



The Influence of Age on the Relationship Between Allergic Rhinitis and Otitis Media

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Abstract

Purpose of Review To examine the relationship between otitis media, allergic rhinitis, and age.

Recent Findings Otitis media and allergic rhinitis are prevalent conditions with a controversial relationship. Some data suggest that these entities are significantly associated, either through allergic rhinitis inducing Eustachian tube dysfunction or through allergic pathophysiology simultaneously occurring intranasally and in the ear. Other studies, however, have refuted this relationship. For example, treatment with antihistamines does not reliably improve OME, making causation and association challenging to establish. Age may have an effect on the nature of the relationship between allergic rhinitis and otitis media, by impacting both the individual conditions and their association. Epidemiological, immunological, and adenoidal studies have suggested that differences occur with age, and this review encapsulates the related data and publications. We begin by evaluating how allergic rhinitis and otitis media each are affected by age, then evaluate the role that age may have in the relationship between the two conditions. Adult and pediatric literature are evaluated so as to include the full impact of age across patients' lifespan.

Summary Age induces changes in immunity, patterns of inflammation, and susceptibility to both allergic rhinitis and otitis media with effusion. Age may also be an effect modifier which impacts the nature of the relationship between these two conditions. The influence of age on the association between these highly prevalent conditions remains a topic of active study.

Keywords Otitis media with effusion · Eustachian tube dysfunction · Allergic rhinitis · Age · Eosinophilic otitis media · Unified airway

Introduction

Otitis media and allergic rhinitis are highly prevalent conditions that have a significant impact on quality of life, healthcare expenditures, and visit burden in both children and adults [1–4, 5]. The role of allergy in the development of otitis media has been the subject of much investigation and may change with age. Given the ongoing controversy, we examine the relationships between these three variables and how they evolve as patients grow older. We begin by evaluating how allergic rhinitis and otitis media independently develop with age, then evaluate the role that age may play on the

relationship between these two entities. Adult and pediatric literature are evaluated so as to include the full impact of age across a patient lifespan.

Allergic Rhinitis and Age

Allergic rhinitis (AR) is a prevalent condition, which affects one in six people in the USA [1, 2] and between 10 and 40% internationally, depending on geographic location [6•, 7]. Allergies are the sixth leading cause of chronic illness in the USA, with an associated annual cost in excess of \$18 billion [6•]. Prompted by a type I hypersensitivity IgE-mediated inflammatory response [8], allergic rhinitis typically presents with three major symptoms: sneezing, nasal obstruction, and mucus discharge. Within minutes of allergen exposure, mast cells release inflammatory mediators, and additional symptoms may develop 4–8 h later as eosinophils, basophils, and T-lymphocytes enter the affected tissue.

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Allergic rhinitis itself evolves with age. This process is typically not present in infants, but can manifest as early as the second year of life [6•]. Exposure and sensitization to allergens is expected to occur prior to the development of allergic symptomatology. In childhood, there is a high incidence of allergic rhinitis, which may be related to the rapid evolution of the immune system in this age group [6•]. An overactive Th2 lymphocyte response prompts a systemic IgE-driven reaction until the child's immune system matures. Prospective studies of children have demonstrated that the prevalence of allergic rhinitis increases with age: 5.4% of 4 year-olds and 14% of 8 year-olds are affected [9]. Once allergy develops, symptoms typically persist, often into adulthood. Up to 80% of patients with allergic rhinitis develop symptoms prior to 20 years of age [10]. Furthermore, pediatric patients are becoming more affected over time. Studies from Brazil have demonstrated increasing rates of allergic rhinitis in adolescents from 2002 to 2012 [11•].

Otitis Media and Age

Otitis media encompasses a variety of inflammatory conditions affecting the middle ear. Acute otitis media (AOM) typically involves viral or bacterial infection in the middle ear, while otitis media with effusion (OME) often implies fluid in the middle ear without infection. OME exists along a spectrum that includes Eustachian tube dysfunction and tympanic membrane retraction, and may be associated with chronic otitis media and cholesteatoma as well. Otitis media is also a highly prevalent condition which leads to frequent ambulatory medical care visits in both the pediatric and adult age groups. Eustachian tube dysfunction and OME have been associated with 2.6 million visits per annum among patients younger than 20 years of age, and 2 million visits among those older than 20 years of age [5•]. OME affects over 50% of children before 12 months of age, and 60% of children younger than 2 years of age [12]. By school age, about 90% of children have experienced at least one episode of OME [4, 13]. Associated costs of OME in the USA amount to approximately \$4 billion [4, 14].

Otitis media also changes according to age. In children, the Eustachian tube is shorter, wider, and more horizontal than in adults; these properties confer less effective function and are associated with higher rates of otitis media in children under 7 years of age. Rates of OME are low in the first few weeks of life, but increase at approximately 10 months of age, peaking between 2 and 5 years of age. By 8 years of age, the prevalence decreases; it is 8% as compared to 20% at the age of 2 years [15•].

The Proposed Association Between Allergic Rhinitis and Otitis Media

A link between allergy and otitis media was first proposed in 1929, when Lewis et al. identified six patients in which the etiology of OME was presumed to be related to allergy [16]. Given a lack of elevated white blood cell count, normal vital signs, a history of allergy in some cases, and observed symptom resolution within 36 h, the authors concluded that many cases of AOM originated as manifestations of allergy, which then subsequently served as a nidus for bacterial suprainfection. Since then, numerous publications have attempted to better characterize the relationship between allergy and OME. Multiple hypotheses exist to explain this association, but a definitive mechanism has remained elusive. In fact, controversy remains regarding the presence of a veritable connection.

The inflammatory process related to OME can vary widely across patients. Some authors have subtyped OME as either exudative or transudative [17]. Rezes et al. supported these categorizations with studies of the albumin to IgG concentration (A/G ratio) in middle ear effusions. The exudative process had a higher relative prevalence of IgG. In contrast, the transudative process, thought to arise from increased local microvasculature permeability with extravasation of albumin, had a higher A/G ratio. There were also differences in cytokines within these two groups, which were thought to describe discrete disease processes. INF-gamma and TNF-a (typically Th1 helper cell response) were present in exudative effusions, while transudative effusions had predominantly IL-4 and IL-10 (typically Th2 helper cell response). This latter cytokine profile suggests a potential role for allergy in OME, since IL-4 stimulates IgE, which binds to basophils and mast cells. Mast cells release histamine, a well-known mediator of type I hypersensitivity. This vasoactive mediator is capable of sustaining a process of local microvasculature permeability as is often seen in transudative reactions. Histamine has been shown to be present in the effusions of patients with chronic OME at higher levels than in serum [18].

Beyond these molecular mechanisms, additional hypotheses have explored a direct relationship between allergic rhinitis and OME. One such hypothesis, the "shock organ" hypothesis, suggests an active secretion mechanism, in which allergic reactions lead to release of cytokines and inflammatory mediators from mast cells in the nasal and nasopharyngeal mucosa. This allergic rhinitis is then thought to lead to Eustachian tube occlusion and subsequent OME [19, 20]. A related second hypothesis proposes that upon Eustachian tube occlusion, poor middle ear ventilation prompts increased nitrogen absorption in the middle ear. This absorption leads to a continuous negative pressure, which then transduces fluid from mucosal capillaries into the middle ear space [21]. Numerous studies have attempted to investigate these hypotheses, but

limited sample sizes, wide variations in the reported prevalence of OME and AR, varying diagnostic criteria, lack of randomization, and potential referral bias have all made the results less definitive and difficult to generalize [22•, 23].

Other hypotheses suggest that there is simply a parallel process occurring in both the nose and the ear. The unified airway framework is a model in which the upper respiratory tract (including the middle ear mucosa, nose, sinuses, and pulmonary tree) all are considered to behave as an organized functional unit [24]. The same mediators that promote reactions in one part of the unified airway are felt to also influence inflammation in all components of this system. Corren reported that 78% of patients with asthma are also impacted by rhinitis, and 38% of patients with rhinitis also have asthma [25]. While studies of the unified airway model more frequently assess the relationship between allergic rhinitis and asthma, the middle ear is also considered a part of the unified airway. From a histological standpoint, the mucosa lining the middle ear, nose, sinuses and lower respiratory tract is similar; it is composed of pseudostratified columnar epithelium which is involved in mucosal transport and clearance.

Moreover, the inflammatory mediators involved in diseases affecting these areas are similar [26]. Nguyen et al. correlated individual patients' middle ear inflammatory profiles to those of the nasopharynx or upper airway; the results suggested that parallel allergic inflammation occurs on both sides of the Eustachian tube, also supporting the concept that the middle ear is part of the unified airway [27]. Additional studies of middle ear effusions have found an inflammatory profile with Th2 cytokines that parallels that of allergic rhinitis and asthma [23, 28, 29]. In addition, activated mast cells and Th2 lymphocytes which produce IL-4, IL-5, and IL-13 (also observed in asthmatic airway inflammation) have been found in the middle ear. In fact, when patients are affected by inflammation in one part of the unified airway, it is important to evaluate other areas of it as well, since it could portend a more diffuse inflammatory process.

Allergic Rhinitis and Otitis Media in Children

The association between allergic rhinitis and otitis media within the pediatric population has been the topic of many investigations. Some studies have shown that allergy is associated with a 2- to 4.5-fold increased incidence of OME, as compared to the non-allergic state [30]. A single-center prospective birth cohort study of children born to asthmatic parents in Denmark demonstrated that OME was associated with allergic rhinitis with an odds ratio of 3.36, but was not associated with other factors such as nasal swelling, nasal eosinophilia, non-allergic rhinitis, asthma, and eczema [31]. Similarly, Kwon determined that allergic rhinitis was more frequently seen in patients with OME than without (33% vs. 16%, $p < 0.05$) [32].

They also found that rates of allergic rhinitis and asthma were significantly higher in those who had serous effusions compared to mucous effusions [32], suggesting that the inflammatory milieu may vary in patients with atopy with subsequent changes in the viscosity of the effusion. Rhinitis at 6 years of age has also been associated with recent OME, as well as with OME occurring in the first 2 years of age [33]. Usonis et al. also found an association of otitis media and allergy among children in Eastern Europe (OR 1.64), although the authors studied AOM and did not look independently at OME [34]. A prospective study by Passali et al. looked specifically at a correlation between nasal allergy and otitis media by studying children with otologic symptoms and evaluating for presence of allergy based on examination, tympanometry, skin prick testing, eustachian tube function, and mucociliary transport time. They found that mucociliary transport time was affected in those with more persistent allergy. Mean blood eosinophilic cationic protein (ECP) levels were also higher in those who were atopic. In patients with allergic rhinitis who required myringotomy, the level of ECP in middle ear effusions was even higher than that of blood. Furthermore, specific IgE levels for certain allergens were found within OME, which implied direct involvement of the middle ear mucosa as a target organ for allergy [35]. Other publications have additionally gone further and suggested that allergy may even lead to impairment of defense mechanisms of the respiratory epithelium, perhaps by altering toll-like receptor mediated immunity, which has been thought to reduce the risk of Th-2 mediated allergic responses [36]. A recent meta-analysis of seven studies evaluating the association between allergy and OME by Cheng et al. showed an increased odds ratio (OR 3.94) for the presence of allergy in OME compared to healthy controls [37•]. However, the quality of the data was somewhat questioned by this group of authors and a high level of inter-study heterogeneity was noted.

Multiple other publications have denied a relationship between allergy and OME in the pediatric population. A birth cohort study by MacIntyre et al. in 2010 showed no consistent association between early life otitis media and allergic rhinitis [38]. In the sixth year of life, there was a positive association between the two, but a temporal relationship could not be established [38]. Admittedly, this study did not differentiate between AOM and OME, which may have influenced the assessment of a connection. A subsequent study by MacIntyre in 2012 supported the hypothesis that frequent otitis media in childhood may be associated with an increased risk of asthma and possible atopic eczema, but this same link did not exist for allergic rhinitis [39]. The observed response of OME to anti-histamine therapy also raises doubt about its relationship to allergy. No lasting benefit and some harm from anti-histamines has been reported when these anti-allergy agents are used for treatment of all patients with OME [40, 41], although treatment of a subset with allergic rhinitis has

not been definitely studied. Because of these findings, multidisciplinary clinical practice guidelines developed by representatives from the American Academy of Otolaryngology-Head and Neck Surgery Foundation, the American Academy of Family Practitioners, and the American Academy of Pediatrics recommend against treating OME with anti-histamines, oral steroids, and intranasal steroids [4, 42•, 43•]. If allergic rhinitis was a straightforward risk factor for OME, one would expect that desensitization and allergy management would be effective treatments for OME, but this has also not been shown to be the case. Thus, while a preponderance of the recent literature has suggested an association between allergic rhinitis and OME in the pediatric population, there is still some doubt, particularly about causation.

Age Is an Effect Modifier of the Association Between Allergic Rhinitis and Otitis Media

A more recent epidemiological study tested the hypothesis that age is an effect modifier which alters the relationship between allergic rhinitis and OME, such that there is a significant association in one age group but no association in another. These national data showed that in children 6 years of age or older, the presence of allergic rhinitis was associated with a significantly increased odds of OME, Eustachian tube dysfunction, and tympanic membrane retractions (OR 4.20, CI 2.18–8.10, $p < 0.001$) [22••]. However, in children less than 6 years of age, no significant association was observed (OR 1.14, CI 0.53–2.46, $p = 0.745$) [22••]. With these data now available, it becomes apparent in retrospect that multiple studies which demonstrated a relationship between OME and allergy were conducted in older children [35, 44], while the lack of relationship was often seen in studies evaluating younger children [38, 39]. Hopefully, future studies focused on OME, allergic rhinitis, and related therapeutics can be performed to further evaluate the impact of age as an effect modifier through further analyses.

Additional studies have assessed the role that age may play in a correlation between allergy and otitis media, although data are limited and sometimes conflicting. One multivariate analysis showed that although there was a significantly higher prevalence of OME in subjects age 4 to 12 years of age with allergic rhinitis, as compared to those with without it, age itself was not an independent risk factor for OME [45••]. Other data suggest that in children at least 5 years of age, a resistant OME is more likely to be from an allergic or atopic etiology [23, 28, 29]. Mahdavinia et al. (2013) compared different age groups of patients affected by chronic rhinosinusitis and found multiple differences in the pathophysiology, immune function, comorbid conditions, histopathology, presence of biofilms, and varying microbial profiles, as well as the inflammatory

pathways involved [46]. While this study focused on chronic rhinosinusitis, it is possible that these age-related findings would also be seen in allergic rhinitis and potentially alter its impact on OME. Further study is warranted to better delineate the endotypes of disease which may facilitate more patient-specific treatment paths.

Evolution of Immune System and Mucins with Age

In human development, the immune system grows and matures with age. This maturation impacts both allergic rhinitis and otitis media. Allergic rhinitis has an increasing prevalence from infancy to adolescence. Male gender, personal history of eczema, wheezing, and elevated atopy markers also contribute to increased risk of allergic rhinitis [33, 47, 48]. The prevalence then decreases over time: 45% at age 21 to 40 years, 30% at age 41 to 60 years, and 15% at age 61 to 86 years [49••]. It is thought that early life events and exposures play a role in programming the immune system. This exposure allows for production of specific IgE antibodies and a hypersensitivity response. Children living Western lifestyles are thought to have less regulatory T cell function, and since they are being exposed to increasing antigens over time, it may partially explain the rising rates of allergy and atopic disease in younger individuals [50•].

The evolution of the immune system during childhood also impacts otitis media. For example, when the immune system is immature, there is an increased risk for infection, including AOM [51]. Furthermore, when the immature immune system is supplemented with the immunomodulatory, anti-inflammatory, and anti-microbial agents in maternal breast milk, that susceptibility is mitigated. Infants who were breastfed exclusively for the first 6 months of life showed 43% less risk of AOM by the age of 24 months when compared to infants who were not exclusively breastfed [52••]. In addition, as the immune system and Eustachian tube function matures, there are higher rates of spontaneous resolution of OME [12]: 22% at 1 year of age, 37% at 2 years, 50% at 3 years, 60% at 4 years, 70% at 5 years, 85% at 7 years, and 95% at 10 years [53]. Similarly, Lack et al. showed that the percentage of bilateral type B tympanograms decreased from 28% at 8 months to 12% at 43 months and 7% at 61 months [41], all showing a decrease in the prevalence of OME with increasing age.

Interestingly, mucin types differ with age. Mucins are large glycoproteins that adhere to bacteria and activate host defense interactions, promoting removal of bacteria via the mucociliary transport system [54]. The mucins with the most notable airway association are MUC5B and MUC5AC [55••]. MUC5B is more common in the middle ear, and data have

shown it is present in 100% of mucoid effusions, as compared to 57% of serous effusions. Both mucoid effusions and MUC5B-positive status are more frequent in children younger than 4 years of age, as compared to older children ($p = 0.038$, $p = 0.045$). MUC5AC is stable across age groups. Thus, the inflammatory milieu and mucociliary transport activation may also vary with age.

Evolution of the Adenoid with Age

The adenoid has also been evaluated as a possible link between OME, Eustachian tube dysfunction, and allergic rhinitis. Adenoid tissue forms a portion of Waldeyer's ring, the circle of lymphoid tissue in the pharynx. The adenoid is a single midline structure, whose lateral borders are positioned adjacent to the crus of the torus tubarius and Eustachian tube orifice. The adenoid increases in size until approximately 6 years of age and then slowly atrophies over the next few years; typically beginning around puberty and nearly disappearing by 16 years of age [56]. The adenoid also contains organized germinal centers which support its role as a lymphoid structure. Thus, while adenoid hypertrophy has been proposed to lead to Eustachian tube dysfunction by physical obstruction due its position in the nasopharynx, the adenoid may also have an immunomodulating function [57, 58•, 59]. Older children with a more mature immune system have differing adenoid profiles than younger children. In Quaranta's analysis, a negative correlation between age and the presence of bacteria and neutrophils from nasal cytology was noted [30, 57]. This finding occurred independent of adenoid size. Also, not all children with adenoid hypertrophy develop OME, suggesting an alternative possibility of local inflammatory mediators or biofilm as a potential link between otitis media and adenoid hypertrophy [60].

Studies have also shown that children with OME have higher levels of histamine in their adenoid tissue and higher levels of subepithelial mast cells, as compared to children without OME [57, 59, 61]. Caffarelli also showed higher rates of nasal eosinophils in OME as compared to control, though no adenoid-specific evaluation was made in their study [62]. Interestingly, a significant inverse correlation between nasal eosinophils and OME was noted in children affected with adenoid hypertrophy in other data [57]. While chronic rhinitis and OME are both common in children with adenoid hypertrophy, combined nasal cytology and skin prick testing could not identify a statistically significant association with allergic rhinitis per se in Quaranta's analysis. Regardless, data from randomized controlled trials have supported clinical practice guidelines which recommend adenoidectomy as an option to treat chronic, symptomatic OME in children over 4 years of age [4, 12].

Eosinophilic Otitis Media: an Adult Phenomenon

Eosinophilic otitis media (EOM) is an example of the unified airway theory manifesting in adult patients. This form of OME was first described by Tomioka et al. [63] and the diagnostic criteria for EOM were developed in 2011 [64]. This entity is a refractory form of otitis media that is found in adults with bronchial asthma with a female:male ratio of 2:1 [64]. Major diagnostic criteria include the identification of eosinophils from the middle ear mucosa on histology or cytology. Minor criteria include the association of bronchial asthma and nasal polyposis, highly viscous yellow effusions, and resistance to more conventional treatment for otitis media [64]. For example, due to the viscosity of effusions, the lumen of a tympanostomy tube may be easily blocked. This disease process confers a high rate of hearing loss overall, with a 6% rate of complete deafness [64]. Besides the association with bronchial asthma, there is a high association with eosinophilic rhinosinusitis, which is also thought to arise from a Th2 inflammatory pattern. Histology of patients with EOM shows high levels of IgE and other eosinophilic chemoattractants. Levels of IL-5 (involved in eosinophil activation and cell survival) and eotaxin in OME were higher in patients with EOM than controls [65]. In patients with EOM, the concentration of eosinophilic cationic protein (ECP) was higher in the sampled effusion than in their serum. These factors were detected at the mRNA level, not only at the protein level, suggesting that the eosinophilic inflammation occurs in the middle ear itself [66]. Similarly, Kanazawa et al. in 2014 suggested that antigen-specific IgE can be locally produced in the middle ear mucosa in patients with EOM [67], further supporting the middle ear as a component of the unified airway.

Since similar pathophysiology affects the unified airway, it may be that treatment options for bronchial asthma may also be effective for this form of otitis media. Omalizumab (Xolair®, Novartis, Basel, Switzerland) is a recombinant DNA-derived humanized IgG1 monoclonal antibody that binds to IgE antibodies. It has been approved for severe allergic asthma and chronic urticaria, but many off-label uses also exist [68], and it is expected to improve conditions associated with eosinophilic inflammation. In 2012, Okude published the first case report of a patient with severe asthma and EOM. In this case, the patient experienced improved symptoms in both EOM and asthma with treatment of omalizumab [69]. Subsequent studies have showed improvement in clinical scores and disappearance of middle ear effusion following at least 3 months of treatment with omalizumab. Eosinophil cationic protein concentrations were decreased following treatment as well [70, 71]. This targeted treatment thus shows promise in treatment of EOM.

The Potential Impact of Age on the Relationship Between Allergic Rhinitis and Otitis Media in Adults

As noted above, EOM is an adult phenomenon, typically diagnosed between 50 and 60 years of age. Bronchial asthma for these patients also seems to develop in adulthood, typically earlier than the middle ear manifestations. Similarly, rhinosinusitis also develops earlier than EOM, often more than 10 years before [72••].

Separate from the specific entity of EOM, the association of allergy and otitis media among adults in Iran was studied by Nemati et al. [73••]. Here, patients with allergic rhinitis and non-allergic rhinitis had a 3.27- and 2.57-fold increased risk of developing ear disease compared to healthy individuals ($p = 0.048$), suggesting allergy worsens OME risk. Allergic rhinitis was defined by the presence of multiple clinical symptoms as well as by positive skin prick testing. Interestingly, when looking only at patients with positive skin prick testing (without including clinical diagnosis), there was no association with OME ($p = 0.23$) [73••].

Challenges in Comparability Across Studies

Heterogeneity among studies also makes it difficult to generalize results across studies, which encompass diverse patient populations and diagnostic methods. Age ranges have been quite variable among studies, as OME and allergic rhinitis affect both adults and children [4, 6••, 15•]. In addition, allergic rhinitis can be diagnosed by history alone, nasal cytology, specific serum IgE testing, skin prick testing, and intradermal testing. Each of these methods carry their own benefits as well as some barriers. For example, IgE serum-specific testing is more expensive, takes longer to obtain results, and may be less sensitive when compared to skin testing. However, it is better tolerated in children, many of whom do not tolerate multiple skin pricks or intradermal testing. Therefore, diagnostic methods may differ with age, making it difficult to obtain uniform assessments across all age groups.

Similar diagnostic challenges exist for the diagnosis of OME. Here, diagnosis can be made by otoscopy alone, pneumatic otoscopy, tympanometry, or middle ear sampling (tympanocentesis). Tympanometry is a simple and atraumatic test that evaluates compliance of the tympanic membrane. While this is fairly well tolerated by most, results are less reliable in very young children [74]. Because of the invasive nature of tympanocentesis, it is typically reserved for cases in which it can be therapeutic as well; this procedure may be done more readily on awake adults, but typically requires general anesthesia in children. Similar findings are noted with otoscopic examination with some variability in the sensitivity of the examination, particularly with young children. Given

that studies performed to identify the link between allergic rhinitis and OME use a variety of diagnostic testing and assessment methods, it is more challenging to compare outcomes due to lack of standardization, which may impact the ability to demonstrate consistent conclusions on this topic across studies.

Conclusion

The relationship between otitis media and allergy remains controversial and may be influenced by patient age. In the pediatric literature, multiple studies have proposed a link between allergic rhinitis and OME, and results are mixed. More recent data have suggested that age is an effect modifier, such that an association exists within older pediatric age groups, but not others. The adult literature is more limited and highlights the entity of eosinophilic otitis media, a disease process which supports the unified airway theory. The current literature demonstrates much variability in age groups and diagnostic criteria in studies, making it difficult to draw consistent conclusions across reports. Future research would ideally further focus on how the relationship between OME and allergic rhinitis specifically differs with age and age-related factors.

Compliance with Ethical Standards

Conflict of Interest Rachel Roditi is a consultant on clinical trials for Knopp, Allakos, Sanofi and Roche Genentech in the study of nasal polyps. Jennifer Shin receives textbook royalties from Evidence-Based Otolaryngology, Shin JJ, Randolph GW, editors; New York: Springer, 2008, and from Otolaryngology Prep and Practice. Shin JJ, Cunningham MJ, editors; Plural Publishing, 2013. JJS is a recipient of the American Academy of the Otolaryngology-Head and Neck Surgery Foundation Maureen Hannley grant, the Brigham Care Redesign Program Award, and the Schlager Family Innovations Fund Award.

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