy; CI, confidence interval; CP, cleft palate; DS, Down syndrome; HA, hearing aids; LFS, longitudinal follow-up study; MEE, middle ear effusion; 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.

[a]Numbers are shown for studies that tested normalization of tympanometry profiles and otoscopy findings.

[b]Clarithromycin: 15 mg/kg/d bid daily in the first week, then changed to a low dose, 5 to 8 mg/kg/d qd, until the tympanogram was type "A."

[c]Cross-sectional study. Parents of children with hearing aids filled out the questionnaires.

[d]Only 5 case-series studies fulfilled enrollment criteria for this systematic review.

Baik and Brietzke[35] applied utility-based Markov decision theory modeling to the question of optimum duration of intubation with TTs. They found that intermediate-type TTs provide the greatest benefit compared with 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 et al[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 with children who did not receive TTs.[37]

Adenoidectomy. The previously cited IPDMA by Boonacker et al[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 and Brigger[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 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 hearing level (HL) over TTs alone. Adjuvant

adenoidectomy reduced audiometric eligibility for revision surgery.

In a retrospective case series of children treated with TTs, Gleinser et al[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 to 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 et al[34] concluded that additional research is needed to support treatment decisions in these at-risk groups.

Kuo et al[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 et al[44] carried out a qualitative study of parents' experiences of OME treatment in children with CP 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 et al[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 et al[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. van Dongen et al[48] used a parental web-based questionnaire to collect retrospective data on tympanostomy tube otorrhea (TTO) incidence. Of 1184 children treated with TTs younger than 10 years, 52% had at least 1 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 upper respiratory infections (URIs) and having older siblings.

Treatment of TTO. In an RCT, van Dongen et al[49] 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.[50]

Cheng and Javia[51] 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[52] of prevention of postoperative 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 2 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 and Lee[53] followed 67 patients who received a mupirocin-coated TT and found early postoperative TTO occurred in only 1 patient, leading the authors to conclude that their product could be effective at preventing this problem.

Complications of TTs. Barati et al[54] reviewed the medical records of all children aged 2 to 4 years who had TTs for OME in 2 hospitals. Eighty-two had otomicroscopy 10 to 11 years later; myringosclerosis was the most common sequela. Of note, none had developed cholesteatoma.

Erdoglija et al[55] 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 et al[56] reviewed the medical records of 208 children followed for 12 to 18 months after TT 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 et al[57] 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[58] 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 vs placebo in children is yet unclear.

A longitudinal cohort study in Greenland looked at evolution of CSOM.[59] 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 vs no swimming in chlorinated pools in children with tympanic

Table 4. Otorrhea Studies.

Lead Author, Year	Type	Population, No. of Participants	Main Outcome(s)	Results (95% CI)
van Dongen, 2013[48]	RS	Children <10 y 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,[49] 2015[50]	Open-label RCT	230 Children aged 1 to 10 y with acute TTO: hydrocortisone-bacitracin-colistin eardrops (76), oral amox-clav suspension (77), observation (77)	TTO at 2 wk	5% eardrops treated, 44% amox-clav treated, risk difference, –39% (–51 to –26); 55% observed, risk difference, –49% (–62 to –37)
			Mean total cost/ patient at 2 wk and at 6 mo	2 wk: US$42.43 for eardrops, US$70.60 for oral antibiotics, and US$82.03 for initial observation At 6 mo: US$368.20, US$420.73, and US$640.44, respectively
Cheng, 2012[51]	RS	Children <18 y with MRSA-positive TTO (41)	ABx resistance patterns and treatment success rates	Fluoroquinolone and clindamycin resistance in 88% and 61% of cases, respectively Ototopical fluoroquinolone and sulfacetamide were associated with successful TTO resolution, *P* = .005, *P* = .009.
Park, 2012[53]	RS	67 patients with mupirocin-coated TTs (98 ears)	Postoperative TTO incidence (at 2 wk)	1 (1.5%) case had postoperative TTO with experimental TT.
Barati, 2012[54]	LFS	10 to 11 y FU of children who underwent TTs at 2 to 4 y (82)	TT complication rate	Myringosclerosis, 17.1%; TM atrophy, 1.2%; permanent TM perforation, 0.6%; TM atelectasis, 0.6%; cholesteatoma, 0%
Erdoglija, 2012[55]	RS	478 children who were treated with TTs (843 ears)	TTs complication rate at 12 to 18 mo FU	Transient TTO, 16.5%; TT obstruction, 9.5%; premature extrusion, 3.9%; chronic TTO, 3.1%; granulation tissue, 1.1%
Saki, 2012[56]	Prospective	Children aged 10 mo to 6 y with TTs (208)	Postoperative TTO incidence, postextrusion complications rate	At 12 to 18 mo 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[57]	Case control	60 children with CLP who underwent TTs vs age- and sex-matched controls	TTO incidence	Controls had 151 cases of TTO, compared with 121 in the CLP group (ratio 1.25:1); difference was not significant (*P* = .52).

Abbreviations: ABx, antibiotic therapy; amox-clav, amoxicillin-clavulanate; CI, confidence interval; CLP, cleft lip and palate; FU, follow-up; LFS, longitudinal follow-up study; MRSA, methicillin-resistant *Staphylococcus aureus*; RCT, randomized controlled trial; RS, retrospective study; TM, tympanic membrane; TT, tympanostomy tube; TTO, tympanostomy tube otorrhea.

membrane (TM) perforations showed no differences in the proportion with discharge or in nasopharyngeal or middle ear microbiology of children who did or did not swim.[60]

CAM. A Cochrane review[61] on the effects of zinc supplementation in preventing OM found mixed results in otherwise healthy children younger than 5 years living in low- and middle-income countries.

Table 5. Chronic Suppurative Otitis Media Studies.

Author, Year	Type	Population, No. of Participants	Intervention	Comparator	Results (95% CI)
Morris, 2012[58]	SR	Children and adults with CSOM, 51 studies	Topical ear cleansing, surgery for cholesteatoma, systemic ABx, topical ABx plus topical corticosteroids, topical antiseptics, topical corticosteroids, tympanoplasty	Various	Children: topical antibiotics may improve Sx compared with antiseptics; other topical treatments are not superior to placebo. Adults: topical antibiotics alone/ with topical corticosteroids may improve Sx compared with placebo or either treatment alone.
Jensen, 2012[59]	LFS	226 children seen at 10 to 12 y FU	Spontaneous healing of the TM		591 children initially examined TM spontaneous healing: 39% Overall CSOM prevalence: 9%
Stephen, 2013[60]	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[61]	SR	10 studies, 6820 children	Zinc supplements, at any dose, given at least once a week, for at least 1 mo	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[62]	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[63]	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[64]	SR	26 studies	Tympanoplasty grafts made with biomolecules (platelet-derived growth factor, platelet-rich plasma, hyaluronic acid, epidermal growth factor and pentoxifylline, b-FGF, combinations) and scaffolding materials (ie, AlloDerm, silk patches)	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.
Kanemaru, 2011[65]	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.

Abbreviations: 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; RCT, randomized controlled trial; RS, retrospective study; SR, systematic review; Sx, symptoms; TEM, tissue-engineered myringoplasty; TM, tympanic membrane; TMF, temporalis muscle fascia.

Surgical treatment. Two systematic literature reviews compared temporalis muscle fascia (TMF) with cartilage tympanoplasty.[62,63] Both reviews reported better structural outcomes (fewer postoperative TM perforations) with a cartilage graft, but no better functional outcomes (similar hearing).

Novel adjuvant therapies. Hong et al[64] reviewed various adjuvant treatments for enhancing TM perforation repair, including biomolecules to stimulate the growth of perforation edges and bioengineered scaffolds. Most of the scaffold materials tested were safe and improved TM perforation healing rates.

Kanemaru et al[65] performed an RCT (included in Hong et al[64]) 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 United States,[66] Japan,[67,68] Korea,[69] the Netherlands,[70] and Spain.[71] 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 ''nonsevere'' 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,[66-68] active immunoprophylaxis with pneumococcal conjugate vaccines (PCVs)[66-69] and influenza vaccine[66] is recommended, and long-term prophylactic antibiotics are discouraged.[66]

Otitis media with effusion. Guidelines on OME were published in Korea,[69] the United States,[72] the Netherlands,[73] and Denmark.[74] 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 >40 dB HL in the better ear), effect on the child's well-being, 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 to 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, particularly 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 suboptimal (eg, in the United Kingdom, Italy, Sweden, Turkey, Serbia, Greece, Israel, the United States).[75-83] In France,[84] guidelines have been effective in changing the antibiotic prescribing habits of pediatricians, and in Denmark,[85] general practitioners (GPs) to a large degree prescribe antibiotics appropriately. In the United Kingdom, the proportion of AOM episodes for which an antibiotic was prescribed was largely unchanged,[75] and the use of a broader spectrum antibiotic (amoxicillin plus clavulanic acid instead of amoxicillin) was the reason for diverging from recommendations in Hungary.[79]

In a small UK audit,[76] adherence to OM guidelines seems independent of medical specialty: GPs, pediatricians, and otolaryngologists were equally noncompliant with antibiotic guidance. In contrast, Italian pediatricians were less likely to prescribe symptom-relieving drugs, such as decongestants and mucolytics, other than antibiotics,[77] and Greek physicians younger than 40 years seem to adhere better to guidelines than those 60 years or older.[80]

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 (eg, cultural/social beliefs about the benefits and harms of antibiotics).[78] Targeting specific scenarios associated with immediate vs delayed or no antibiotics prescribing for AOM (eg, diagnosis on weekends vs weekdays, urgent care vs clinical setting, family care vs specialist care) may be effective in reducing unnecessary prescribing.[82] Electronic health record–based clinical decision support and performance feedback systems were found effective in improving adherence to OM guidelines; combining these 2 interventions, however, was no better than either delivered alone.[86]

Complications of Otitis Media

Acute mastoiditis. Differing trends in acute mastoiditis (AM) incidence have recently been reported, with small series suggesting an increase,[87,88] while larger series suggesting no change or even a decline.[89-94] Many of these studies have methodological limitations. A large US insurance claims database of children younger than 6 years suggested that AM incidence has declined following the introduction of

Table 6. Selected National Guidelines for AOM.

Country	Age	Diagnosis/Instruments	Management	First-Line Antibiotics[a]
United States, 2013[66]	6 mo to 12 y	Stringent criteria Key factors: TM bulging or new-onset otorrhea, use of pneumatic otoscopy and tympanometry, treat pain	ABx: children ≥6 mo with severe AOM, nonsevere bilateral AOM in children 6 to 23 mo WW: nonsevere unilateral AOM in children <23 mo, nonsevere AOM in children >24 mo	High-dose amox; high-dose amox-clav in children receiving amoxicillin in the previous 30 d or with otitis-conjunctivitis
Japan, 2013[68]	0-15 y	Accurate diagnosis Otomicroscopy or otoscopic observation, pneumatic otoscopy acceptable	Mild AOM: 3 d 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[69] 2012	0-15 y	Definitive (Sx and TM findings) vs suspicious (Sx without objective findings) diagnosis	WW: possible, FU visit after 2 to 3 d ABx: severe AOM, <6 mo, 6 to 24 mo with definite AOM, when FU is impossible, comorbidities	High-dose amox Severe AOM: high-dose amox-clav
The Netherlands, 2014[70]	0-18 y	Patient's history, Sx, and otoscopy findings; treat pain	Immediate ABx: infants <6 mo, severe AOM Consider ABx: children <2 years and bilateral AOM, otorrhea, persisting Sx	Low-dose amox Amox-clav if no improvement after 48 h

Abbreviations: ABx, antibiotic therapy; amox, amoxicillin; amox-clav, amoxicillin-clavulanic acid; AOM, acute otitis media; FU, follow-up; TM, tympanic membrane; WW, watchful waiting.
[a]High-dose amoxicillin/amox-clav: 80 to 90 mg/kg/d amoxicillin; low-dose amoxicillin: 40 mg/kg/d amoxicillin.

PCVs, especially PCV-13.[94] Nevertheless, *Streptococcus pneumoniae* remains the most common cause of AM across the globe.[87,90,92,95-105] Country-wide hospital data from Denmark and Sweden show that there has been no increase in the incidence of AM[96,103] since the introduction of guidelines to reduce antibiotic use for AOM, released a few years earlier.

Several case series show that 33% to 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.*

While AM treatment traditionally involved cortical mastoidectomy, there is a recent trend toward nonsurgical 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% and 93% of patients with mastoiditis; this variation may represent differences in clinical practice rather than disease severity.† 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.[103] In eastern Denmark,[96] 183 of 214 (86%) pediatric AM cases were treated with myringotomy and antibiotics, and 31% 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 of 24 (57%) children with a subperiosteal abscess were successfully treated with needle aspiration and myringotomy and did not require mastoidectomy.[107,108]

Chesney et al[109] 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,[105,110,111] with an estimated incidence of 1 per million per annum.[112] 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.[113]

The role of anticoagulation in otogenic sigmoid sinus thrombosis remains controversial. Au et al[114] reviewed the

*References 87, 90, 92, 96, 98-100, 102, 103.
†References 90, 91, 95, 96, 99, 100, 102, 103, 105-107.

literature and found that anticoagulation was employed in 39 of 68 (57%) cases; 84% achieved partial or complete recanalization. However, 3 of 4 (75%) patients not treated with anticoagulation also achieved partial or complete recanalization. Reviews by Cochrane[115] and by the European Pediatric Neurology Society[116] 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.[115,116] Several retrospective reviews report no complications of anticoagulation in patients with otogenic sinus thrombosis.[117-122]

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 are key to reducing overdiagnosis and overtreatment 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.

Author Contributions

Anne G. M. Schilder, panel chair, conception, acquisition and interpretation of data, drafting and revising, final approval; **Tal Marom**, conception, acquisition and interpretation of data, drafting and revising, final approval; **Mahmood F. Bhutta**, conception, acquisition and interpretation of data, drafting and revising, final approval; **Margaretha L. Casselbrant**, conception, acquisition and interpretation of data drafting and revising, final approval; **Harvey Coates**, conception, acquisition and interpretation of data drafting and revising, final approval; **Marie Gisselsson-Solén**, conception, acquisition and interpretation of data drafting and revising, final approval; **Amanda J. Hall**, conception, acquisition and interpretation of data drafting and revising, final approval; **Paola Marchisio**, conception, acquisition and interpretation of data drafting and revising, final approval; **Aino Ruohola**, conception, acquisition and interpretation of data drafting and revising, final approval; **Roderick P. Venekamp**, conception, acquisition and interpretation of data drafting and revising, final approval; **Ellen M. Mandel**, panel cochair, conception, acquisition and interpretation of data, drafting and revising, final approval

Disclosures

Competing interests: Anne G.M. Schilder, evidENT team supported by NIHR Research Professorship grant, joint coordinating editor of Cochrane ENT, ZonMw (The Netherlands Organization for Health Research and Development): grant support for pain management trial; Amanda J. Hall, travel grant from Oticon to attend 2015 ISOM meeting, research grant from Cochlear UK to investigate management of OME/hearing loss in Down syndrome; Roderick P. Venekamp, grant from ZonMw (The Netherlands Organization for Health Research and Development) for a trial on pain management of AOM, Editor of Cochrane ENT and Cochrane Acute Respiratory Infections Group, lead and co-author various reviews on otitis media; Ellen M. Mandel, Alcon, consulting.

Sponsorships: None.

Funding source: None.

References

1. Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS One*. 2012;7:e36226.
2. Ahmed S, Shapiro NL, Bhattacharyya N. Incremental health care utilization and costs for acute otitis media in children. *Laryngoscope*. 2014;124:301-305.
3. Marchisio P, Chonmaitree T, Leibovitz E, et al. Panel 7: Treatment and comparative effectiveness research. *Otolaryngol Head Neck Surg*. 2013;148(4)(suppl):E102-E121.
4. Tapiainen T, Kujala T, Renko M, et al. Effect of antimicrobial treatment of acute otitis media on the daily disappearance of middle ear effusion: a placebo-controlled trial. *JAMA Pediatr*. 2014;168:635-641.
5. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;6:CD000219.
6. Venekamp RP, Damoiseaux RA, Schilder AG. Acute otitis media in children. *BMJ Clin Evid*. 2014;2014(Sept16):pii:0301.
7. Casey JR, Block SL, Hedrick J, Almudevar A, Pichichero ME. Comparison of amoxicillin/clavulanic acid high dose with cefdinir in the treatment of acute otitis media. *Drugs*. 2012;72:1991-1997.
8. Arguedas A, Soley C, Kamicker BJ, Jorgensen DM. Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media. *Int J Infect Dis*. 2011;15:e240-e248.
9. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database Syst Rev*. 2013;12:CD004975.
10. Wood DN, Nakas N, Gregory CW. Clinical trials assessing ototopical agents in the treatment of pain associated with acute otitis media in children. *Int J Pediatr Otorhinolaryngol*. 2012;76:1229-1235.
11. Principi N, Bianchini S, Baggi E, Esposito S. No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media. *Eur J Clin Microbiol Infect Dis*. 2013;32:151-160.
12. Sinha MN, Siddiqui VA, Nayak C, et al. Randomized controlled pilot study to compare homeopathy and conventional therapy in acute otitis media. *Homeopathy*. 2012;101:5-12.
13. Pichichero ME, Casey JR, Almudevar A. Reducing the frequency of acute otitis media by individualized care. *Pediatr Infect Dis J*. 2013;32:473-478.

14. Kujala T, Alho OP, Luotonen J, et al. Tympanostomy with and without adenoidectomy for the prevention of recurrences of acute otitis media: a randomized controlled trial. *Pediatr Infect Dis J*. 2012;31:565-569.
15. Lous J, Ryborg CT, Thomsen JL. A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media. *Int J Pediatr Otorhinolaryngol*. 2011;75:1058-1061.
16. Cheong KH, Hussain SS. Management of recurrent acute otitis media in children: systematic review of the effect of different interventions on otitis media recurrence, recurrence frequency and total recurrence time. *J Laryngol Otol*. 2012;126:874-885.
17. Boonacker CW, Rovers MM, Browning GG, Hoes AW, Schilder AG, Burton MJ. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. *Health Technol Assess*. 2014;18:1-118.
18. Marchisio P, Consonni D, Baggi E, et al. Vitamin D supplementation reduces the risk of acute otitis media in otitis-prone children. *Pediatr Infect Dis J*. 2013;32:1055-1060.
19. Cohen R, Martin E, de La Rocque F, et al. Probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children: a randomized, double-blind, placebo-controlled study. *Pediatr Infect Dis J*. 2013;32:810-814.
20. Vernacchio L, Corwin MJ, Vezina RM, et al. Xylitol syrup for the prevention of acute otitis media. *Pediatrics*. 2014;133:289-295.
21. van Zon A, van der Heijden GJ, van Dongen TM, Burton MJ, Schilder AG. Antibiotics for otitis media with effusion in children. *Cochrane Database Syst Rev*. 2012;9:CD009163.
22. Chen K, Wu X, Jiang G, Du J, Jiang H. Low dose macrolide administration for long term is effective for otitis media with effusion in children. *Auris Nasus Larynx*. 2013;40:46-50.
23. Bhargava R, Chakravarti A. A double-blind randomized placebo-controlled trial of topical intranasal mometasone furoate nasal spray in children of adenoidal hypertrophy with otitis media with effusion. *Am J Otolaryngol*. 2014;35:766-770.
24. Yang F, Zhao Y, An P, et al. Longitudinal results of intratympanic injection of budesonide for otitis media with effusion in children over 12 years and adults. *Otol Neurotol*. 2014;35:629-634.
25. Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. *Cochrane Database Syst Rev*. 2011;(9):CD003423.
26. Ertugay CK, Cingi C, Yaz A, et al. Effect of combination of montelukast and levocetirizine on otitis media with effusion: a prospective, placebo-controlled trial. *Acta Otolaryngol*. 2013; 133:1266-1272.
27. Fixsen A. Should homeopathy be considered as part of a treatment strategy for otitis media with effusion in children? *Homeopathy*. 2013;102:145-150.
28. Califano L, Salafia F, Mazzone S, D'Ambrosio G, Malafronte L, Vassallo A. A comparative randomized study on the efficacy of a systemic steroid therapy vs. a thermal therapy in otitis media with effusion in children [published online November 13, 2014]. *Minerva Pediatr*.
29. Qureishi A, Garas G, Mallick A, Parker D. The psychosocial impact of hearing aids in children with otitis media with effusion. *J Laryngol Otol*. 2014;128:972-975.
30. Perera R, Glasziou PP, Heneghan CJ, McLellan J, Williamson I. Autoinflation for hearing loss associated with otitis media with effusion. *Cochrane Database Syst Rev*. 2013;5:CD006285.
31. Bidarian-Moniri A, Ramos MJ, Ejnell H. Autoinflation for treatment of persistent otitis media with effusion in children: a cross-over study with a 12-month follow-up. *Int J Pediatr Otorhinolaryngol*. 2014;78:1298-1305.
32. Miller BJ, Elhassan HA. Balloon dilatation of the Eustachian tube: an evidence-based review of case series for those considering its use. *Clin Otolaryngol*. 2013;38:525-532.
33. Hellström S, Groth A, Jörgensen F, et al. Ventilation tube treatment: a systematic review of the literature. *Otolaryngol Head Neck Surg*. 2011;145:383-395.
34. Berkman ND, Wallace IF, Steiner MJ, et al. *Otitis Media with Effusion: Comparative Effectiveness of Treatments*. Rockville, MD: Agency for Healthcare Research and Quality; 2013. AHRQ Publication No. 13-EHC091-EF.
35. Baik G, Brietzke S. How much does the type of tympanostomy tube matter? A utility-based Markov decision analysis. *Otolaryngol Head Neck Surg*. 2015;152:1000-1006.
36. Khodaverdi M, Jørgensen G, Lange T, et al. Hearing 25 years after surgical treatment of otitis media with effusion in early childhood. *Int J Pediatr Otorhinolaryngol*. 2013;77:241-247.
37. Hong HR, Kim TS, Chung JW. Long-term follow-up of otitis media with effusion in children: comparisons between a ventilation tube group and a non-ventilation tube group. *Int J Pediatr Otorhinolaryngol*. 2014;78:938-943.
38. Mikals SJ, Brigger MT. Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2014;140: 95-101.
39. MRC Multicentre Otitis Media Study Group. Adjuvant adenoidectomy in persistent bilateral otitis media with effusion: hearing and revision surgery outcomes through 2 years in the TARGET randomised trial. *Clin Otolaryngol*. 2012;37:107-116.
40. Gleinser DM, Kriel HH, Mukerji S. The relationship between repeat tympanostomy tube insertion and adenoidectomy. *Int J Pediatr Otorhinolaryngol*. 2011;75:1247-1251.
41. Marchica CL, Pitaro J, Daniel SJ. Recurrent tube insertion for chronic otitis media with effusion in children over 6 years. *Int J Pediatr Otorhinolaryngol*. 2013;77:252-255.
42. Ackerman S, Reilly B, Bernier R. Tympanostomy tube placement in children with autism. *J Dev Behav Pediatr*. 2012;33: 252-258.
43. Kuo CL, Tsao YH, Cheng HM, et al. Grommets for otitis media with effusion in children with cleft palate: a systematic review. *Pediatrics*. 2014;134:983-994.
44. Tierney S, O'Brien K, Harman NL, Madden C, Sharma RK, Callery P. Risks and benefits of ventilation tubes and hearing aids from the perspective of parents of children with cleft palate. *Int J Pediatr Otorhinolaryngol*. 2013;77:1742-1748.
45. Mohiuddin S, Payne K, Fenwick E, O'Brien K, Bruce I. A model-based cost-effectiveness analysis of a grommets-led care pathway for children with cleft palate affected by otitis media with effusion. *Eur J Health Econ*. 2015;16:573-587.

46. Paulson LM, Weaver TS, Macarthur CJ. Outcomes of tympanostomy tube placement in children with Down syndrome—a retrospective review. *Int J Pediatr Otorhinolaryngol*. 2014;78:223-226.
47. Wang MC, Wang YP, Chu CH, Tu TY, Shiao AS, Chou P. The protective effect of adenoidectomy on pediatric tympanostomy tube re-insertions: a population-based birth cohort study. *PLoS One*. 2014;9(7):e101175.
48. van Dongen TM, van der Heijden GJ, Freling HG, Venekamp RP, Schilder AG. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. *PLoS One*. 2013;8:e69062.
49. van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *N Engl J Med*. 2014;370:723-733.
50. van Dongen TM, Schilder AG, Venekamp RP, de Wit GA, van der Heijden GJ. Cost-effectiveness of treatment of acute otorrhea in children with tympanostomy tubes. *Pediatrics*. 2015;135:e1182-e1189.
51. Cheng J, Javia L. Methicillin-resistant *Staphylococcus aureus* (MRSA) pediatric tympanostomy tube otorrhea. *Int J Pediatr Otorhinolaryngol*. 2012;76:1795-1798.
52. Syed MI, Suller S, Browning GG, Akeroyd MA. Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes (grommets) in children. *Cochrane Database of Systematic Reviews* 2013;4:CD008512.
53. Park KH, Lee CK. Mupirocin ointment prevents early post-tympanostomy tube otorrhea: a preliminary study. *Korean J Audiol*. 2012;16:130-133.
54. Barati B, Hashemi SM, Goljanian Tabrizi A. Otological findings ten years after myringotomy with tympanostomy tube insertion. *Iran J Otorhinolaryngol*. 2012;24:181-186.
55. Erdoglija M, Sotirović J, Baletić N. Early postoperative complications in children with secretory otitis media after tympanostomy tube insertion in the Military Medical Academy during 2000-2009. *Vojnosanit Pregl*. 2012;69:409-413.
56. Saki N, Nikakhlagh S, Salehe F, Darabifard A. Incidence of complications developed after the insertion of ventilation tube in children under 6 years old in 2008-2009. *Iran J Otorhinolaryngol*. 2012;24:15-18.
57. Smillie I, Robertson S, Yule A, Wynne DM, Russell CJ. Complications of ventilation tube insertion in children with and without cleft palate: a nested case-control comparison. *JAMA Otolaryngol Head Neck Surg*. 2014;140:940-943.
58. Morris P. Chronic suppurative otitis media. *BMJ Clin Evid*. 2012;2012(Aug6):pii:0507.
59. Jensen RG, Koch A, Homøe P. Long-term tympanic membrane pathology dynamics and spontaneous healing in chronic suppurative otitis media. *Pediatr Infect Dis J*. 2012;31:139-144.
60. Stephen AT, Leach AJ, Morris PS. Impact of swimming on chronic suppurative otitis media in Aboriginal children: a randomised controlled trial. *Med J Aust*. 2013;199:51-55.
61. Gulani A, Sachdev HS. Zinc supplements for preventing otitis media. *Cochrane Database Syst Rev*. 2014;6:CD006639.
62. Iacovou E, Vlastarakos PV, Papacharalampous G, Kyrodimos E, Nikolopoulos TP. Is cartilage better than temporalis muscle fascia in type I tympanoplasty? Implications for current surgical practice. *Eur Arch Otorhinolaryngol*. 2013;270:2803-2813.
63. Mohamad SH, Khan I, Hussain SS. Is cartilage tympanoplasty more effective than fascia tympanoplasty? A systematic review. *Otol Neurotol*. 2012;33:699-705.
64. Hong P, Bance M, Gratzer PF. Repair of tympanic membrane perforation using novel adjuvant therapies: a contemporary review of experimental and tissue engineering studies. *Int J Pediatr Otorhinolaryngol*. 2013;77:3-12.
65. Kanemaru S, Umeda H, Kitani Y, Nakamura T, Hirano S, Ito J. Regenerative treatment for tympanic membrane perforation. *Otol Neurotol*. 2011;32:1218-1223.
66. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964-e999.
67. Subcommittee of Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children (Japan Otological Society Japan Society for Pediatric Otorhinolaryngology, Japan Society for Infectious Diseases in Otolaryngology). Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan. *Auris Nasus Larynx*. 2012;39:1-8.
68. Kitamura K, Iino Y, Kamide Y, et al. Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan—2013 update. *Auris Nasus Larynx*. 2015;42:99-106.
69. Lee HJ, Park SK, Choi KY, et al. Korean clinical practice guidelines: otitis media in children. *J Korean Med Sci*. 2012;27:835-848.
70. Damoiseaux RA. Acute otitis media: do not change the Dutch practice guideline [in Dutch]. *Ned Tijdschr Geneeskd*. 2012;156:A3795.
71. Del Castillo Martín F, Baquero Artigao F, de la Calle Cabrera T, et al. Consensus document on the aetiology, diagnosis and treatment of acute otitis media [in Spanish]. *An Pediatr (Barc)*. 2012;77:345.e341-348.
72. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. *Otolaryngol Head Neck Surg*. 2013;149(1)(suppl):S1-S35.
73. Venekamp RP, Damoiseux RAMJ, Schoch AG, et al. NHG-guideline otitis media with effusion in children (third revision). *Huisarts Wet*. 2014;57:649.
74. Danish Health and Medicines Authority. National Clinical Guidelines for management of otitis media in preschool children. *Sundhedsstyrelsen*. www.sst.dk. Accessed August 13, 2015.
75. Hawker JI, Smith S, Smith GE, et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. *J Antimicrob Chemother*. 2014;69:3423-3430.
76. Smith NS. Antibiotic treatment for acute otitis media. *Int J Pediatr Otorhinolaryngol*. 2013;77:873-874.
77. Marchisio P, Tagliabue M, Klersy C, et al. Patterns in acute otitis media drug prescriptions: a survey of Italian pediatricians and otolaryngologists. *Expert Rev Anti Infect Ther*. 2014;12:1159-1163.
78. Célind J, Södermark L, Hjalmarson O. Adherence to treatment guidelines for acute otitis media in children: the necessity of an effective strategy of guideline implementation. *Int J Pediatr Otorhinolaryngol*. 2014;78:1128-1132.

79. Lakić D, Tadić I, Odalović M, Tasić L, Sabo A, Mećava A. Analysis of antibiotic consumption for treating respiratory tract infections in children and compliance with the National Clinical Guidelines. *Med Pregl*. 2014;67:282-289.
80. Maltezou HC, Katerelos P, Asimaki H, Roilides E, Theodoridou M. Antibiotic prescription practices for common infections and knowledge about antibiotic costs by private-practice pediatricians in Greece. *Minerva Pediatr*. 2014;66:209-216.
81. Dinleyici EC, Yuksel F, Yargic ZA, Unalacak M, Unluoglu I. Results of a national study on the awareness of and attitudes toward acute otitis media (AOM) among clinicians and the estimated direct healthcare costs in Turkey (TR-AOM Study). *Int J Pediatr Otorhinolaryngol*. 2013;77:756-761.
82. Grossman Z, Silverman BG, Miron D. Physician specialty is associated with adherence to treatment guidelines for acute otitis media in children. *Acta Paediatr*. 2013;102:e29-e33.
83. Shviro-Roseman N, Reuveni H, Gazala E, Leibovitz E. Adherence to acute otitis media treatment guidelines among primary health care providers in Israel. *Braz J Infect Dis*. 2014;18:355-359.
84. Levy C, Pereira M, Guedj R, et al. Impact of 2011 French guidelines on antibiotic prescription for acute otitis media in infants. *Med Mal Infect*. 2014;44:102-106.
85. Ryborg CT, Søndergaard J, Lous J, et al. Factors associated with antibiotic prescribing in children with otitis media. *ISRN Family Med*. 2013;2013:587452.
86. Forrest CB, Fiks AG, Bailey LC, et al. Improving adherence to otitis media guidelines with clinical decision support and physician feedback. *Pediatrics*. 2013;131:e1071-e1081.
87. Amir AZ, Pomp R, Amir J. Changes in acute mastoiditis in a single pediatric tertiary medical center: our experience during 2008-2009 compared with data for 1983-2007. *Scand J Infect Dis*. 2014;46:9-13.
88. Marchisio P, Bianchini S, Villani A, et al. Diagnosis and management of acute mastoiditis in a cohort of Italian children. *Expert Rev Anti Infect Ther*. 2014;12:1541-1548.
89. Pritchett CV, Thorne MC. Incidence of pediatric acute mastoiditis: 1997-2006. *Arch Otolaryngol Head Neck Surg*. 2012;138:451-455.
90. Kordeluk S, Orgad R, Kraus M, et al. Acute mastoiditis in children under 15 years of age in southern Israel following the introduction of pneumococcal conjugate vaccines: a 4-year retrospective study (2009-2012). *Int J Pediatr Otorhinolaryngol*. 2014; 78:1599-1604.
91. Palma S, Bovo R, Benatti A, et al. Mastoiditis in adults: a 19-year retrospective study. *Eur Arch Otorhinolaryngol*. 2014;271: 925-931.
92. Halgrimson WR, Chan KH, Abzug MJ, Perkins JN, Carosone-Link P, Simões EA. Incidence of acute mastoiditis in Colorado children in the pneumococcal conjugate vaccine era. *Pediatr Infect Dis J*. 2014;33:453-457.
93. Walls A, Pierce M, Krishnan N, Steehler M, Harley EH. Pediatric head and neck complications of Streptococcus pneumoniae before and after PCV7 vaccination. *Otolaryngol Head Neck Surg*. 2015;152:336-341.
94. Marom T, Tan A, Wilkinson GS, Pierson KS, Freeman JL, Chonmaitree T. Trends in otitis media-related health care use in the United States, 2001-2011. *JAMA Pediatr*. 2014;168:68-75.
95. Daniel M, Gautam S, Scrivener TA, Meller C, Levin B, Curotta J. What effect has pneumococcal vaccination had on acute mastoiditis? *J Laryngol Otol*. 2013;127(suppl 1):S30-S34.
96. Anthonsen K, Høstmark K, Hansen S, et al. Acute mastoiditis in children: a 10-year retrospective and validated multicenter study. *Pediatr Infect Dis J*. 2013;32:436-440.
97. Glatstein M, Morag S, Scolnik D, Alper A, Reif S, Grisaru-Soen G. Acute mastoiditis before pneumococcal vaccination: the experience of a large tertiary care pediatric hospital [published online October 3, 2014]. *Am J Ther*.
98. Tamir SO, Roth Y, Dalal I, Goldfarb A, Marom T. Acute mastoiditis in the pneumococcal conjugate vaccine era. *Clin Vaccine Immunol*. 2014;21:1189-1191.
99. Laulajainen-Hongisto A, Saat R, Lempinen L, Markkola A, Aarnisalo AA, Jero J. Bacteriology in relation to clinical findings and treatment of acute mastoiditis in children. *Int J Pediatr Otorhinolaryngol*. 2014;78:2072-2078.
100. Gorphe P, de Barros A, Choussy O, Dehesdin D, Marie JP. Acute mastoiditis in children: 10 years experience in a French tertiary university referral center. *Eur Arch Otorhinolaryngol*. 2012;269:455-460.
101. Kontorinis G, Psarommatis I, Karabinos C, Iliodromiti Z, Tsakanikos M. Incidence of non-infectious 'acute mastoiditis' in children. *J Laryngol Otol*. 2012;126:244-248.
102. Giannakopoulos P, Chrysovergis A, Xirogianni A, et al. Microbiology of acute mastoiditis and complicated or refractory acute otitis media among hospitalized children in the postvaccination era. *Pediatr Infect Dis J*. 2014;33:111-113.
103. Groth A, Enoksson F, Hermansson A, Hultcrantz M, Stalfors J, Stenfeldt K. Acute mastoiditis in children in Sweden 1993-2007—no increase after new guidelines. *Int J Pediatr Otorhinolaryngol*. 2011;75:1496-1501.
104. Chien JH, Chen YS, Hung IF, Hsieh KS, Wu KS, Cheng MF. Mastoiditis diagnosed by clinical symptoms and imaging studies in children: disease spectrum and evolving diagnostic challenges. *J Microbiol Immunol Infect*. 2012;45:377-381.
105. Mattos JL, Colman KL, Casselbrant ML, Chi DH. Intratemporal and intracranial complications of acute otitis media in a pediatric population. *Int J Pediatr Otorhinolaryngol*. 2014;78:2161-2164.
106. Stenfeldt K, Enoksson F, Stalfors J, Hultcrantz M, Hermansson A, Groth A. Infants under the age of six months with acute mastoiditis: a descriptive study of 15 years in Sweden. *Int J Pediatr Otorhinolaryngol*. 2014;78:1119-1122.
107. Psarommatis IM, Voudouris C, Douros K, Giannakopoulos P, Bairamis T, Carabinos C. Algorithmic management of pediatric acute mastoiditis. *Int J Pediatr Otorhinolaryngol*. 2012;76:791-796.
108. Psarommatis I, Giannakopoulos P, Theodorou E, Voudouris C, Carabinos C, Tsakanikos M. Mastoid subperiosteal abscess in children: drainage or mastoidectomy? *J Laryngol Otol*. 2012;126:1204-1208.
109. Chesney J, Black A, Choo D. What is the best practice for acute mastoiditis in children? *Laryngoscope*. 2014;124:1057-1058.
110. Wu JF, Jin Z, Yang JM, Liu YH, Duan ML. Extracranial and intracranial complications of otitis media: 22-year clinical experience and analysis. *Acta Otolaryngol*. 2012;132:261-265.
111. Sun J. Intracranial complications of chronic otitis media. *Eur Arch Otorhinolaryngol*. 2014;271:2923-2926.

112. Lildal TK, Korsholm J, Ovesen T. Diagnostic challenges in otogenic brain abscesses. *Dan Med J*. 2014;61:A4849.
113. Luntz M, Bartal K, Brodsky A, Shihada R. Acute mastoiditis: the role of imaging for identifying intracranial complications. *Laryngoscope*. 2012;122:2813-2817.
114. Au JK, Adam SI, Michaelides EM. Contemporary management of pediatric lateral sinus thrombosis: a twenty year review. *Am J Otolaryngol*. 2013;34:145-150.
115. Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. *Cochrane Database Syst Rev*. 2011;(8):CD002005.
116. Lebas A, Chabrier S, Fluss J, et al. EPNS/SFNP guideline on the anticoagulant treatment of cerebral sinovenous thrombosis in children and neonates. *Eur J Paediatr Neurol*. 2012;16:219-228.
117. Ulanovski D, Yacobovich J, Kornreich L, Shkalim V, Raveh E. Pediatric otogenic sigmoid sinus thrombosis: 12-year experience. *Int J Pediatr Otorhinolaryngol*. 2014;78:930-933.
118. Ropposch T, Nemetz U, Braun EM, Lackner A, Walch C. Low molecular weight heparin therapy in pediatric otogenic sigmoid sinus thrombosis: a safe treatment option? *Int J Pediatr Otorhinolaryngol*. 2012;76:1023-1026.
119. Novoa E, Podvinec M, Angst R, Gürtler N. Paediatric otogenic lateral sinus thrombosis: therapeutic management, outcome and thrombophilic evaluation. *Int J Pediatr Otorhinolaryngol*. 2013;77:996-1001.
120. Csákányi Z, Rosdy B, Kollár K, Móser J, Kovács E, Katona G. Timely recanalization of lateral sinus thrombosis in children: should we consider hypoplasia of contralateral sinuses in treatment planning? *Eur Arch Otorhinolaryngol*. 2013;270:1991-1998.
121. Rosdy B, Csákányi Z, Kollár K, et al. Visual and neurologic deterioration in otogenic lateral sinus thrombosis: 15 year experience. *Int J Pediatr Otorhinolaryngol*. 2014;78:1253-1257.
122. Zangari P, Messia V, Viccaro M, et al. Genetic prothrombotic factors in children with otogenic lateral sinus thrombosis: five case reports. *Blood Coagul Fibrinolysis*. 2012;23:158-163.