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POSITION PAPER

Otitis Media With Effusion (OME) and Eustachian Tube Dysfunction: The Role of Allergy and Immunity—An EAACI Position Paper

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ABSTRACT

IgE-mediated allergies play a significant role in respiratory diseases. Given the similar mucosal epithelium of the upper and lower respiratory tracts and their shared (patho)physiological immune responses, the "unified airways" concept views these tracts as a single system. Recently, this model has been extended to include the middle ear, with studies confirming that the Eustachian tube and middle ear are both anatomically and functionally part of the upper airways. However, the relationship between allergies and middle ear disorders remains controversial, with conflicting findings regarding pathogenesis and treatment. The increasing prevalence of allergies highlights the importance of further research. In Germany, the current sensitization rate to aeroallergens is 33.6%, with similar trends across Europe, where rates commonly range up to 30%. This widespread increase underscores the urgent need for a deeper understanding of the correlation between allergies and middle ear disorders across diverse European populations. Ineffective pharmacotherapy or possibly harmful medication for acute and chronic OME, such as systemic steroids, is most likely used globally in an uninformed way, due to a lack of evidence on the connection between allergic inflammation and eustachian tube dysfunction. Further research is essential to clarify the mechanisms linking IgE-mediated allergies to middle ear pathologies and to develop effective treatment strategies. Addressing these knowledge gaps is critical for improving patient outcomes and managing the rising burden of allergic diseases.

Abbreviations: AIT, allergen immunotherapy; APC, antigen presenting cells; AR, allergic rhinitis; DC, dendritic cells; ECP, eosinophilic cationic protein; eOM, eosinophilic otitis media; ET, eustachian tube; ETD, eustachian tube dysfunction; ETDQ7, eustachian tube dysfunction questionnaire; IDT, intradermal dilutional testing; Ig, immunoglobulin; IL, interleukin; INCS, intransal corticosteroids; LPS, lipopolysaccharide; MBP, major basic protein; MCTt, mucociliary transport time; MEE, middle ear effusion; NK cells, natural killer cells; OME, otitis media with effusion; OVA, ovo-albumin; PAMP, pathogen associated molecular pattern; The cells, T-helper cells; TLR, toll-like-receptor; TMM, tubomanometry.

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1 | Nasal Immunity

Innate immune system and mucosal barrier: The local immune system of the nose includes mechanical as well as non-specific cellular and humoral defense mechanisms [1]. The nasal mucociliary functional unit, which serves as a clearance system of upper and lower airways, acts as the first line of defense. Intruders, such as microbes, foreign particles, and irritants, are trapped in a layer of mucus containing antimicrobial substances (e.g., IgA, enzymatic proteins), which are then combatted and eliminated by ciliary movements. Antimicrobial peptides, interleukins, and complement components contribute to the inactivation of intruders at the humoral level [2]. At the cellular level, granulocytes, macrophages, and natural killer (NK) cells play a crucial role as depicted in Figure 1.

This article aims to shed more light on the current data situation regarding previous findings on the connection between allergic rhinitis (AR), immunity, and middle ear diseases.

2 | Allergic Rhinitis

With a prevalence of reported AR in the world population ranging from 15% to 25%, AR is a widespread disease [3]. In Europe, the prevalence of AR is estimated up to 30% [4, 5]. Typical secondary or concomitant diseases are chronic sinusitis, pollen-associated food allergy syndrome, and bronchial asthma. Inflammation of the middle ear is rarely mentioned in this context, although there are numerous recent indications of an association (Figure 2). Many epidemiological studies have confirmed that AR –and especially persistent AR [6] is a risk factor for the development of otitis media with effusion (OME) in children [7–12]. A meta-analysis including 24 trials showed allergy or atopy as a significant risk factor for chronic and recurrent otitis media [13]. In a birth cohort study with 411 children of asthmatic mothers, an association between OME and AR was observed [14]. A recent study found among 159 children with AR twelve (7.5%) with tympanic effusion (OME). By clear contrast, among 185 children without AR, the study only found three (1.6%) with serous effusion (OME) [15]. Serous effusions appear to be more frequently associated with AR than mucous effusions [9].

3 | The Development of the Middle Ear In Utero

According to the "unified airway" model, the middle ear is often described as an extension of the respiratory tract [6, 11, 16, 17].

FIGURE 2 | Secondary or concomitant diseases of Allergic Rhinitis (AR): In addition to AR, an allergy to aeroallergens can also be associated with Middle Ear Effusion (MEE), Chronic Rhinosinusitis (CRS), Rhinitis, Oral Allergy Syndrome (OAS), or Conjunctivitis.

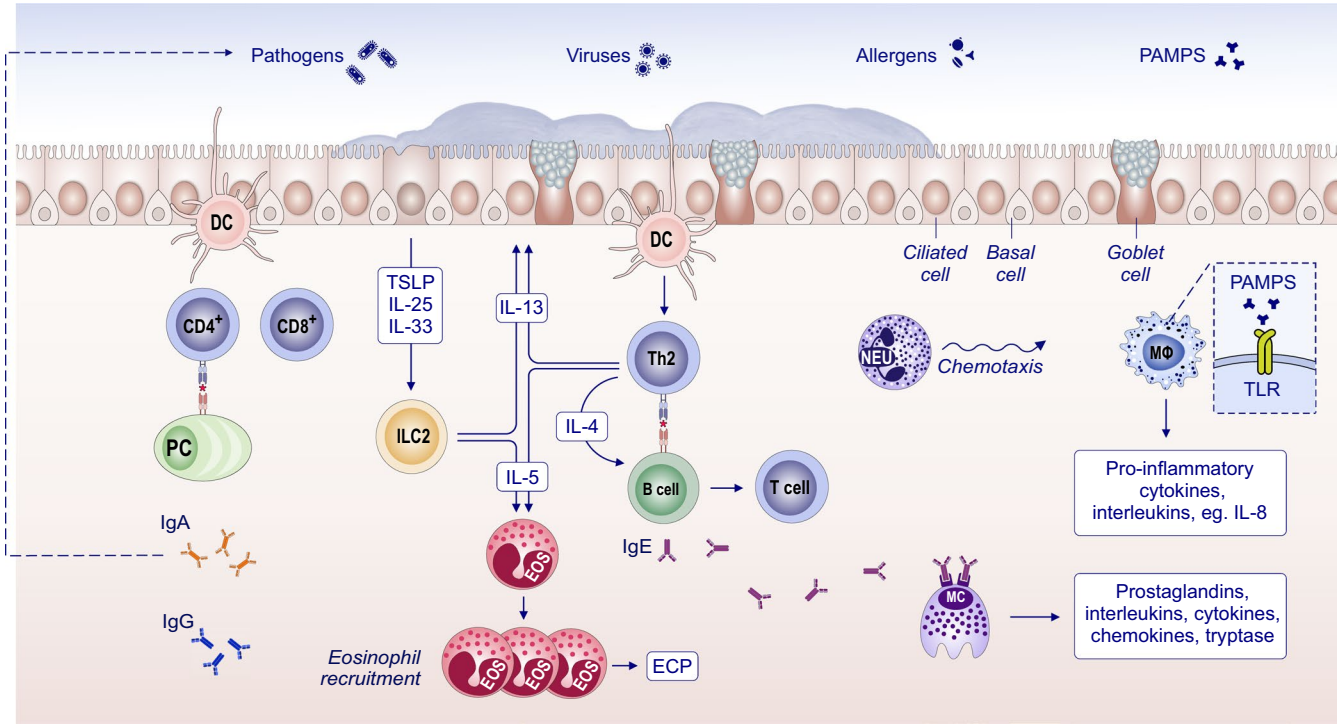

FIGURE 1 | Graphical illustration providing an in-depth depiction of nasal immunity detailing innate and acquired immune components, illustrating both cellular and humoral mechanisms. DC, dendritic cells; ECP, eosinophil cationic protein; EOS, eosinophilic cells; IL, interleukin; ILC2, type 2 innate lymphoid cells; MØ, macrophage; PAMP, pathogen associated molecular pattern; PC, plasma cell; TCR, T-cell receptor; TLR, toll-like receptor; TSLP, thymic stromal lymphopoietin.

The middle ear mucosa develops from the same ectoderm as the upper airway epithelium [18] and histologically consists of the same ciliated pseudostratified columnar epithelium [16, 19]. Therefore, evolutionary the middle ear is developed in the same way as the upper airway. Hurst and Venge describe it as "fifth sinus which happens to harbor the organ of hearing" [20].

4 | Otitis Media With Effusion

4.1 | Characteristics of Otitis Media With Effusion

OME (synonyms: seromucotympanon, seromucous otitis media, secretory otitis media, chronic tube middle ear catarrh) is characterized by a non-purulent serous or mucous middle ear secretion [21]. It is usually painless and shows no signs of infection [21]. Often—and more frequently in allergy sufferers than in non-allergy sufferers [20]–it occurs after an acute otitis media, but can also present without previous signs of infection [22] and remains undetected by approximately 40%–50% of those affected [10]. OME is one of the most common childhood diseases and the most common cause of hearing impairment and language development delay among children in industrialized countries, with relevant educational implications for speech and reading development [23–25]. Chronic OME is defined as OME with a duration of 3 or more months. The diagnosis is usually carried out otoscopically and using tympanometry. Clinically relevant hearing impairment should be assessed using otoacoustic emissions or audiometry, depending on the patient's age.

4.2 | Epidemiology and Association With Allergic Rhinits

Epidemiological studies have found 30%–50% of children with middle ear effusion (MEE) to have AR [9, 12, 26–28], whereby atopic children seem to be predisposed to bilateral tympanic effusions: a study found that among 310 children aged 5–6 years and screened for OME, almost 80% of the atopic subjects had bilateral OME versus 56% in the non-atopic group [27]. Depending on the methodology, the percentage of children with seromucotympanum and a positive allergy test varies between 29% and 100% [7, 11, 29], although the wide range could be based on different conceptual criteria, for example, different diagnostic methods, age, or ethnic groups, respectively. Two studies, in which a clear distinction was made between allergic sensitisation and allergic disease, document an association between OME and AR, but not between OME and a positive prick test [26, 30]. Sensitisation to inhalant allergens is more often associated with OME than sensitisation to food. Hurst et al. showed in a study of 29 patients with OME that 20 patients had sensitisation only to airborne allergens, two patients only to food allergens, and nine patients had sensitisation to both [31]. Moreover, nasal congestion and rhinorrhoea are common respiratory manifestations of acute food allergic reactions in early childhood [32, 33]. Early life otitis media has been shown to be associated with asthma and eczema in a birth cohort [34].

The results of a recent American cross-sectional retrospective database study [35] with an analysis on 1.5 million datasets show a significant positive association between MEE and AR in children aged 6 years and older, whereas in younger children there was no such association. Yang et al. reported in a study on 887 children a significant correlation between atopy and OME compared to non-atopic children [36]. Conversely, in another study from New Zealand on 89 patients, the prevalence of AR in 6- to 7-year-old children with OME was equal to that of the control group [37], suggesting a limited influence of allergy in the pathogenesis of OME in this age group. The age factor thus appears to have a modulating effect on the influence of AR on OME [35]. This finding is congruent with the observations that the anatomical immaturity, in particular a more horizontal position and shorter length of the Eustachian tube in childhood, may play a greater role in the development of infection-related rather than allergy-related otitis media with effusion [38] and that the prevalence of OME decreases with age [10]. Also, the onset of age for AR may play a role in this paradox.

4.3 | Etiology and Risk Factors for Otitis Media With Effusion

OME is usually the result of a viral infection such as the common cold or a tube ventilation disorder due to mechanical or functional disability that has lasted long enough to impair clearance. The etiology is often multifactorial and is based on complex interactions between viral and/or bacterial pathogens and environmental or genetic factors [18]. Other possible causes are adenoids, septal deviation, and turbinate hypertrophy [39], ciliary dysfunction, rhinosinusitis, gastroesophageal reflux [40, 41], craniofacial malformations, tumors, and immunological disorders [21]. Adenoids as a possible cause of OME are well known, but others like turbinate hypertrophy and CRS are still under debate, and clearer evidence is needed. Atopic diseases had often been underestimated as a risk factor for recurrent and persistent otitis media in the past [42]. Allergy, with a 2–4.5 higher incidence for OME compared to healthy children, is a much higher risk factor than the other risk factors mentioned [8]. A child with atopic predisposition and acute otitis media thus has a 3-fold higher risk of developing OME than a non-atopic child [18]. Juszczak et al. recently reviewed a strong relationship between AR and Eustachian tube dysfunction (ETD) [43].

5 | Eustachian Tube Function

Nose and middle ear form an anatomical and functional continuum via the Eustachian tube (ET) [44]. The ET plays a key role in regulating the air pressure in the middle ear in relation to atmospheric pressure in the ear canal, allowing an unhindered vibration of the eardrum with optimal transmission to the inner ear via the ossicular chain [45]. In addition to this perhaps most important function of middle ear ventilation [46], ET protects the middle ear from barotrauma, has a drainage function for middle ear secretion, and a mechanical and immunological protective function [44, 47]. The drainage of middle ear secretion is carried out by the mucociliary transport system of the respiratory epithelium, which lines the cartilaginous tube section and prevents the penetration of pathogens [44, 48] (Figure 3).

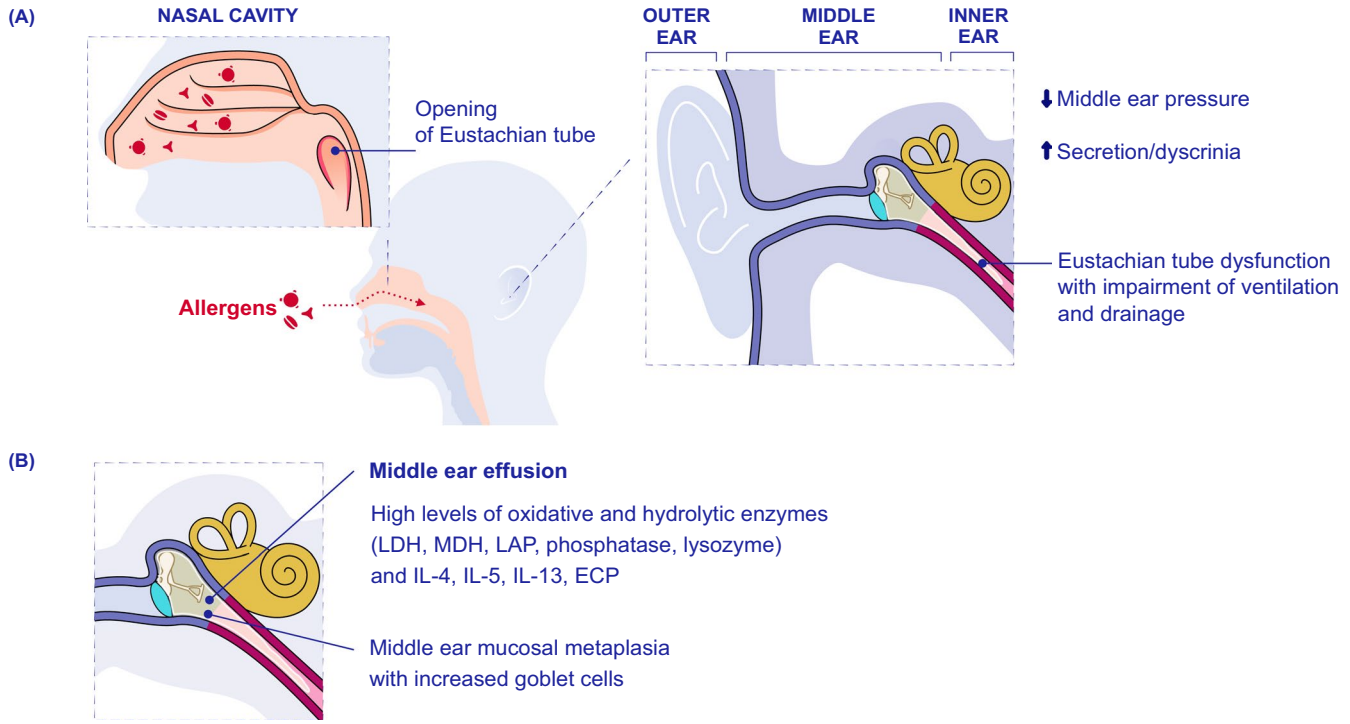

FIGURE 3 | Eustachian tube function: Pathophysiological relationship between allergic rhinitis (AR) and otitis media with effusion (OME): (A) Eustachian tube dysfunction with ventilation and drainage impairment. Negative pressure in the middle ear. Increased secretion/dyscrinia. (B) Middle ear mucosal metaplasia with increased goblet cells. Middle ear effusion containing oxidative and hydrolytic enzymes (LDH, MDH, LAP, phosphatase, lysozyme) and ILs (e.g., IL-4, IL-5, IL-13, ECP) are detectable in the secretion as typical effectors of Type II inflammation.

5.1 | Factors Contributing to Eustachian Tube Dysfunction

Ohiri et al. reported in a cohort of 106 adults with eosinophilic otitis media (eOM) that various anatomical aspects favor the development of ET dysfunction (ETD), for example, low angle and short length of the ET as well as the absence of peri-ET air cells or petrous apex cells [49]. Tubal dysfunction is defined as either an obstruction, abnormal patency of the tube, or an inadequate function of the ciliated tubular epithelium [50]. Abnormal patency of the eustachian tube causes symptoms similar to obstruction and can be detected visibly as respiration-synchronous movements of the ear drum. However, apart from impairment of quality of life, no harm is connected to this abnormality [51]. Inflammatory causes for tube dysfunction cause obstruction either due to swelling of the tubal and adjacent mucosa, altered mucociliary activity, or hypersecretion of seromucosal glands [22]. As outlined above, the anatomy of the skull and skull deformities, skull bone development and growth, trauma and surgery, as well as gravity and hydrostatic pressure will have influence on middle ear drainage to a greater or lesser extent [52]. While there is insufficient evidence in terms of controlled studies about the influence of upper body position on eustachian tube drainage, it might be disadvantageous to feed children in a supine body position; however, also the duration of breastfeeding was influential in an opposite way [53]. Any obstruction results in persistent negative middle ear pressure conditions, which in turn can lead to increased oxygen absorption by the middle ear epithelium, accumulating secretion production in the middle ear, and eardrum retraction or atelectasis [50]. All these factors and mechanisms promote the development of OME.

5.2 | Impact of Allergic Inflammation on Eustachian Tube and Middle Ear

Various mechanisms are described by which a nasal allergic inflammatory process can contribute to the development of a chronic OME [48, 50]: either the allergic inflammatory process can be localized in the mucous membrane of the tube and/or middle ear, or it can take place in adjacent tissues such as the nasopharynx, adenoids, or lymphatic tissue. An allergic inflammatory process that primarily takes place in the nasal mucosa can affect the tube and middle ear in two ways [50]: (1) by the release of mediators, cytokines, and other factors that migrate into the nasal secretion and further towards the tube ostium, or (2) by a primary AR, characterized by nasal mucosal oedema and nasal hypersecretion due to epithelial barrier defects. This makes the mucosa less resistant against pathogen intrusion, leading to a higher risk of recurrent infections [54, 55]. The oedema expands to the nasal tube ostium or leads to nasal obstruction, which indirectly affects tube ventilation. Interestingly, Merkulova et al. recently reported in a study with 100 children with different forms of AR that the prevalence of ETD accounted for the high number of over 30% in these patients, mainly on both sides, regardless of the subtype of AR [56]. Pediatric hyperplastic adenoids are also frequently linked to allergic conditions such as allergic rhinitis. Chronic allergen exposure triggers immune responses that contribute to lymphoid hyperplasia, leading to airway obstruction and recurrent infections. Studies suggest that children with allergies have a higher prevalence of adenoid hypertrophy, indicating that managing allergies may reduce adenoid size and related complications. Moreover, studies show that

allergic children often experience more severe symptoms after adenoidectomy, implying that underlying allergic inflammation plays a key role in adenoid pathology. This suggests that simply removing the adenoids may not be sufficient, as the persistent immune response continues to contribute to symptoms. Therefore, treating the underlying allergy is crucial to achieving long-term symptom relief and preventing adenoid-related morbidity [57–62].

5.3 | Connection Between Allergic Rhinitis and Eustachian Tube Dysfunction

The connection between AR and ET obstruction has been proven in many studies (reviewed in [63]) and demonstrated by nasal provocation tests [48, 57, 64, 65]. Depending on the extent of the allergic inflammatory process, the transient opening of the tube may also be blocked during the swallowing process [64]. However, researchers were unable to induce OME after several nasal provocation challenges with aeroallergens consecutively over 4–5 days (in humans and animal models) [28, 52, 57, 66], but this was possible in adults aged 20–31 years; thus, it is not clear which factors are most relevant. There is a general agreement that prolonged allergen exposure and/or tube ventilation dysfunction is necessary to induce OME [57, 64, 66], and it may be that it is due to a combination of both factors.

This brings air quality, pollution, and environmental factors in general into consideration, which should be acknowledged when assessing patient history. There are indicators that air pollution and high exposure to allergens will have a negative impact on eustachian tube function, although this cannot be linked to one specific factor [67]. This hypothesis is supported by a comparative study of mucociliary transport times between intermittent and persistent AR in children with OME or other ear problems that showed significantly longer transport times in persistent than in intermittent AR [6].

In general, patients and especially children with AR have a higher risk of tubal dysfunction [63, 68], not least because of the impairment of tubular mucociliary activity [6, 38]. This, and the resulting negative pressure in the middle ear, can facilitate possible reflux or aspiration of bacteria from the nasopharynx [38]. In addition, the impaired epithelial barrier function of the nasal mucosa due to AR increases the susceptibility to infections. The dysregulated epithelial cell repair process leads to prolonged impairment by mucosal oedema, derived from the nasopharynx and tubal ostia [46]. Infections can be more easily transmitted to the middle ear, which is also supported by the fact that bacteria were detected in over 70% of children's tympanic effusions [38]. According to a 2015 study, the detection rates of bacteria do not differ between allergic and non-allergic children [38]. However, atopic children are more prone to recurrent OME after medical treatment and/or adenoidectomy than non-atopic children [6]. The question of bacterial infection possibly leading to acutely exacerbated otitis media, with or without fever, points out that different subcategories of middle ear inflammation need to be accounted for.

Simple ETD without effusion, chronic sterile and indolent effusion, recurrent acute otitis and its complications are all possibly affected by the presence of nasal pathologies and chronic sinonasal inflammation. A meta-analysis from De Corso et al. linked allergic inflammation to children with OME and acute re-exacerbations with MEE, which should be considered in the diagnostic workup of the respective diseases [69]. A more recent controlled prospective study observed differences neither in the incidence of AR nor in the number of eosinophils and IgE concentration in serum and tympanic secretion in children with and without OME. Moreover, nasal provocation had no effect on tube function in the group of patients with AR [70].

For the evaluation of ETD, the tubomanometry (TMM) may be utilized. In a recent study from Oehlandt et al. data on 219 patients revealed that TMM results are affected by pollen allergy and by any other criteria examined [71]. A prospective cross-sectional study on 118 patients with AR due to house dust mite allergy or healthy controls revealed that 33.9% of patients with AR and 5.9% in the control group had an ETD according to EDTQ-7 and TMM. One month of treatment with antiallergic drugs including intranasal corticosteroids (INCS) and antihistamines in the AR group resulted in significant improvement of ET function [72].

6 | Hearing

Some studies have examined the influence of AR on hearing capacity [27, 50]. In young adults (16–26 years) with a history of bilateral chronic OME since childhood and suspected allergy, significant decreases in middle ear pressure and hearing threshold were observed after nasal allergen provocation [50]. In 300 5–6-year-old children with OME over a period of > 3 months, the prevalence of flat tympanograms and lower hearing thresholds was significantly higher in atopic (at least one positive reaction in skin prick test) compared to non-atopic children [27]. A retrospective study by Callioglu et al. [73] compared the surgical success of tympanoplasty for OME in patients with and without AR. There was no significant difference for patients with and without AR.

Plenty of studies have shown that the human middle ear system is capable of an allergic inflammatory process comparable to that of the paranasal sinuses and upper airways [19, 20, 74, 75]. Hurst and Venge [20] and Sobol et al. [29] provided evidence of increased Th2 cytokine expression and eosinophilic and mast-cell mediators in tympanic effusions. Analogously, mast cell myeloperoxidase in the tympanic secretions of children with objectively documented allergy was statistically significantly higher than that of non-atopic children [76]. Nguyen et al. detected comparable Th2-typical cytokine and cell profiles in the middle ear and nasopharynx region of atopic children [77].

7 | Evidence of Late-Phase Allergic Immunity in EOM

The allergic late phase is characterized by the influx of eosinophils and eosinophil cationic protein (ECP), but also IL-4, IL-5, and other cytokines [18, 74]. In studies of atopic children with chronic OME, significantly increased ECP levels were measured in the MEE compared to non-atopic children;

similarly, ECP values were higher in the serum of atopic versus non-atopic children [6, 76]. This suggests a direct involvement of the middle ear mucosa as the target organ for an allergic inflammatory response [6, 76]. ECP worsens ciliary function and consequently also ET clearance [18]. In accordance with this, Passali et al. found a significant association between ECP values in the MEE and a delayed mucociliary transport time (MCTt) [6].

Apart from increased numbers of eosinophils and T lymphocytes in the tympanic secretion of atopic patients, several controlled studies document significantly increased IL-4 and IL-5-expressing cells [17, 29, 78]. The detection of IL-5 mRNA and the eosinophil mediator MBP (Major Basic Protein) in the middle ear mucosa biopsy [79] provides strong evidence that the middle ear is actively involved in a Th2 response [18, 79].

8 | The Role of Eosinophils Promoting OME

Eosinophilia can persist if there is continued exposure to allergens, resulting in permanent mast cell degranulation [18, 80]. Analysis of middle ear mucosa and secretion of atopic patients with chronic OME shows a predominance of eosinophils and high IL-5 levels, which are characteristic of the late-phase allergic response [74, 81]. Hurst states that OME is often an IgE-mediated late-phase disease [18]. However, the mere presence of eosinophils is not specific for an IgE-mediated disease, but rather may reflect a non-IgE-mediated hypersensitivity [18]. ECP and MBP detected in middle ear secretion are also typical of particularly refractory forms of asthma and rhinosinusitis [18]. An eOM mouse model demonstrated that allergy caused significant changes in the pathology and morphology of the ET mucosa, affecting the normal function of the ET, which played an important role in the occurrence and development of eOM [82].

In summary, chronic OME in atopic patients, analogous to asthma and AR, is characterized by an allergic pattern cell profile with an increase in Th2 cytokines [77]. The meanwhile significant data presented above indicates that chronic OME in atopic patients can be a local allergic immune reaction [74]. This is also supported by observations in animal models, showing that allergy-specific inhibitory cytokines can prevent the production of middle ear secretion [83].

9 | Role of IgE and Other Diagnostic Tests in OME

Hurst et al. detected specific IgE in the middle ear secretions of children and adults with OME [20]. Studies have confirmed a correlation between IgE in the serum and IgE in both recurrent middle ear secretion [84, 85] and recurrent adenoids (adenoids that regrow post-adenoidectomy) [84]. Becker et al. who observed a correlation between levels of specific IgE to aeroallergens in the middle ear, nasopharynx, and serum, estimate that 20%–30% of the tympanic effusions (OME) are secondary to allergic processes [84]. In another study, in 62% of MEEs in patients with eOM, one or more allergen-specific IgEs were found (vs. 11% in the control group), whereas there were no differences in serum IgE levels between the groups [86]. Moreover, in contrast to the findings in 11 MEEs, there were no mold-specific IgEs detected in the corresponding sera, and the OME severity was significantly higher in the IgE-positive group [86].

In accordance with these findings, in comparison to AR, Hurst describes chronic OME to be a "low-level" IgE disease with specific IgE to aeroallergens to be below 100 mg/L in two thirds of cases [18]; of note, this was independent of total IgE levels. Hurst–therefore–explained the finding of negative skin prick test results in 80% of cases with OME due to low IgE levels and, for this reason, prefers intradermal testing with aeroallergens in patients with OME [18]; by intradermal testing instead of skin prick tests, 72%–100% of patients with OME are detected to be atopic [18, 87]. To increase diagnostic certainty, nasal provocation testing can be added to the work-up in certain cases [88]. Furthermore, Hurst et al. recently reported in a study with 106 adults and children with OME that intradermal dilutional testing (IDT) identified 57% more patients with OME as being allergic than would have been diagnosed using only SPT [89]. Therefore, the authors suggest that IDT might be preferable in detecting an allergy in patients with OME. Data on the sensitivity in detecting allergies in patients with OME are currently not available.

However, some studies have shown conflicting results, for example, lower IgE levels in MEE compared to their serum-IgE [47, 90].

10 | The Role of Bacterial Otitis Media and AR

Some studies have looked at the link between AR and purulent otitis media. The majority observed a positive association analogous to that observed with OME [30, 91, 92] and only a few were unable to establish a connection [30, 93]. Studies have investigated the effects of allergy on OME in an animal model and secondarily the effect of intratympanally applied lipopolysaccharide (LPS) on Th1 and Th2 responses of the middle ear mucosa [94, 95]. LPS is a membrane component of gram-negative bacteria and a virulence factor that can cause an inflammatory reaction by releasing numerous pro-inflammatory cytokines [95].

After intratympanal LPS instillation, 100% of the allergic mice (allergy induced by intraperitoneal injection of ovo-albumin (OVA) followed by nasal challenge with OVA; thereby, OME or "allergic otitis media" resp. was developed in 75%) and 100% of the control mice developed OME, with an inflammatory reaction and expression of Th1 and Th2 cytokines being more pronounced in the allergic group [94]. The authors conclude from their observations that a bacterial infection can lead to an excessive reaction in patients with pre-existing allergic predisposition [94]. LPS/TLR4 interactions have been shown to be critical for otitis media development [96]. Interaction between allergy and middle-ear infection has previously been suggested with increased susceptibility of atopic patients to upper respiratory tract infections, including middle ear infections, by facilitating the penetration of pathogens [22]. This is, however, simplistic. More recent work has shown that exposure to pollen weakens innate immune responses against respiratory viruses [97].

11 | Therapy

The therapy of otitis media with effusion without allergic comorbidities is well established. Many cases without complicating factors allow for a watch-and-wait procedure due to the self-limiting nature of the disease. If symptoms persist, INCS can be prescribed, and in refractory cases, grommets can be inserted [21]. This is especially relevant for speech development in children with OME and hearing impairment [24]. Saline nasal irrigation and inhalation therapy have also been shown to have a positive effect on clinical symptoms of OME without AR [98, 99]. Many studies have examined the effects of anti-allergic treatment on OME based on the research outlined above. Despite the reported association between AR and OME, most studies with antihistamine therapy have shown no efficacy in eliminating the tympanic effusion in OME [74, 100]. A systematic Cochrane review concluded that antihistamines and decongestants do not have statistical or clinical benefit on OME, neither individually nor in combination, but do have side effects (in 11% of cases) and are therefore not recommended [101]. Assuming that OME is a late-phase allergic response, the lack of effectiveness of these medications is not surprising [74]. The International Federation of Oto-rhino-laryngological Societies published an international consensus in 2017, stating a clear recommendation against using systemic steroids, antibiotics, decongestants, or antihistamines to treat OME, because of side effects, cost issues, and no convincing evidence of long-term effectiveness [102].

While intranasal corticosteroids (INCS) are the gold standard treatment of AR, their use in the treatment of chronic OME is controversial. Some studies have documented efficacy for the use of INCS in children [19, 103, 104]; however, a Cochrane review concluded that topical and oral corticosteroids are of no benefit for short- or long-term treatment of OME in children [105]. In another meta-analysis, antibiotics were shown to have a limited effect on recurrent OME and short-term elimination of OME, but no effect longer-term [106].

The leukotriene antagonist montelukast has so far only been investigated in a few studies that report different effects. Two studies observed efficacy in children with OME [16, 107], although the difference compared to the placebo group was statistically significant in only one study [107]. In another, similarly designed children's study, there was no advantage detected in the active group (montelukast) versus placebo [108].

A single study has so far investigated and documented the success of allergen immunotherapy (AIT) for the treatment of OME in 85% of patients [87]. In this study of 89 OME patients (52 children <15 years, 37 adults) warranting myringotomy and ventilation tubes or chronic drainage from a perforation or tube, AIT to house dust mite, pollen, or molds (in patients sensitized on testing) provided complete resolution of effusion or drainage in 85% of 127 ears. Hurst et al. reviewed in 2020 that 72% of children with OME are atopic and specific AIT completely resolved diseased ears in children, and they all, children <15 and most adults in the treatment group, resolved within 4 months and remained free of disease while on AIT for 2– 8 years of follow-up [109] (Figure 4). Despite these promising data, the further evaluation of the effectiveness of AIT on eustachian tube dysfunction remains a priority for future studies that must not be overlooked in future study design.

The American Clinical Practice Guideline for chronic OME advises against medical treatment with antihistamines, decongestants and INCS due to their ineffectiveness [110], but raises the point, that in the subgroup of allergic children "with concomitant OME and AR, there may be a role for INCS, since they do target the inflammatory component of AR, which may be a contributing factor to OME."

In conclusion, anti-allergic, modern, and unharmful therapeutic strategies need to be considered in a proven or likely connection between eustachian tube dysfunction and allergic inflammation, with respect to current limited knowledge. With or without allergic inflammation, current guidelines and recommendations for the management of OME must be respected, and the palette of surgical management of OME, especially in pediatric OME, delivers reliable results [102, 111]. Additive and targeted anti-inflammatory approaches are likely to be of benefit given the extensive evidence of effectiveness in other organs but need to be evaluated continuously in an orchestrated fashion.

12 | Summary

Epidemiology and the current understanding of inflammatory, humoral, and neuronal processes make an association between OME and allergy plausible. Several reviews or meta-analyses conclude that atopy is a risk factor for the development of OME [19, 112, 113]. Although these results support the hypothesis that OME is a late-phase response allergic disease, there is a lack of consistent evidence for a direct causal relationship [94].

FIGURE 4 | Treatment options for MEE caused by a respiratory allergy: In case of Middle Ear Effusion (MEE) due to allergic rhinitis (AR), intranasal corticosteroids (INCS) and allergen immunotherapy (AIT) can be used as treatments.

One of the main reasons for the controversial discussion is different populations, uncontrolled studies, and different diagnostic criteria for confirming allergy, with a high number of negative SPT in sensitized patients compared to intradermal tests [8, 18, 38]. However, not every atopic patient develops OME, and not every patient with tympanic effusion (OME) has inhalant allergies [18]. Some experts take the view that inhalant allergies are only involved in the maintenance of an OME but are not primarily responsible for its development [28, 52]. The intermittent nature of the allergy makes it difficult to recognize the connections.

In summary, not all OME are the result of allergy. Currently, it is unclear why the middle ear mucosa becomes the target organ for certain allergies, while the lungs or skin are affected in other allergic reactions [18]. Since allergy is a risk factor for the development of OME, and with a sensitisation rate of approximately 30% in the main predilection age between 3 and 6 years for OME, we propose the basic diagnosis should be extended by an allergological clarification, particularly in prolonged courses of OME. Anti-allergic therapeutic measures, in particular the use of topical steroids and AIT in line with guidelines for AR, may benefit the standard treatment if the test results are positive. In adults, the phenomenon of eosinophilic otitis media with or without comorbid eosinophilic asthma or CRSwNP, which can be independent from type-I hypersensitivity, is still under investigation with regards to its origin and therapeutic strategies, which include biologic therapy in comorbid cases [114].

Current non-surgical treatments for OME in allergic children include antihistamines, decongestants, and INCS; however, despite good tolerability and safety, these generally show limited and heterogeneous efficacy. In adults, we assume an even broader variety of pharmacological treatment is being applied for chronic and acute OME regardless of allergic association. AIT, however, has shown promise in resolving OME in allergic patients.

Given the limited published evidence, this position paper is based on expert consensus: a trial of INCS is recommended for children with plausible allergic airway disease and chronic OME before considering surgery, provided it is not urgent. The allergy diagnosis might be more challenging in an OME-only phenotype; thus, precise testing and a variety of methods are crucial. With respect to current European and national guidelines [115], AIT needs to be considered in cases with significant aero-allergy with eustachian tube dysfunction. Further research, real-world evidence, and randomized controlled trials are imperative to develop more effective management strategies and improve patient outcomes. Addressing these knowledge gaps is critical for optimizing the treatment of OME in the context of allergic diseases.

Author Contributions

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