# Role of Nasal Allergy in Chronic Secretory Otitis Media

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Nasal allergy seems to be one of the important causes of chronic secretory otitis media (SOM) in children and adults. Chronic SOM is unequivocally related to disturbed function of the eustachian tube, which facilitates communication of the middle ear with the nasopharynx, nasal cavity, and indirectly with paranasal sinuses. The most serious consequences of chronic SOM are decreased elasticity of the tympanic membrane and hearing impairment. Allergic reactions in the nasal mucosa leading to release of various mediators result in development of three types of nasal response characterized predominantly by nasal obstruction. Eustachian tube functions can be affected directly by the mediators released in the nasal mucosa or indirectly by the nasal obstruction. Nasal challenges with allergens performed by rhinomanometry, combined with tympanometry and eventually audiometry, may be a useful diagnostic supplement for this disorder.

## Introduction

Otitis media is an inflammatory state of the middle ear (ME) that is regularly associated with ME effusion (secretions) [1–7,8•]. Otitis media can be classified according to various criteria (eg, features of effusion, causal factors, presumed mechanism, pathogenesis) [1–7,8•,9]. Secretory otitis media (SOM), also called otitis media with effusion, occurs in acute, recurrent, and chronic forms [1–4]. Acute SOM is common in younger children, whereas recurrent and chronic SOM are seen more in older children and adults [1–7,8•,9,10••,11•,12–14]. Acute SOM is usually caused by bacterial or viral upper respiratory infections, whereas chronic SOM presumably has multifactorial causes [1–5,7,13,14]. Acute SOM is usually associated with ME effusion [1–4,7,8•,15–17]. Chronic SOM is also presumed to be accompanied by ME effusion; however, in some patients, especially adults, no evidence of ME effusion is found [1–4].

## Incidence of Chronic SOM

The incidence of chronic SOM in children is estimated to vary from 15% to 64%, but it has not been systematically investigated in adults [2–6,8•,15]. The clinical importance of chronic/recurrent SOM is emphasized by its impact on the development of hearing impairment, speech disturbance, and learning capacity [1–7,8•,13–16,18,19•].

The role of the upper airways and nasal allergy in the etiology of chronic SOM is still not fully understood [5,9,12,13]. Allergic rhinitis is qualified as a comorbid condition by some authors [3,13,18,20,21], as one of the causal factors of chronic SOM by others [1–5,7,14], and designated as part of the so-called united airways concept by other investigators [8•,15]. Nevertheless, growing evidence indicates direct causal involvement of nasal allergy in chronic SOM.

## Pathogenesis of Chronic SOM and the Role of the Eustachian Tube

The pathogenesis of chronic SOM is clearly related to the abnormal function (dysfunction) of the eustachian tube (ET) [1–5,7,8•,10••,11•,12–16,22–28]. The ET facilitates communication between the ME cavity and the nasopharynx, nasal cavity, nasal mucosa, and (indirectly) the paranasal sinuses [1–5,8•,9,10••,11•,12–16,22–31]. From this point of view, the ET plays a pivotal role in some ME disorders by executing three basic functions: 1) protecting the ME from the nasopharyngeal secretions and sound pressure; 2) draining the ME secretions into the nasopharynx; and 3) ventilating the ME cavity to regulate the air pressure in the ME with the atmospheric pressure, replenish oxygen that has been absorbed, and allow the gases produced in the ME cavity to escape [1–5,8•,10••,12,24–26]. Active opening of the ET is accomplished by contractions of the tensor veli palatini muscle during swallowing, yawning, crying, or sneezing. This mechanism stabilizes the slightly negative pressure in the ME cavity from 0 to -150 mm $H_2O$ deciPascals [1–4,12,23,24,29]. Alternatively, cough, forced expira-

tion with closed mouth, blowing of the nose, diving, and ascending in an airplane dramatically increase the positive pressure in the nasopharynx, leading to the closing of the ET as a protective mechanism of the ME [1–4,23,24,29].

ET dysfunction includes its obstruction, abnormal patency, and the nonoptimally functioning ciliated epithelium that lines the ET [1–5,8•,9,10••,11•,12–14,22,25]. ET obstruction can be caused by extrinsic factors, such as adenoid hypertrophy or edema of the mucosal membrane in the posterior nasopharynx, which are due to infection or allergy subsequently producing secondary peritubal obstruction of the ET's nasopharyngeal orifice. It also can be caused by intrinsic factors, such as infection or allergy. ET obstruction can be divided into two forms: mechanical and functional. The mechanical form is caused by the previously mentioned extrinsic and intrinsic factors. The functional form can be caused by increased tubal compliance due to an abnormally active opening mechanism or by nasal obstruction—the so-called Toynbee phenomenon. In this form, allergy plays a predominant role. Functional ET obstruction results in high negative ME pressure (MEP), which can be associated with a retraction or collapse of the tympanic membrane (eardrum atelectasis). It is suspected that in cases of inadequate ET ventilation, the tubes remain persistently collapsed. Such a situation can result in a progressive increase in negative pressure in the ME, followed by aspiration of nasopharyngeal secretions into the ME cavity and development of acute otitis media with effusion. Alternatively, ineffective ventilation caused by persistent ET obstruction may lead to increased oxygen absorption by the ME epithelium, a state called *local hypoxia/hypercapnia*, which results in increased production and accumulation of secretions in the ME cavity. All these factors lead to disturbance of ET functions and may result in otitis media. ET dysfunction and SOM pathogenesis have been described in more detail in many excellent papers [1–4,7,25–28,32,33].

## Mechanisms of Allergy Involvement in Chronic SOM

The involvement of nasal allergy in chronic SOM can be realized through different mechanisms and pathways [1–7,8•,10••,11•,12–17,20–22,25–28,31–47]. They are as follows:

1. The allergic reaction (the antigen–antibody interaction or antigen-sensitized T-helper type 1 [Th1]–lymphocyte interaction) with subsequent steps, such as generation and release of various mediators and factors and their effects on the particular cells, tissues receptors, and structures, takes place primarily in the mucosal membrane of the ET and/or ME cavity. In this case, the ME mucosal membrane is the primary target organ.
2. The allergic reaction occurs primarily in the mucosal membrane of the nasopharynx and/or its related structures, such as the lymphatic or adenoid tissue, and the released mediators and activated cells affect the peritubal and tubal mucosa of the ET, with subsequent progression into the ME cavity.
3. The allergic reaction originates primarily in the nasopharynx and in the ET and unrelated tissues, and the released mediators and immunocompetent cells may reach the mucosal membrane of the ET and, subsequently, the ME through the hematogenic way.
4. The allergic reaction occurring primarily in the nasal mucosa does not cause any nasal response (NR), but the released mediators and relevant cells migrate into the nasal secretions and are then transported to the nasopharyngeal orifice of the ET.
5. The allergic reaction occurring primarily in the nasal mucosa leads to the primary NR, characterized by nasal mucosal edema and causing subsequent nasal obstruction and stimulation of the nasal mucosal glands, which results in hypersecretion and stimulation of the local mucosal nerve network, resulting in sneezing.

The nasal mucosal edema can affect the ET by direct expansion to the nasopharyngeal ET orifice or through nasal obstruction. Nasal obstruction can then lead to an increase in negative pressure in the nasopharynx, resulting secondarily in decreased ET patency, disturbance of its ciliary epithelium function, and obstruction of the ET, with subsequent increase in the negative pressure in the ME cavity. This process causes an accumulation of secretions and gases in the ME cavity, with subsequent thickening of the ME mucosal membrane due to the edema and/or infiltration, and changed ME functions. However, in some circumstances, nasal obstruction can also lead to an increase in the positive nasopharyngeal pressure, causing aspiration of nasopharyngeal secretions into the ET and ME cavity and positive pressure in the ME.

One special mechanism, which may also participate in development of chronic SOM due to allergy, is the so-called trapping mechanism [5,22,30]. The allergenic particles escaping the filtering functions of the nasal mucosa reach the nasopharyngeal orifice of the ET, become trapped, and cause an antigen–antibody interaction with subsequent steps.

Nasal mucosal edema leading to an edematic obstruction of the nasopharyngeal ET orifice, decreased patency of ET, and disturbance of its ciliary epithelium functions may not only produce an accumulation of secretions and gases in the ME cavity and the infiltration and edema of the ME mucosal membrane, resulting in its thickening, but also other changes on the tympanic membrane. These changes include abnormal position (retraction or atelectasis), limited mobility, decreased translucency, changed color (from slightly bluish-red to reddish-yellow),

increased vascularization and thickening, and decreased light reflex [1–3,10••,14,23,24]. Chronic SOM also may be accompanied by symptoms such as tinnitus, otalgia, and vertigo [1–3]. The most serious consequences of chronic SOM—especially SOM due to allergy—may be fibrotic changes and decreased elasticity of the eardrum and hearing impairment [1–7,8•,9,12,14,18,19•,23,24,29].

Nevertheless, there is a dearth of information about why nasal allergy induces chronic SOM in some patients but does not influence the ET and ME in others [1,3]. Another still unanswered question concerns the mode of nasal allergy involvement in ET dysfunction [10••,22,31]. Is this process realized through the primary nasal mucosal edema with subsequent nasal obstruction or through the released mediators and other factors directly affecting the nasopharyngeal ET orifice? Or is it a combination of both mechanisms? Results of our studies suggest possible involvement of both mechanisms [10••,22,31]. Most of the positive NRs to allergen challenge were accompanied by significant changes in the MEP, indicating the involvement of nasal mucosal edema in ET dysfunction. The tympanometric changes, including increased MEP negativity with slightly decreased compliance, may correspond to a combination of the B and C tympanogram types. However, the arbitrary classification of the particular tympanogram types [23,29] can be questionable because various subtypes of tympanogram have been reported. The appearance of MEP changes during some negative NRs (ie, in nasal mucosal edema absence) cannot be explained satisfactorily. The data from our study did not allow any conclusion to be drawn about whether released mediators directly affected the ET and ME functions without causing any edema of the nasal mucosa because no mediators were measured in the nasal secretions. The lack of significant MEP changes during the nasal challenges in the controls would not confirm findings of investigators who reported ET obstruction due to the nasal challenges with allergen in individuals with allergic rhinitis but without ME disease [27]. Another interesting observation in our studies was the recording of negative NRs and no MEP changes in some patients with chronic SOM. This finding probably can be explained by involvement of allergens different from those that have been tested or by different site of allergic reaction (eg, nasopharynx or direct ET). Further research is needed to clarify the answers to these questions.

A great deal of research regarding the pathophysiology and mechanism(s) of SOM has been published during the past decade. Many cytokines, mediators, and other factors, as well as cell types have been detected in the ME effusion, ME mucosal membrane, related structures (Waldeyer's ring), and blood serum of patients suffering from chronic SOM and allergy. In these studies, increased concentrations of these factors and/or cells recorded in patients with SOM likely due to allergy were compared with controls or with SOM patients without allergy. The following compounds have been detected:

1. ME effusion:
   - Cytokines: interleukin (IL)-1, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 [3,5,11•,15–17,20,21,32,35,36,38,41,42], tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and granulocyte-macrophage colony-stimulating factor [2,11•,15–17,32,36,38,42–44].
   - Immunoglobulins: IgE, IgG, IgG1, IgG2, IgM, IgA, and secretory IgA [1–5,7,16].
   - Other factors: Macrophage migration inhibition factor, histamine, tryptase, endotoxins, ecalectin, eotaxin-1, prostaglandin (PG)$F_{2\text{-alpha}}$, $PGE_2$, $PGD_2$, intercellular adhesion molecule-1, vascular cell adhesion molecule, vascular cell adhesion molecule-1, platelet/endothelial cell adhesion molecule-1, leukotriene (LT)$B_4$, $LTE_4$, selectines L and E, eosinophil-derived neurotoxin, neutrophil chemotactic factor, platelet-activating factor, eosinophil cationic protein, major basic protein, RANTES (regulated on activation, normal T-cell expressed and secreted), and myeloperoxidase [2–5,8•,11•,16,20,21,33,37,41,44,45].
   - Cells: mast cells; eosinophils; neutrophils; and T lymphocytes of the helper phenotype, subsets Th1 (expressing IFN-γ and TNF-β) and Th2 (expressing IL-4, IL-5, IL-9, and IL-25) [2–5,7,8•,11•,15,16,21,32,33,35,37].
2. ME mucosa (biopsy): IL-5, major basic protein, eosinophil cationic protein, ecalectin, eotaxin, eosinophils, T lymphocytes, various microscopic changes (eg, pseudostratified, thickened, and edematous epithelium), scattered mononuclear and polymorphonuclear cells, $EG_2$, and ecalectin-positive cells [2,3,20,41].
3. ET mucosa (biopsy): IL-4 and IL-5 mRNA-positive cells [15].
4. Adjacent lymphatic tissues (nasopharyngeal adenoid, palatine tonsils, ET peritubal tissue): IL-2, IL-4, IL-5, IL-10, IFN-γ, $CD4^+$/$CD45RO^+$ cells, and Th1 lymphocytes [3,15,35,46].
5. Nasal polyps: T lymphocytes Th1 (IFN-γ, IL-2) and Th2 (IL-4, IL-5) [47].
6. Blood serum: IL-2, IL-4, IL-5, IFN-γ, and TNF-α [3,32,35].

However, an appearance of these factors—even in an increased concentration—documented by a single measurement cannot be accepted as confirmation of their active involvement in the immunologic mechanisms underlying chronic SOM. The basic disadvantage of all these studies is the lack of repeated measurement of these factors related to a well-defined intervention (eg, nasal challenge with allergen).

## Diagnostic Confirmation of the Nasal Allergy Involvement in Chronic SOM

Diagnostic confirmation of the involvement of allergy and nasal allergy in the dysfunction of ET and chronic SOM is not easily accomplished. In practice, skin tests are usually performed and/or the specific IgE antibody in the serum is determined (radioallergoimmunosorbent [RAST], CAP) [1–5,9,13–16,22,25–27,34,37]. These are easy to perform, a high number of allergens can be tested together, and the results are available quickly. However, these tests provide evidence only of an increased amount of specific IgE antibody in the skin or blood serum, which cannot be related directly to any particular organ. These tests are performed on one organ, and their results cannot be applied to other organs without limitations. They do not provide evidence of local antibodies in other organs and their mucosal membranes. Furthermore, the serum RAST (CAP) estimates only the specific IgE antibody and does not evaluate possible involvement of antibodies of other classes or T lymphocytes in that immunologic event [22,30,31,34,48–50].

Moreover, the important question concerning the clinical interpretation of results generated by these tests remains unanswered. Are the antibodies—in this case the specific IgE—only a part of the allergic reaction, or should they also be considered a consequence of this reaction, or is their involvement a combination of both roles? If the antibodies act only as an integrated part of the allergic reaction, then the "consumption effect" would lead to a decrease in circulating antibodies after the positively passed allergic reaction. In such a case, the postchallenge decrease (and not increase) in the specific IgE would be an indicator for the activation of the immunologic system that results in a positive clinical allergic reaction. Moreover, the increased postchallenge concentration of these antibodies in the serum and/or the skin would argue for nonactivation of the immunologic system, thus allowing their accumulation [10••,22,30,31,34].

From such a point of view, a combination of both roles of IgE antibodies—a part of some stages and yet a consequence of other stages of hypersensitivity mechanism(s)—seems to be one of the probable explanations for this phenomenon [22]. Under such circumstances, the single increase in the concentration of the specific IgE antibody in the serum or elsewhere cannot be interpreted as unequivocal confirmation of the positive allergic reaction—in this case in chronic SOM. Finally, these tests performed as a single measurement do not reveal any information about the dynamic aspects of the hypersensitivity mechanism(s) [22].

A similar dilemma concerns the interpretation of the results of other immunologic tests that record the changes in the concentrations of various mediators, cytokines, factors, and cells in the ME secretions (effusion), mucosal membranes, and other tissues as a single measurement, which fails to record the dynamic aspects of the involvement of these factors and cells in the particular pathologic and immunologic processes.

Moreover, these data cannot distinguish the participation of different etiologic agents from each other (eg, infectious agents from allergens) or the mode of their involvement in the particular disorder (eg, chronic SOM) [10••,22]. From this point of view, the nasal challenge with allergen (nasal provocation test [NPT]) in combination with the recording of variable parameters indicative of ET and ME functions and their changes (eg, tympanometry) is the only method that can approach this problem structurally [1–4,10••,22,25,26,31,48–52]. The NPTs combined with tympanometry and eventually with audiometry are a suitable method for confirming the causal involvement of a certain allergen in the nasal mucosa and in ET and ME complaints that results in appearance of a certain type of response (immediate, late, or delayed). This response then can be quantitatively measured and recorded during its dynamic course (Fig. 1 and Fig. 2). In this way, the causal relationship between a certain type of hypersensitivity mechanism (allergic reaction) and a specific allergen on one hand and the disorder of an organ—in this case, ET and ME represented by concrete symptoms—on the other hand can be confirmed unequivocally [10••,22,31,50–52]. Although NPT is a laborious, time-consuming technique requiring special equipment, special facilities, and well-trained personnel, it generates extremely important clinical data that cannot be gathered using other diagnostic tests. It directly demonstrates the causal involvement of a specific allergen in a specific end organ that may display a certain type of response. By combining the recorded parameters, the NPTs can confirm the causal role of one organ in the response of another—in this case the role of nasal mucosa and nasal allergy in the ET and ME disorder [10••,22,30,31,34,48–52].

The NPTs also can distinguish the participation of the allergy and the nonspecific hyperreactivity component in the patient's complaints [22,28]. Another important advantage is their ability to follow relative values of the parameters, comparing postchallenge with prechallenge data. In this way, the NPTs are not dependent on the absolute values of the parameters, which often display high variations [22,30,51].

Results of our studies showing three basic types of nasal and ME response—immediate, late, or delayed (Fig. 1 and Fig. 2)—are in partial agreement with other investigators' findings using the nasal challenge model with allergen in patients or laboratory animals [2–4,25–27]. This agreement predominantly involves the pivotal role of nasal allergy in ET dysfunction with subsequent development of SOM, the existence of nonimmediate types of nasal and ME responses, and the important position of NPTs in the diagnostic work-up of allergic rhinitis and chronic SOM. The nasal challenges with histamine or other chemical compounds performed by other investigators reflect the role of nonspecific hyperreactivity in the development of nasal complaints and derived response of ET and ME [28].

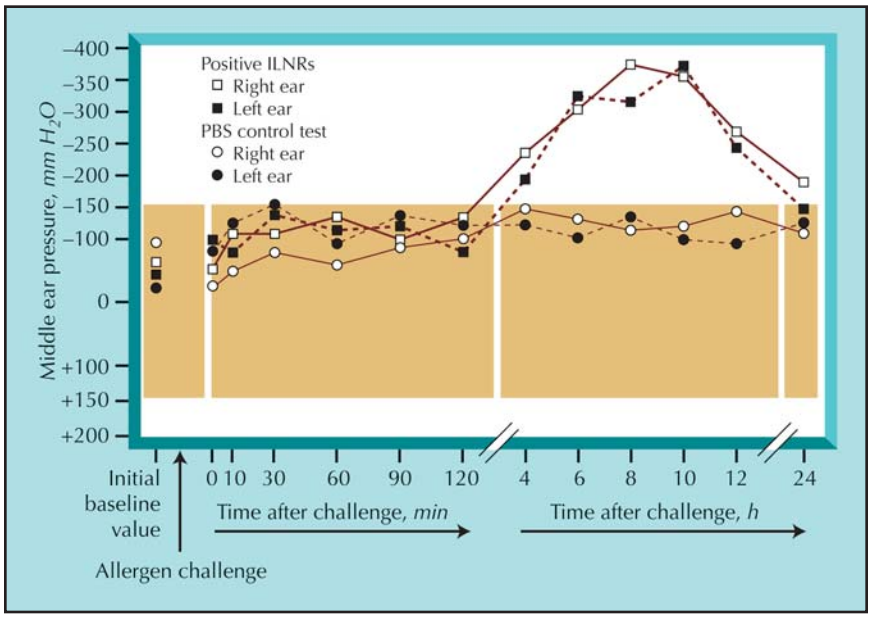


**Figure 1.** Middle ear response accompanying the isolated late nasal response (ILNR). The mean values of middle ear pressure were recorded during 42 positive ILNRs and 42 phosphate-buffered saline (PBS) control tests. (*From* Pelikan [10••]; with permission.)

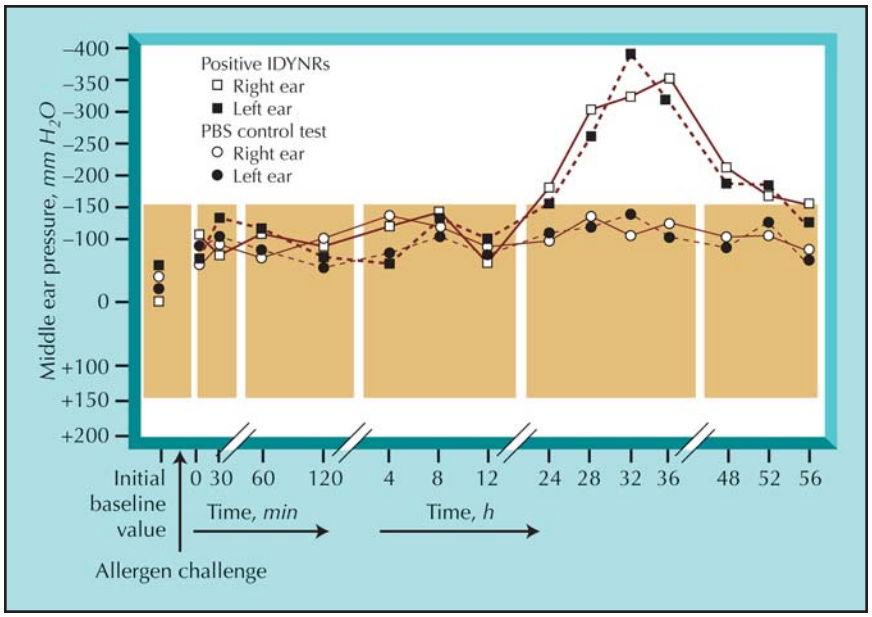


**Figure 2.** Middle ear response accompanying the isolated delayed nasal response (IDYNR). The mean values of middle ear pressure were recording during the 18 positive IDYNRs and 18 phosphate-buffered saline (PBS) control tests. (*From* Pelikan [10••]; with permission.)

## Chronic SOM and Food Allergy

Adverse reaction to food, especially food allergy, also may be involved in the pathogenesis of chronic SOM in some patients. However, there is a dearth of information on the role of food allergy in ME disorders. In practice, the possible role of food allergy in chronic SOM is usually investigated only by skin tests and/or determination of specific IgE in the serum [53–55]. Few studies have been conducted on this topic [22,34,52–57]. In most of our patients, the secondary ME response induced by the primary NR to food ingestion was recorded by tympanometry in combination with rhinomanometry [56,57]. However, in some of these patients, the primary ME response to food ingested—in the absence of any NR—was also observed. Three types of ME response (similar to the three basic types of NR [immediate, late, or delayed]) were recorded [34,57]. Chronic SOM due to food allergy was significantly prevented by oral disodium cromoglycate [22,34,52]. Nevertheless, additional concurrent investigations will be needed to clarify the mechanisms by which food allergy may be involved in chronic SOM.

## Therapeutic Intervention and Management of Chronic SOM Due to Nasal Allergy

The surgical intervention that includes myringotomy followed by temporary insertion of ventilation tubes (and, if indicated, adenotomy/adenectomy, tonsillectomy, and correction of the nasal septum [1–3,8•,9,16]) should be considered a supportive rather than a causal treatment.

General treatment consists of allergen avoidance as much as possible and rinsing of the nose with sterile saline. Immunotherapy remains a controversial issue [2,3,22,30,58].

Pharmacologic treatment includes nasal decongestants; prophylactic antimicrobial therapy (if indicated) [1–3]; and various drugs administered intranasally or orally, such as histamine-1 (H1)-receptor antagonists, anticholinergics, glucocorticosteroids, disodium cromoglycate, nedocromil sodium, and anti-LTs. Reports concerning the clinical effects of particular drugs in patients with chronic SOM due to nasal allergy vary greatly [1–5,8•,16,18,19•,22, 31,39,59,60•]. The sometimes controversial variation of the clinical effectiveness of particular drugs may be caused by selection of not completely comparable patients and/or by inadequate diagnostic procedures, especially the lack of nasal challenges with allergen. Results of our previous studies using NPTs with allergens demonstrated excellent protective effects of intranasal glucocorticosteroids on the delayed NR [22,50], significant effects on the late NR [22,49], and no effects on the immediate NR [22,48]. In contrast, intranasal cromolyn significantly prevented the immediate NR and diminished the late NR, whereas it had no effect on the delayed NR [22,30,31,48–50]. H1-receptor antagonists and anticholinergics reduced the nonspecific hyperreactivity in the nasal mucosa but did not affect the NR to allergen challenge of any type [8•,22,30,60•]. LT antagonists demonstrated some protective effects on bronchial asthma and coexisting SOM [39].

## Conclusions

Chronic SOM due to ET dysfunction caused by allergy occurs much more frequently in adults than had been initially realized. The recording of the three basic types of ME response (Fig. 1 and Fig. 2) analogous to the three basic types of NR (immediate, late, or delayed) may indicate involvement of various hypersensitivity mechanisms in chronic SOM. NPTs with allergens performed by rhinomanometry in combination with tympanometry and eventually with audiometry may be a useful diagnostic procedure in patients with chronic SOM and also have an important impact on the therapeutic management of this disorder.

## Disclosure

No potential conflict of interest relevant to this article was reported.

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No evidence for significant effectiveness of H1-receptor antagonists and decongestants in treatment of chronic SOM has been found.