Managing Risk Factors in Otitis Media

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Introduction

The cumulative incidence of at least one episode of otitis media (OM) by the age of 7 years is reported to be 61–99%, depending on the population [1–3]. Risk factors for otitis media include a spectrum of nonmodifiable and modifiable qualities specific to the patient. They can be described as patient characteristics, genetic influences, opportunistic morbidities, and socioeconomic practices (Table 27.1). A complete birth and medical history is the first step to identifying some of these risk factors. Frequent recurrence and co-morbidities may prompt referral for other testing and in some cases genetic testing. Regardless, educating parents and patients of their risk factors and how to minimize them is crucial to decrease the incidence of otitis media in children.

Table 27.1 Risk factors in otitis media: nonmodifiable, potentially modifiable, and modifiable

Risk factors in otitis media		
Nonmodifiable	Potentially modifiable	Modifiable
Patient characteristics	*Genetic influences*	*Socioeconomic behaviors*
Young age (2 yo, 4–5 yo)	Monozygotic twins	Second- and third-hand smoke
Male sex	Family history, sibling with history of OM	Obesity
Older sibling(s)	Aerodigestive tract mucociliary disorders (primary ciliary dyskinesia and cystic fibrosis)	Daycare
Ethnicity (Native American, Canadian Eskimo, and Australian Aborigine)	Immunodeficiency (hypogammaglobulinemia and leukocyte adhesion deficiency)	Short-term breastfeeding
Cesarean section delivery	Specific genotypes (ISL1 polymorph, A2LM1, SAMD9—MIRAGE syndrome)	Pesticide exposure in utero
Lo	*Opportunistic morbidities*	
	Upper respiratory infection	
	Winter season	
	Cleft palate	
	Trisomy 21 (Down's syndrome)	
	Craniofacial deformity	
	Adenoid hypertrophy	
	Environmental/food allergies	
	Gastroesophageal reflux	

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Nonmodifiable Risk Factors

Patient Characteristics

Risk factors for otitis media related to a patient's characteristics are inherently nonmodifiable. However, parent and patient education is helpful in offering reassurance and explaining why it does not necessarily portend serious underlying disorders. The first of these risk factors include male sex, which account for 51–55% of pediatric otitis media cases, as well as young age, with a bimodal increased incidence at 6–18 months old and 4–5 years old [1, 3–7]. While the slight male preponderance has been fairly consistent, no explanations have been proven as to why otitis media is more prevalent in males. Alternatively, it is widely accepted that the risk of young age is related to short, relatively horizontal eustachian tubes, which elongate and eventually develop a 30–40° upward angle toward the middle ear with increasing age [8]. Having an older sibling at home is also a risk factor, presumably due to earlier exposure to upper respiratory tract infections, which is supported by further increased risk if a room is shared with them [7].

Native American, Canadian Eskimo, and Australian Aborigine ethnicities have an increased risk for otitis media, compared to Caucasians [3, 7]. This is likely due to anatomical characteristics of the eustachian tube of these ethnicities. Children with Black ethnic backgrounds have a decreased risk [3, 5], though causality is unknown in all cases. Lastly, children delivered via cesarean section have a slightly increased risk of otitis media, as compared to nonoperative vaginal delivery [9, 10]. The hypothesis is that there are differences in the gut biome of children born by cesarian section and via vaginal delivery [10]. Interestingly, patients born via an operative vaginal delivery (defined as instruments placed in the birth canal) have the same increased risk as cesarean section [9]. Low birth preterm children are also at an increased risk for otitis.

Potentially Modifiable Risk Factors

Genetic Influences

It is clear that genetics play a strong role in the risk for otitis media as epidemiology studies have identified family history of a sibling with prior otitis media as a risk factor [4, 7, 11]. Even more telling, this association is stronger between monozygotic twins and triplets compared to dizygotic twins and triplets, though this difference no longer remains significant after 4 years of age [11]. While genetic counseling is not necessary for the majority of patients with otitis media, advances in genomics and genetic therapies may prompt genetic testing for patients with recurrent or severe disease. Arguably, the otolaryngologist's role in minimizing genetically influenced risk factors for otitis media is identification of the underlying cause, or more realistically, timely referral for work-up. The presence of these risk factors may also sharpen clinical acumen for the need of more aggressive preventive measures and more frequent follow-up to ensure hearing is protected.

Ciliary Motility Disorders

Genetic diseases that lead to aerodigestive motility disorders are important considerations for recurrent otitis media. Primary ciliary dyskinesia is a rare (1:10,000–20,000 live births) genetic disorder affecting the cilia of the upper respiratory tract which can lead to chronic rhinosinusitis, bronchiectasis, and otitis media. Clinical screening questionnaires and expired nasal nitric oxide concentrations are potentially cost-effective methods for identifying patients who warrant formal genetic testing [12]. Historically, cystic fibrosis was considered protective against otitis media due to well-aerated temporal bones and overly tenacious nasal secretions making translocation to the middle ear more difficulty [13]. However, recent review has noted increased incidence of otitis media coinciding with increased identification of subclinical genotypes [14]. Interestingly, cystic fibrosis patients without otitis media were found to have a lower density of goblet cells on postmortem analysis as compared to cystic fibrosis patients with otitis media, yet most have inner ear damage due to ototoxic drugs [13].

Immunodeficiency

Immunodeficiency is another important consideration. Leukocyte adhesion deficiency leads to a defect in transporting leukocytes to regions of tissue injury. A recent cohort analysis identified an otitis media prevalence of 10–21% in these patients. Suspicion is worked up with cytometric analysis of CD18 and CD11 expression of leukocytes, and diagnosis can be confirmed by the identification of a defect in the ITGβ2 gene [15]. Similarly, a cross-sectional study of pediatric patients with hypogammaglobulinemia identified an otitis media prevalence of 49%, which led to conductive hearing loss in 73% of patients. This includes X-linked agammaglobulinemia, common variable immunodeficiency, IgA deficiency, and hyper-IgM syndrome [16].

Specific Genotypes

The ubiquity of genomics has also led to the identification of specific genotypes with higher risk for otitis media with unclear etiology, which includes ISL1 and A2LM1 polymorphisms and SAMD9 mutations [17–19]. ISL1 is part of the insulin gene enhancer protein 1 homeodomain that regulates the insulin gene. Specific polymorphisms of this gene relating to different exons have been found to increase the risk of otitis media [19]. The A2LM1 encodes the α-2 macroglobulin-like-1 protein. A variant of which was identified in a Filipino community to have a significant odds ratio of 3.7 for OM [18]. SAMD9, or sterile alpha motif domain containing 9, encodes a protein of unknown significance; however, mutations in this gene are responsible for MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital problems, and enteropathy) syndrome. MIRAGE syndrome has been associated with increased risk of otitis media. This may be related to cytopenias but has not been investigated [17]. Of note, other mutations of SAMD9 can also lead to normophosphatemic familial tumoral calcinosis but has not been linked to otitis media [20].

Alternatively, some genotypes may be protective, such as IFI44L minor homozygotes, who have a significate incidence rate ratio of 0.77 compared to other allele combinations [21]. IFI44L is a protein-encoding gene for the interferon-induced protein 44-like which has viral antiproliferative activity; however, the mechanism of this property is unknown [22].

The prevalence of otitis media in children with Down's syndrome has been reported to be 81–83% [23, 24]. Temporal bone studies have identified that Down's syndrome patients have smaller middle ear compartments and more collapsible eustachian tubes due to immature development of eustachian tube cartilage and the tensor veli palatini muscle [25]. These patients can also have immunodeficiencies that contribute to their increase risk of otitis media [26]. Otitis media in Down's syndrome patients has been shown to commonly cause significant physical symptoms and hearing loss [27]. While tympanostomy tubes significantly improve these symptoms, it is common for their otitis media to stay unresolved requiring subsequent tubes for a majority of young age [24, 27].

Opportunistic Morbidities

Several morphological morbidities have been identified as risk factors for otitis media, which offers an opportunity for potential medical or surgical intervention. Identifying these risk factors and educating parents and patients offers better informed perspectives of preventing OM. It may also obviate the need for further testing and offer reassurance regarding the overall health of the patient.

Upper Respiratory Infections

Likely the most common risk factor for otitis media is current or recent upper respiratory infection. In a prospective cohort study of 294 children aged 1–3 years, otitis media was found to complicate upper respiratory infection 61% of the time. While there were no associations with sex or ethnicity, age was significant with each increasing month of life after 1 year reducing the risk of otitis media by 4%. Interestingly, there was also a significant difference in the incidence of otitis media by virus type with adenovirus and coronavirus being the most associated with otitis media. The proposed pathophysiology of this association is nasopharyngeal edema leading to eustachian tube dysfunction, as well as increased production of mucus in the middle ear [28]. Similarly, as viral upper respiratory infections are most common in the fall and winter seasons [29], so is otitis media [30]. Intranasal steroids, antihistamines, and decongestants are not helpful as treatment for otitis media [31], and this likely holds true for prevention as well during an upper respiratory infection. However, symptomatic care with oral hydration and nasal saline irrigation are safe adjuncts [32]. Furthermore, yearly influenza vaccines have been linked to significant reductions in otitis media, and similarly, the pneumococcal conjugate vaccine [33, 34].

Craniofacial Abnormalities

Extra vigilance should be practiced in patients with craniofacial abnormalities that can predispose to otitis media. Patients with cleft palate ultimately have poor middle ear ventilation due to poor function of the palatine muscles and frequent velopharyngeal reflux [35, 36]. Greater than 95% of children with cleft palate have otitis media prior to palatal closure [37, 38], which can improve somehow along with hearing status at about 6–12 months after surgery [39]. However, pediatric patients with cleft palate have similar long-term chronicity and audiological outcomes when treated with tympanostomy tubes as compared to pediatric patients without cleft palate [40]. Patients with other forms of craniofacial deformity should also be considered to be at an increased risk for otitis media. Specifically, changes in the relative positions of the mandible, skull base, middle ear, sphenoid, and palate can increase the risk of otitis media [41].

Adenoids

The adenoid tissue can act as a reservoir for otitis media pathogens and can also cause eustachian tube dysfunction if enlarged and encroaching onto the tori tubarius [42, 43]. Inflammatory changes to the adenoids can also cause increased inflammation of the middle ear [44]. Interestingly, Streptococcus pneumoniae is the most common adenoidal pathogen in patients 7 years of age or younger and Staphylococcus aureus is the most common in those older than 7 years of age. However, there is no association between the risk of otitis media and the pathogen(s) colonizing adenoid tissue [45]. Adenoidectomy in the setting of hypertrophy has been shown to improve middle ear ventilation [46]. It may also decrease the number of repeated tympanostomy tube in children older than 4 years of age [47].

Allergies

While the relationship between environmental allergies and otitis media is complicated and controversial, immunological studies have identified IgE-mediated middle ear disease. Furthermore, the middle ear mucosa is an extension or the upper airway mucosa and has similar physiologic and immune mechanisms, including inflammation due to allergies. The prevalence of atopy, including allergic rhinitis in patients with recurrent otitis, ranges from 24% to 89% [48].

Because of the multifactorial nature of OM, it is difficult to measure the impact of allergy-related middle ear disease in the setting of other known risk factors. However, allergy testing can be considered for children with signs of atopia [49]. Similarly, the impact of food allergies and the need for avoidance practices remains controversial. Nonrandomized, prospective studies have researched food allergy associations and impact of dietary avoidance among children with OM with positive results [50, 51]. However, there remains a dearth of definitive studies and subsequent consensus statements. While food allergy is a consideration and can be tested, the risks and benefits of dietary avoidance therapy should be critically appraised specific to the patient and other risk factors should be minimized.

GERD

Gastroesophageal reflux in early childhood is another important concern, as it significantly increases the risk for otitis media [52, 53]. In fact, increasing the severity of reflux symptoms increases the risk of eustachian tube dysfunction, hearing loss, and tympanostomy tube placement [52]. Part of this may be related to pepsin or pepsinogen identified in middle ear aspirates, putting even laryngopharyngeal reflux patients at risk. However, this connection has not been confirmed [54].

Modifiable Risk Factors

Socioeconomic Practices

Lifestyle and access to healthy and clean food has important implications beyond the incidence of otitis media but may offer a tangible and evidence-based opportunity to educate parents and improve social and environmental factors affecting the patient. One of the most important in this category is exposure to second- and third-hand smoking. Passive smoke exposure is a clear, reproducible risk factor across ethnicities [4, 5, 18, 55–57]. The pathophysiology for this association has not been established; however, second- and third-hand smoke have been linked to significant alterations in the respiratory microbiome, with exposed children more likely to have inflamed upper airways with pathogenic and polymicrobial flora [58, 59].

Obesity has a significant role in increasing the risk of otitis media, though it is likely multifactorial. Obesity leads to poor eustachian tube dysfunction secondary to an increase in the Ostmann fat pad of the nasopharynx. There is also an increased risk of acid reflux, which is an independent risk factor for otitis media. Most importantly, obesity also leads to a local immune dysfunction of the middle ear with reduction in toll-like receptor-mediated expression of mRNA for multiple cytokines [60].

Daycare

Daycare attendance has an odds ratio of 1.3–1.5 for otitis media [61, 62]. However, an increasing number of caregivers is not significant [62], highlighting the increased microbial transmission rates among young children, inherent to their behavior. The risk is even higher when daycare attendance is started prior to age 12 months [63, 64], which emphasizes the multifactorial nature of risk factors for otitis media. While recommending removal from daycare may lead to significant concerns, such as the effects on social development, suggesting delaying admission and ensuring hygienic practices of the facilities, especially for patients with multiple risk factors, may be better received.

Breastfeeding

Breastfeeding has repeatedly been shown to reduce the risk of otitis media in infancy by 40–50% [65]. This risk reduction is most robust in infants who are breastfed ≥12 months as compared to those breastfed <6 months [66, 67]. This benefit may be derived from milk fat globule membranes, or fat globules, which transport high concentrations of phospholipids, gangliosides, and proteins [68]. Milk fat globule membrane-supplemented formula significantly reduces the incidence of otitis media compared to nonsupplemented, formula-fed infants [69]. Similarly, prospective research has correlated pesticide exposure in utero to increased risk of otitis media in childhood, as compared to mothers who consumed an organic, pesticide-free diet [70]. Breastfeeding position seems to cause different changes in negative pressure in the middle ear, and breastfeeding a child in the "flat" position might be related to increased risk of otitis media [71, 72].

Common Misconceptions

Pacifier use has had a long history of reported association with increased risk for otitis media. However, significant correlations fail to remain significant after multivariate logistic regression analysis [73]. Furthermore, other studies contradict this association, linking increased otitis media prevalence with decreased pacifier use [74]. This represents sampling errors. Likely more important, otitis media within the first month of life increases the risk of recurrent otitis media fourfold [75]. Given the clear reduction in sudden infant death syndrome [76] and the paucity of definitive relationships to otitis media, pacifier use should not be discouraged.

Swimming can often be a confusing topic for parents and caregivers of children with otitis media. While swimming can increase the risk of otitis externa [77], it does not increase nor decrease the risk of otitis media [78]. Similarly, there is no increased risk for otitis media in patients with tympanostomy tubes 1 month after placement and current tympanostomy tube guidelines do not recommend avoiding water exposure [79, 80].

Effects of Social Distancing During the COVID-19 Pandemic

SARS-CoV2 (server acute respiratory syndrome coronavirus 2) and the subsequent COVID-19 (2019 novel corona virus disease) pandemic has led to a radical change in daily life for most people around the world. Social distancing, social isolation, and increased frequency of hygienic practices have clearly mitigated the risk of contracting SARS-CoV2 and developing COVID-19 [81]. As such, these practices have simultaneously mitigated the risk of contact with other viruses, subsequentially leading to a significant 5–10 fold reduction in the incidence of otitis media in children [82, 83]. Interestingly, this has also led to a significant increase in resolution of chronic otitis media with effusion [83]. Though social distancing and isolation are likely not an appropriate measure for most children given the need for social development, it does highlight the importance of ensuring hygienic practices and a possible short-term adjunct for children severely affected by otitis media.

References

1. Todberg T, Koch A, Andersson M, Olsen SF, Lous J, Homoe P. Incidence of otitis media in a contemporary Danish National Birth Cohort. PLoS One. 2014;9(12):e111732.
2. Paradise JL, Rockette HE, Colborn DK, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. Pediatrics. 1997;99(3):318–33.
3. Infante-Rivard C, Fernandez A. Otitis media in children: frequency, risk factors, and research avenues. Epidemiol Rev. 1993;15(2):444–65.
4. Froom J, Culpepper L, Green LA, et al. A cross-national study of acute otitis media: risk factors, severity, and treatment at initial visit. Report from the International Primary Care Network (IPCN) and the Ambulatory Sentinel Practice Network (ASPN). J Am Board Fam Pract. 2001;14(6):406–17.
5. Qureishi A, Lee Y, Belfield K, Birchall JP, Daniel M. Update on otitis media—prevention and treatment. Infect Drug Resist. 2014;7:15–24.
6. Chen CH, Lin CJ, Hwang YH, Ku CJ. Epidemiology of otitis media in Chinese children. Clin Otolaryngol Allied Sci. 2003;28(5):442–5.
7. Baraibar R. Incidence and risk factors of acute otitis media in children. Clin Microbiol Infect. 1997;3(Suppl 3):S13–22.
8. Bluestone CD, Doyle WJ. Anatomy and physiology of eustachian tube and middle ear related to otitis media. J Allergy Clin Immunol. 1988;81(5 Pt 2):997–1003.
9. Auger N, Soullane S, Luu TM, Lee GE, Wei SQ, Quach C. Association of cesarean delivery with childhood hospitalization for infections before 13 years of age. J Pediatr. 2021;231:178.
10. Hartley M, Woolcott CG, Langley JM, Brown MM, Ashley-Martin J, Kuhle S. Birth by caesarean section and otitis media in childhood: a retrospective cohort study. Sci Rep. 2020;10(1):5219.
11. Casselbrant ML, Mandel EM, Rockette HE, et al. The genetic component of middle ear disease in the first 5 years of life. Arch Otolaryngol Head Neck Surg. 2004;130(3):273–8.
12. Brennan SK, Molter D, Menezes M, et al. Implementation of a screening tool for primary ciliary dyskinesia (PCD) in a pediatric otolaryngology clinic. Int J Pediatr Otorhinolaryngol. 2020;142:110586.
13. Yildirim N, Sone M, Mutlu C, Schachern PA, Paparella MM, Le CT. Histopathologic features of the temporal bone in patients with cystic fibrosis. Arch Otolaryngol Head Neck Surg. 2000;126(1):75–8.
14. McCoy JL, Kaffenberger TM, Yang TS, Shaffer AD, Dohar JE. Middle ear disease in CF? It's not just about the sinuses anymore! Int J Pediatr Otorhinolaryngol. 2020;134:110032.
15. Kambli PM, Bargir UA, Yadav RM, et al. Clinical and genetic spectrum of a large cohort of patients with leukocyte adhesion deficiency type 1 and 3: amulticentric study from India. Front Immunol. 2020;11:612703.
16. Tavakol M, Kouhi A, Abolhassani H, et al. Otological findings in pediatric patients with hypogammaglobulinemia. Iran J Allergy Asthma Immunol. 2014;13(3):166–73.
17. Tanase-Nakao K, Olson TS, Narumi S. MIRAGE syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews((R)). Seattle, WA: University of Washington; 1993.
18. Santos-Cortez RL, Reyes-Quintos MR, Tantoco ML, et al. Genetic and environmental determinants of otitis media in an indigenous Filipino population. Otolaryngol Head Neck Surg. 2016;155(5):856–62.
19. Kondyarpu A, Ray CS, Panda KC, Biswal NC, Ramchander PV. Association of ISL1 polymorphisms and eosinophilic levels among otitis media patients. J Clin Lab Anal. 2021;35:e23702.
20. Jiang Q, Quaynor B, Sun A, et al. The Samd9L gene: transcriptional regulation and tissue-specific expression in mouse development. J Invest Dermatol. 2011;131(7):1428–34.
21. Lempainen J, Korhonen LS, Kantojarvi K, et al. Associations between IFI44L gene variants and rates of respiratory tract infections during early childhood. J Infect Dis. 2021;223(1):157–65.
22. Busse DC, Habgood-Coote D, Clare S, et al. Interferon-induced protein 44 and interferon-induced protein 44-like restrict replication of respiratory syncytial virus. J Virol. 2020;94(18):e00297-20.
23. Roizen NJ, Wolters C, Nicol T, Blondis TA. Hearing loss in children with Down syndrome. J Pediatr. 1993;123(1):S9–12.
24. Shott SR, Joseph A, Heithaus D. Hearing loss in children with Down syndrome. Int J Pediatr Otorhinolaryngol. 2001;61(3):199–205.
25. Nogaki T, Paparella MM, Cureoglu S. A structural analysis of tympanic compartments of the middle ear in patients with Down's syndrome: atemporal bone study. Otol Neurotol. 2020;41(8):1149–57.

26. Verstegen RHJ, Kusters MAA. Inborn errors of adaptive immunity in Down syndrome. J Clin Immunol. 2020;40(6):791–806.
27. Labby A, Mace JC, Buncke M, MacArthur CJ. Quality of life improvement after pressure equalization tube placement in Down syndrome: a prospective study. Int J Pediatr Otorhinolaryngol. 2016;88:168–72.
28. Chonmaitree T, Revai K, Grady JJ, et al. Viral upper respiratory tract infection and otitis media complication in young children. Clin Infect Dis. 2008;46(6):815–23.
29. Dasaraju PV, Liu C. Infections of the respiratory system. In: Baron S, editor. Medical microbiology. Galveston, TX: University of Texas Medical Branch; 1996.
30. Kim TH, Jeon JM, Choi J, Im GJ, Song JJ, Chae SW. The change of prevalence and recurrence of acute otitis media in Korea. Int J Pediatr Otorhinolaryngol. 2020;134:110002.
31. Rosenfeld RM, Shin JJ, Schwartz SR, et al. Clinical practice guideline: otitis media with effusion executive summary (update). Otolaryngol Head Neck Surg. 2016;154(2):201–14.
32. Marchisio P, Bortone B, Ciarcia M, et al. Updated guidelines for the management of acute otitis media in children by the Italian Society of Pediatrics: Prevention. Pediatr Infect Dis J. 2019;38(12S Suppl):S22–36.
33. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–99.
34. de Sevaux JL, Venekamp RP, Lutje V, et al. Pneumococcal conjugate vaccines for preventing acute otitis media in children. Cochrane Database Syst Rev. 2020;11:CD001480.
35. Azman A, Manuel AM. Otological outcome in cleft lip and palate children with middle ear effusion. Int J Pediatr Otorhinolaryngol. 2020;138:110274.
36. Hocevar-Boltezar I, Jarc A, Kozelj V. Ear, nose and voice problems in children with orofacial clefts. J Laryngol Otol. 2006;120(4):276–81.
37. Dhillon RS. The middle ear in cleft palate children pre and post palatal closure. J R Soc Med. 1988;81(12):710–3.
38. Paradise JL, Bluestone CD, Felder H. The universality of otitis media in 50 infants with cleft palate. Pediatrics. 1969;44(1):35–42.
39. Acharya P, Sahana BA, Desai A, Jalisatgi RR, Kumar N. Pre-operative and post-operative audiological assessment in cleft lip and palate patients-a prospective study. J Oral Biol Craniofac Res. 2021;11(2):321–9.
40. Inoue M, Hirama M, Kobayashi S, Ogahara N, Takahashi M, Oridate N. Long-term outcomes in children with and without cleft palate treated with tympanostomy for otitis media with effusion before the age of 2 years. Acta Otolaryngol. 2020;140(12):982–9.
41. Gremba AP, Weinberg SM, Swarts JD, Casselbrant ML. Craniofacial shape in children with and without a positive otitis media history. Int J Pediatr Otorhinolaryngol. 2016;84:110–5.
42. Musher DM. Pneumococcal vaccine-direct and indirect (“herd”) effects. N Engl J Med. 2006;354:1522–4.
43. Wright ED, Alden JP, Manoukian JJ. Laterally hypertrophic adenoids as a contributing factor in otitis media. Int J Pediatr Otorhinolaryngol. 1998;45:207–14.
44. Abdullah B, Hassan S, Sidek D, Jaafar H. Adenoid mast cell and their role in the pathogenesis of otitis media with effusion. J Laryngol Otol. 2006;120:556–60.
45. Ungkanont K, Jootakarn S, Leelaporn A, et al. Association between adenoid bacteriology and clinical characteristics of adenoid-related diseases in children. SAGE Open Med. 2021;9:20503121211006005.
46. Manno A, Iannella G, Savastano V, et al. Eustachian tube dysfunction in children with adenoid hypertrophy: the role of adenoidectomy for improving ear ventilation. Ear Nose Throat J. 2021; https://doi.org/10.1177/0145561321989455.
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. https://doi.org/10.1371/journal.pone.0101175.
48. Lack G, Caulfield H, Penagos M. The link between otitis media with effusion and allergy: a potential role for intranasal corticosteroids. Pediatr Allergy Immunol. 2011;22:258–66.
49. Hurst DS. The role of allergy in otitis media with effusion. Otolaryngol Clin N Am. 2011;44(3):637–54, viii–ix.
50. Aydogan B, Kiroglu M, Altintas D, Yilmaz M, Yorgancilar E, Tuncer U. The role of food allergy in otitis media with effusion. Otolaryngol Head Neck Surg. 2004;130(6):747–50.
51. Nsouli TM, Nsouli SM, Linde RE, O’Mara F, Scanlon RT, Bellanti JA. Role of food allergy in serous otitis media. Ann Allergy. 1994;73(3):215–9.
52. Lee JA, Schaffer CE, Mehta CH, Close MF, Nguyen SA, Meyer TA. Impact of early gastroesophageal reflux disease on childhood otologic outcomes. Int J Pediatr Otorhinolaryngol. 2020;134:110069.
53. Wu ZH, Tang Y, Niu X, Sun HY, Chen X. The relationship between otitis media with effusion and gastroesophageal reflux disease: ameta-analysis. Otol Neurotol. 2021;42(3):e245–53.
54. Lechien JR, Hans S, Simon F, et al. Association between laryngopharyngeal reflux and media otitis: asystematic review. Otol Neurotol. 2021;42:e801.
55. Tarhun YM. The effect of passive smoking on the etiology of serous otitis media in children. Am J Otolaryngol. 2020;41(3):102398.
56. Kalcioglu MT, Sallavaci S, Hrncic N, et al. Prevalence of and factors affecting otitis media with effusion in children in the region from Balkans to Caspian basin; a multicentric cross-sectional study. Int J Pediatr Otorhinolaryngol. 2021;143:110647.
57. van Ingen G, le Clercq CMP, Touw CE, et al. Environmental determinants associated with acute otitis media in children: a longitudinal study. Pediatr Res. 2020;87(1):163–8.
58. Kelley ST, Liu W, Quintana PJE, et al. Altered microbiomes in thirdhand smoke-exposed children and their home environments. Pediatr Res. 2021;90:1153.
59. Bugova G, Janickova M, Uhliarova B, Babela R, Jesenak M. The effect of passive smoking on bacterial colonisation of the upper airways and selected laboratory parameters in children. Acta Otorhinolaryngol Ital. 2018;38(5):431–8.
60. Ahmed S, Arjmand E, Sidell D. Role of obesity in otitis media in children. Curr Allergy Asthma Rep. 2014;14(11):469.
61. van Ingen G, le Clercq CMP, Jaddoe VWV, et al. Identifying distinct trajectories of acute otitis media in children: a prospective cohort study. Clin Otolaryngol. 2021;46:788.
62. Chen KK, Huang DT, Chou LT, Nieh HP, Fu RH, Chang CJ. Childhood otitis media: relationship with daycare attendance, harsh parenting, and maternal mental health. PLoS One. 2019;14(7):e0219684.
63. Lee JY, Kim SH, Song CI, Kim YR, Kim YJ, Choi JH. Risk factors for persistent otitis media with effusion in children: a case-control study. Yeungnam Univ J Med. 2018;35(1):70–5.
64. Korvel-Hanquist A, Koch A, Lous J, Olsen SF, Homoe P. Risk of childhood otitis media with focus on potentially modifiable factors: a Danish follow-up cohort study. Int J Pediatr Otorhinolaryngol. 2018;106:1–9.
65. Lodge CJ, Bowatte G, Matheson MC, Dharmage SC. The role of breastfeeding in childhood otitis media. Curr Allergy Asthma Rep. 2016;16(9):68.
66. Ardic C, Yavuz E. Effect of breastfeeding on common pediatric infections: a 5-year prospective cohort study. Arch Argent Pediatr. 2018;116(2):126–32.

67. Stordal K, Lundeby KM, Brantsaeter AL, et al. Breast-feeding and infant hospitalization for infections: large cohort and sibling analysis. J Pediatr Gastroenterol Nutr. 2017;65(2):225–31.
68. Raza GS, Herzig KH, Leppaluoto J. Invited review: milk fat globule membrane-a possible panacea for neurodevelopment, infections, cardiometabolic diseases, and frailty. J Dairy Sci. 2021;104:7345.
69. Ambrozej D, Dumycz K, Dziechciarz P, Ruszczynski M. Milk fat globule membrane supplementation in children: systematic review with meta-analysis. Nutrients. 2021;13(3):714.
70. Vigar V, Myers S, Oliver C, Arellano J, Robinson S, Leifert C. A systematic review of organic versus conventional food consumption: is there a measurable benefit on human health? Nutrients. 2019;12(1):7.
71. Narayanan I, Singh S, Mathur R, Jain BK. Ear infection and infant feeding practices. Indian J Pediatr. 1989;56(3):399–402. https://doi.org/10.1007/BF02722311.
72. Tully SB, Bar-Haim Y, Bradley RL. Abnormal tympanography after supine bottle feeding. J Pediatr. 1995;126(6):S105–11. https://doi.org/10.1016/s0022-3476(95)90249-x.
73. Salah M, Abdel-Aziz M, Al-Farok A, Jebrini A. Recurrent acute otitis media in infants: analysis of risk factors. Int J Pediatr Otorhinolaryngol. 2013;77(10):1665–9.
74. Ilia S, Galanakis E. Clinical features and outcome of acute otitis media in early infancy. Int J Infect Dis. 2013;17(5):e317–20.
75. Megged O, Abdulgany S, Bar-Meir M. Does acute otitis media in the first month of life increase the risk for recurrent otitis? Clin Pediatr (Phila). 2018;57(1):89–92.
76. Hauck FR, Omojokun OO, Siadaty MS. Do pacifiers reduce the risk of sudden infant death syndrome?A meta-analysis. Pediatrics. 2005;116(5):e716–23.
77. Caramia G, Serafini V, Loggi A. [The swimmer's otitis. An up to date and prevention options]. Pediatr Med Chir. 2013;35(4):177–82.
78. Sanchez L, Carney AS, Esterman A, Sparrow K, Turner D. Does access to saltwater swimming pools reduce ear pathology and hearing loss in school children of remote arid zone aboriginal communities? A prospective 3-year cohort study. Clin Otolaryngol. 2019;44(5):736–42.
79. Miyake MM, Tateno DA, Cancado NA, Miyake MM, Tincani S, Sousa Neto OM. Water protection in patients with tympanostomy tubes in tympanic membrane: a randomized clinical trial. Einstein (Sao Paulo). 2019;17(2):eAO4423.
80. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg. 2013;149(1 Suppl):S1–35.
81. Lio CF, Cheong HH, Lei CI, et al. Effectiveness of personal protective health behaviour against COVID-19. BMC Public Health. 2021;29(1):827.
82. Torretta S, Capaccio P, Coro I, et al. Incidental lowering of otitis-media complaints in otitis-prone children during COVID-19 pandemic: not all evil comes to hurt. Eur J Pediatr. 2021;180(2):649–52.
83. Alde M, Di Berardino F, Marchisio P, et al. Effects of COVID-19 lockdown on otitis media with effusion in children: future therapeutic implications. Otolaryngol Head Neck Surg. 2021;165:710.