

Allergic rhinitis, histamine, and otitis media

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ABSTRACT

Otitis media (OM) is a common and costly medical condition, especially in children. Most episodes of OM are associated with an upper respiratory viral infection and are short-lived and self-limiting with or without medical treatment. However, chronic OM with effusion (OME) has significant sequelae, is refractory to most medical treatments, and frequently requires surgical intervention. The pathophysiology of OME is complex and involves both eustachian tube (ET) dysfunction and middle ear pressure dysregulation. OM likely results from an increase in blood flow to and, thus, gas loss from the middle ear, in combination with a dysfunctional ET that can not resupply that gas. These processes could be induced by viral and/or allergen-driven inflammation. A large body of epidemiologic and mechanistic evidence supports a role for allergic rhinitis as a risk for OM. Indeed, evidence also supports a role for histamine in both conditions. However, not all such evidence is supportive of this relationship and a causal relationship between the two conditions has not been definitively proven. Moreover, therapeutic trials using common allergy therapies have either not been conducted or showed no benefit in OM. This prompted the 2004 clinical practice guidelines on OM to conclude that no recommendations could be made for "... allergy management as a treatment for OME based on insufficient evidence of therapeutic efficacy or a causal relationship between allergy and OME." Nonetheless, given the strong likelihood of allergy as a risk factor for OM, allergic rhinitis patients should be evaluated for OM and patients with OME should be considered for an allergy evaluation. If significant allergic rhinitis is diagnosed in a patient with OME, it should be treated aggressively (as in any case of moderate to severe allergic rhinitis) until further studies are conducted. No definitive conclusions about a role for food allergy in causing or treating OM can be made. Clearly, more studies are needed to examine the relationship between these two important conditions.

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Key words: Allergic rhinitis, ear, eustachian tube, histamine, middle ear pressure, otitis media, viral infections

Allergic rhinitis is a very common and costly disease in both children and adults.^{1–4} The same is true for otitis media (OM).^{5,6} Although most OM episodes are short-lived and self-limiting, even without medical treatment, some OM episodes are characterized by persistence for months to years.⁷ This condition is termed chronic OM with effusion (OME). OME is the most common cause of conductive hearing loss,⁷ and in young children, has been related to abnormal speech and language development.⁸ Moreover, OME is asso-

ciated with infrequent, but serious, sequelae that include permanent sensorineural hearing loss.⁹ OME is resistant to most medical treatments including antibiotics,¹⁰ but the surgical procedure of adenoidectomy was shown to promote disease resolution in some cases,^{11,12} while insertion of tympanostomy tubes produced resolution almost uniformly.^{12,13} A literature search through PubMed was performed with terms such as allergy, histamine, and OM, and articles that met the criteria for this review were included.

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OVERVIEW OF OM PATHOGENESIS

Known Risk Factors

Known risk factors for the development of OM include viral upper respiratory tract infection, immature/impaired immunologic function, eustachian tube (ET) dysfunction, craniofacial anatomy, secondhand smoke, day care centers, lack of breast-feeding, and allergy,^{14–16} as well as gastroesophageal reflux disease (GERD)¹⁷ and bacterial biofilms.¹⁸

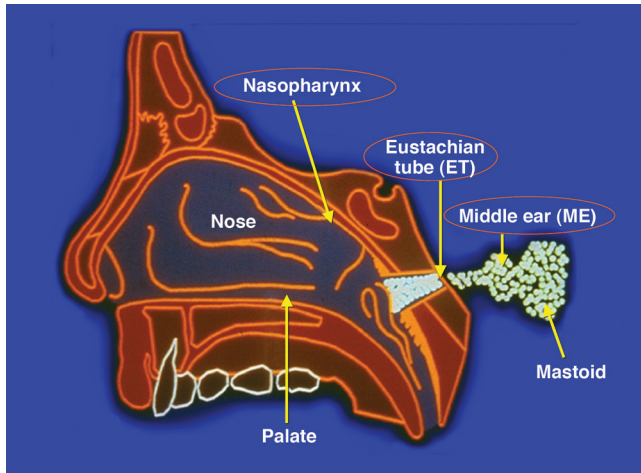


Figure 1. Potential target organs of viral and allergic inflammation.

Central Role of ET and Middle Ear Pressure Regulation

For most or all etiologies of OM, suspected pathogenic pathways include ET dysfunction and middle ear pressure dysregulation as central components.¹⁵ When free of disease, the middle ear is a closed, air-filled cavity located between the eardrum and the cochlea or hearing organ of the inner ear (Fig. 1). The middle ear couples sound pressures presented at the eardrum to fluid pressures within the cochlea to enable us to hear sounds. The efficiency of that process is dependent on the ease of eardrum vibration that, in turn, depends on maintaining an air-filled, fluid-free middle ear at near ambient environmental pressure. However, the pressure balance between the middle ear and environment is intrinsically unstable because ambient pressure changes constantly with changes in elevation and weather, while middle ear pressure also changes as a result of diffusive gas loss to blood flowing locally. When free of disease, pressure gradients between the middle ear and environment are periodically relieved by transient, muscle-assisted openings of the ET, a complex anatomic structure extending from the middle ear to the nasopharynx.¹⁵ Hence, a healthy ET serves to balance the pressure between the middle ear and the nasopharynx *via* supplying airflow when the middle ear demands it. The ET is usually closed to airflow, but opens during certain activities such as swallowing and yawning, among others. Processes (*i.e.*, allergy and infection) that may serve to increase middle ear blood flow (and thus decrease middle ear gas and increase gas demand) or interfere with normal ET ventilation of the middle ear (decrease gas supply) or both could have obvious consequences in the pathogenesis of OM.

In experimental allergic and infectious models of OM disease pathogenesis, OM development proceeds through an ordered series of events, which starts off by

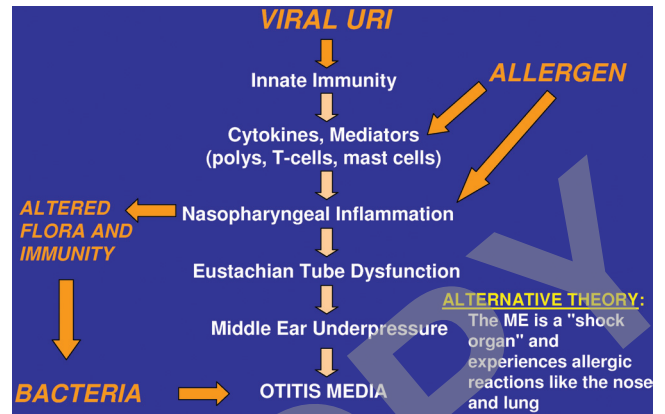


Figure 2. Proposed pathogenesis of OM.

a hindrance of the function of the ET (Fig. 2). When the ET becomes hindered, the gas exchange to the middle ear does not occur, leading to middle ear underpressure (negative). Prolonged, significant middle ear underpressure can then lead to OME *via* the process termed *hydrops ex vacuo* or when the demand for gas by the middle ear surpasses the supply from the ET. Although there are several risk factors associated with the development of OM, dysregulation of middle ear pressure is likely to be the crucial shared factor between every one of the etiologies.¹⁵

Although the direct cause of OM still has not been determined, researchers believe viruses and allergens to be among the top sources. In the case of the former, such an infection could produce inflammation that brings increased blood flow into the middle ear. The increased blood flow could reduce the amount of gas inside the middle ear and result in negative pressure buildup. The inflammation of the nasopharynx and ET during the infection could prohibit airflow between the middle ear and nasopharynx, initiating middle ear underpressure and OME. Similar to the effects of viruses, an allergen also could lead to OME. When an allergen enters one's nostrils, the ET and nasopharynx inflame and do not allow sufficient gas supply to the middle ear. Once again, middle ear underpressure could take place and result in OME. Although an abundance of evidence supports a role for ET obstruction in the induction of OM by viruses and allergens, evidence for a role for increased middle ear blood flow and gas loss has only been forthcoming from animal models thus far.^{19,20}

RELATIONSHIP BETWEEN ALLERGIC RHINITIS, HISTAMINE, AND OM

Evidence From Epidemiologic Studies (Human)

Most but not all epidemiologic studies have provided evidence that supports a relationship between allergic rhinitis and OM²¹⁻⁴⁴ (Table 1). An association between allergy and OME was supported by case-

Table 1 Epidemiologic studies of allergy and otitis media (OM) in children

Reference and Population Studied	Type of Recruitment Clinic	Prevalence of OM	Prevalence of AR	Method of AR Diagnosis
Jordan (1949) ²² Children and adults with SOM (<i>n</i> = 123)	Otolaryngology		73.98%	Nasal smears, skin testing, and response to allergic therapy
Lecks (1961) ²³ Children with recurrent SOM, hearing loss, and suspicion of allergy (<i>n</i> = 82)	Otolaryngology		87.8%	Skin testing by scratch and intradermal
Fernandez and McGovern (1965) ²⁴ Infants and children with chronic SOM (<i>n</i> = 113)	Allergy		83%	History and symptoms
McGovern <i>et al.</i> (1967) ²⁵ Infants and children with allergy and chronic SOM (<i>n</i> = 512)	Pediatrics		98%	History and symptoms
Bernstein and Reisman (1974) ²⁶ Infants and children with single (<i>n</i> = 112) or multiple (<i>n</i> = 88) tubings for SOM	Otolaryngology		24% of all 200 patients, 35% of those with multiple tubings	History, physical exam, and intradermal skin testing
McMahan, Calenoff, <i>et al.</i> 1981 ²⁷ Infants and children with chronic SOM (<i>n</i> = 153)	Otolaryngology		93.3% (only 119 patients tested for allergies)	RAST
Bernstein <i>et al.</i> (1983) ²⁸ Children with recurrent OME with previous tubes (<i>n</i> = 77)	Allergy		42%	History, physical exam, skin prick testing, and RAST
Kraemer <i>et al.</i> (1983) ²⁹ Children with PMEE and tubes (<i>n</i> = 76) compared with control group (<i>n</i> = 76)	Otolaryngology		Nasal congestion - 59.2% (vs 25% for control) atopic disease (SAR, asthma, or eczema) - 28.9% (vs 14.4% for control)	Interview of parents

Table 1 Epidemiologic studies of allergy and otitis media (OM) in children (Continued)

Reference and Population Studied	Type of Recruitment Clinic	Prevalence of OM	Prevalence of AR	Method of AR Diagnosis
Pukander <i>et al.</i> (1985) ³⁰ Children aged 2–3 yr were placed in three groups based on the number of AOM attacks—3 or more ($n = 188$), 1–2 ($n = 76$), or 0 (control group, $n = 207$)	Otolaryngology		Parents reporting AR more than other children by group—3 or more attacks (25%), 1–2 attacks (7%), control (1%)	Parental questionnaire
Tomonaga <i>et al.</i> (1988) ³¹ Children with chronic OME ($n = 259$), children with nasal allergy ($n = 605$), and control ($n = 104$). Corey <i>et al.</i> (1994) ³² Children aged 1–18 yr with OME requiring myringotomy and tubes ($n = 89$) and control ($n = 59$)	Otolaryngology	Among children with nasal allergy—21% (vs 6% in control group)	Among children with chronic OME—50% (vs 17% in control group)	Routine nasal allergy and otologic tests
Bernstein and Doyle (1994) ³³ Children with OME study 1—single tube insertions ($n = 112$), multiple tube insertions ($n = 88$); study 2—recurrent OME ($n = 100$)	Otolaryngology		61% of the OME group had positive RAST (vs 41% of control group)	History and RAST
Fireman <i>et al.</i> (1996) ³⁴ Twin ($n = 132$ same-sex pairs) and triplet ($n = 2$ same-sex sets) children with recurrent AOM	Otolaryngology		Study 1—23% in both groups, 35% in children with multiple insertions; study 2—35% Only 65 children tested for allergy—18% had increased IgE and 38% had positive skin prick; only 3 of these children were categorized as “otitis prone” and all 3 were IgE normal and negative for skin prick.	Study 1—history, physical exam, and intradermal skin test; study 2—history, physical exam, skin prick testing, and specific and total IgE antibodies Total serum IgE and skin-prick test

Table 1 Epidemiologic studies of allergy and otitis media (OM) in children (Continued)

Reference and Population Studied	Type of Recruitment Clinic	Prevalence of OM	Prevalence of AR	Method of AR Diagnosis
Veletic <i>et al.</i> (2000) ³⁵ Children with SOM (<i>n</i> = 16) or recurrent OM (<i>n</i> = 14)	Otorhinolaryngology		23% of total patients	Allergological anamnesis, skin-prick test, and specific IgE
Rylander and Mégevand (2000) ³⁶ Children aged 4-5 yr (<i>n</i> = 304)	Environmental medicine	24%	24% (of these, 33% had ear infections vs 21% of children with no allergy)	Parental questionnaire
Tikkanen <i>et al.</i> (2000) ³⁷ Children with milk allergy diagnosed in infancy reexamined at age 10 yr (<i>n</i> = 56) and control group (<i>n</i> = 204)	Pediatrics and dermatology	27% (vs 12% in control)	59% (vs 20% in control)	Physical exam, skin-prick test, total IgE, and specific IgE
Alles <i>et al.</i> (2001) ³⁸ Children with chronic or recurrent OME (<i>n</i> = 209)	Glue ear/allergy		89%	History, physical exam, nasal smears, and skin-prick testing
Doner <i>et al.</i> (2004) ³⁹ Children with recurrent OME, adenoidectomy, and tubes (<i>n</i> = 22) and control (<i>n</i> = 24)	Otolaryngology		36.4% (vs 8.3% in control group)	Skin-prick testing
Nguyen <i>et al.</i> (2004) ⁴⁰ Children with OME, adenoidectomy, and tubes (<i>n</i> = 45)	Otolaryngology		24.4%	Skin-prick testing
Yeo <i>et al.</i> (2007) ⁴¹ Children with OME (<i>n</i> = 123) and control (<i>n</i> = 141)	Otolaryngology		28.4% (vs control group 24.1%)	Skin-prick testing and RAST
Pelikan (2007) ⁴² Young adults (aged 16-26 yr) with chronic or recurrent bilateral SOM and suspected AR (<i>n</i> = 69)	Allergy and immunology		78.3%	History, intradermal skin test, and nasal challenges

AOM = acute otitis media; AR = allergic rhinitis; OME = otitis media with effusion; PMEE = persistent middle-ear effusions; SOM = secretory otitis media; RAST = radioallergosorbent test; SAR = seasonal allergic rhinitis.

control studies reporting higher frequencies of OME in allergic children compared with age-matched, nonallergic children or higher frequencies of allergy in children with OME compared with children without OME.

Dr. Rylander and Dr. Megevand³⁶ conducted a study by surveying parents of 304 children between the ages of 4 and 5 years, in Geneva, Switzerland. The parents answered questions pertaining to the relationship between several risk factors and respiratory and/or ear infections. For all infections, allergy was classified as a risk factor. Interestingly, mold and humid conditions in the home were significant risk factors for OM. The identification of humidity in the home, which is conducive to mold growth, and molds as risk factors for OM may be important, especially because of the perennial nature of exposure to this particular allergen (see potential importance of perennial allergens later in this article). However, these and other data collected based on parental perceptions should be interpreted with caution, because of the low reliability of such perceptions.

In particular, one previously published study observed nasal allergy and chronic OME in various pediatric populations.³¹ In a control group of 104 children, it was found that 17% had nasal allergy, 6% had OME, and 1.9% had both OME and nasal allergy. One experimental group consisted of 605 children with nasal allergy. Of those 605 children, 21% experienced OME (much higher than in the control population). Another experimental group involved children with chronic OME. A population of 259 children was observed and 50% were found to have nasal allergy (again, much higher than in the control population). The possible relationship of nasal allergy and OM is evident from these results.

Despite the extensive base of epidemiologic evidence supportive of a relationship between allergy and OM, the possibility of referral bias underlying these findings can not be ruled out. In that regard, Alles *et al.* studied 209 children with a history of chronic or recurrent OM referred to a "Glue Ear/Allergy" Clinic.³⁸ The diagnosis of allergy was evaluated by medical history, physical examination, nasal smears, and skin-prick testing in all children and by blood eosinophil counts and total IgE levels in a subset. The investigators diagnosed allergic rhinitis in 89% of the children, asthma in 36%, and eczema in 24%. Skin tests were positive to at least one of eight common aeroallergens in 57% of children and, in the identified subset, blood eosinophilia was documented in 40% and an elevated serum IgE in 28%. Unequivocally, allergy was more common in this group of children with OM when compared with the general population. However, the results may be compromised by possible referral bias to the Glue Ear/Allergy Clinic, thus inflating the prevalence of allergy in OM patients. This referral bias may compli-

cate the interpretation of other epidemiologic studies as well.

In another study, Velepik *et al.* tested 30 patients, aged 2–14 years, with OME ($n = 16$) or recurrent OM ($n = 14$), for allergy by skin-prick tests and specific serum IgE antibodies, and for GERD by 24-hour esophageal pH monitoring.³⁵ Eighteen of the children were diagnosed with reflux (60%) and seven were diagnosed with allergy (23%), four of whom also had reflux. They concluded that GERD was significantly more frequent than allergy in patients with OM.

In another study, South Korean otolaryngology investigators prospectively analyzed the prevalence of allergic rhinitis, serum eosinophil count, and IgE concentrations in serum and middle ear effusions in 123 children with OME and in 141 controls.⁴¹ Moreover, ET function after a nasal provocation test was compared between patients with allergic rhinitis and controls. The prevalence of allergic rhinitis in children with OME (28.4%) and control subjects (24.1%) did not differ significantly. These two groups also showed no differences in eosinophil count and serum and middle ear effusion IgE concentration. Abnormalities in ET function were the same in patients with allergic rhinitis and controls. The authors concluded that allergic rhinitis may not be related to the development of OME in children. Taken together, the aforementioned results show the high variability in estimates of allergy prevalence in OM patients.

In 2000, Tikkanen and colleagues³⁷ assessed the relationship between cow's milk allergy and OME. A group of 56 subjects, aged 10 years, with previously diagnosed milk allergy during infancy, were reexamined. The control group consisted of 204 subjects of the same age to which the results were compared. Results reported that all but four study subjects of the cow's milk allergy group developed tolerance to small amounts of milk protein, but two-thirds of the cow's milk allergy subjects had positive skin-prick tests to other antigens. Forty-five percent of the study subjects and 15% of the control subjects reported gastrointestinal symptoms after milk consumption. The frequency of allergic rhinitis and recurrent OM was three to four times higher in cow's milk allergy subjects in comparison with the controls. In addition to implying that allergies to other substances are linked with milk allergy, these results suggest that recurrent OM is associated to an underlying allergic susceptibility rather than the specific milk protein allergic reactions.

Evidence From Mechanistic Studies (Human and Animal Models)

ET Obstruction. There are a number of ways to study ET function,¹⁵ including sonotubometry, the nine-step pressure swallow tympanometry test, the Toynbee test

Table 2 Inducers of eustachian tube obstruction in humans

Allergen exposure in allergic rhinitis subjects
Natural exposure
Nasal challenge
Early and late-phase reactions
Pollen and dust mites
Nasal challenge with inflammatory mediators in subjects with and without allergic rhinitis
Histamine (eustachian tube hyperresponsiveness in allergic rhinitis)
Prostaglandin D ₂
Other inflammatory mediators
Viral upper respiratory infections in subjects with and without allergic rhinitis
Rhinovirus
Influenza
Respiratory syncytial virus

(pinch nose while swallowing), and the Valsalva test (exhale while pinching nose with mouth closed). The method most commonly used in our laboratories was sonotubometry. This involves placing a sound source in the nostril and a tiny microphone in the external auditory canal. Under normal conditions, when the ET opens briefly during the swallowing procedure, an increase in sound transmission is detected by the microphone. Conversely, increased sound transmission is not detected when the ET is obstructed by viral or allergen-driven inflammation and fails to open during swallowing.

Table 2 lists a number of the known inducers of ET obstruction. Natural exposure to relevant allergen (grass pollen) in allergic rhinitis subjects was shown to cause ET obstruction.⁴⁵ It seems possible that the prolonged ET obstruction required for the development of OM could occur during a 6- to 8-week pollen season, but this possibility seems even more likely as a result of daily exposure to a perennial aeroallergen such as dust mites. In that regard, intranasal challenge with dust mites was shown to cause ET obstruction in dust-mite allergic adult subjects.⁴⁶ Interestingly, in parallel with the temporal pattern of allergic reactions in the nose and lung, the ET underwent "priming" during natural pollen exposure in pollen allergic subjects,⁴⁷ and experienced both early (within 2 hours) and late (4–12 hours)-phase obstructive responses after intranasal challenge with relevant allergen.⁴⁸ The latter responses were correlated with the release of inflammatory mediators such as histamine.

In addition, nasal challenge with inflammatory mediators, such as histamine and prostaglandin D₂, in subjects with and without allergic rhinitis, produced ET obstruction.^{49,50} One early study even showed an

ET hyperresponsiveness to histamine in allergic rhinitis subjects.⁴⁹ Accordingly, Gentile *et al.* tested for a hyperresponsiveness to IL-6, a potent regulator of nasal inflammation,⁵¹ using a double-blind, placebo-controlled, crossover study design. Topical nasal challenges with placebo (saline) or with increasing doses (0, 0.01, 0.1, and 1 $\mu\text{g/mL}$) of recombinant IL-6 were conducted in 10 symptomatic allergic, 10 asymptomatic allergic, and 10 nonallergic adult patients. All subjects received pretreatment with intranasal histamine 15 minutes before the experimental challenge sequence. Although IL-6 challenge caused increased secretions (confined to the allergic subgroup), no effect was noted for nasal resistance, ET function, and middle ear pressure. These data support a hyperresponsiveness of allergic subjects with respect to secretion production. Past intranasal challenge studies using other inflammatory mediators (*e.g.*, histamine) also documented a differential response of allergic and nonallergic subjects with respect to nasal secretion production, but not other outcomes.⁵⁰ Together, these observations suggest that mucosal hypersecretion in response to inflammation characterizes allergic rhinitis patients, but that, contrary to the earlier observation,⁴⁹ the hyperresponsiveness does not extend to the ET and middle ear.

Middle Ear Pressure/Challenge. Although intranasal challenge with relevant allergen in allergic rhinitis subjects reproducibly caused ET obstruction (see aforementioned data), changes in middle ear pressure were more difficult to establish during those procedures. One study conducted in Europe did show, however, that middle ear pressures of allergic subjects shifted in a negative direction during natural exposure to relevant allergen.⁵²

In most or all of the earlier studies using the human model of nasal allergen challenge, subjects with middle ear disease were specifically excluded. In contrast, one recent challenge study selected AR subjects with a history or concurrent evidence of middle ear disease and documented a more rapid development of middle ear ambient underpressures after challenge with a relevant allergen when compared with control subjects.⁴² In 69 young adults with chronic or recurrent secretory OM (SOM), 173 nasal challenges with allergens were performed by anterior rhinomanometry combined with tympanometry. In 42 control subjects with only allergic rhinitis and no history of middle ear disease, 42 nasal challenges with allergens were repeated and combined with tympanometry. The study design was a placebo-controlled comparison. Dust mites and grass pollen were the allergens used most commonly for nasal challenge. Of the 129 positive nasal responses, 117 were accompanied by significant negative changes in middle ear pressure. Three types of nasal responses

were observed: immediate (within 2 hours of allergen exposure), late (3–24 hours later), and delayed (24–56 hours later). Interestingly, the middle ear pressure changes coincided temporally with those of the respective nasal responses. The author concluded that these results may confirm the occurrence of chronic SOM in some adult patients and the possible involvement of nasal allergy in chronic SOM and that the nasal challenges with allergen performed by rhinomanometry, combined with tympanometry, seem to be a valuable supplementary tool for the diagnosis of this disorder.

Downs *et al.* examined the consequences of middle ear histamine challenge on ET function using a rat model.⁵³ Histamine or saline control was directly injected into the middle ear mucosa through the tympanic membrane and ET function was assessed. Compared with controls, histamine caused an increase in the pressures required to passively open the ET and also the pressures at which the tube passively closed. These results support an increase in the periluminal tissue pressures of the ET and a decrease in the efficiency of ET opening. Also, in histamine challenged ears, the time required for dye placed into the middle ear to reach the nasopharynx was increased. This is a standard test of the ET clearance function, and taken together with the aforementioned results, suggests that the pressure regulating and clearance functions of the ET are compromised by middle ear histamine.

In a study of the role of mast cells in OM, wild-type mice, mast cell-deficient mice, and mast cell-deficient mice whose mast cell populations were restored by transplantation of bone marrow-derived mast cells were challenged by using models of bacterial and allergic middle ear inflammation.⁵⁴ In those models, middle ear ovalbumin and bacterial challenges were conducted. The results indicated that mast cells accounted for a substantial proportion of the innate immune response to bacteria in the middle ear. Moreover, combination challenge with both bacteria and allergen in allergen-sensitized, wild-type mice delayed recovery. The authors concluded that this mechanism may link responses to allergy and infection in the middle ear mucosa, and thus the mast cell may be a critical control element in the pathogenesis of OM.

Middle Ear Fluid/Biopsy. A variety of inflammatory mediators have been detected in the middle ear fluid and/or biopsy specimens from children with OME, including major basic protein, eosinophil cationic protein, myeloperoxidase, and mast-cell mediators such as histamine and tryptase.^{55–61} Moreover, a localized specific immunoglobulin E production in the middle ear fluid was supported in one study.⁶²

Cytokines levels have also been measured in middle ear biopsy specimens or fluids. Middle ear mucosal biopsy specimens were obtained at surgery from eight

Table 3 Potential allergy-based therapeutic approaches for eustachian tube dysfunction and otitis media

Environmental controls—no studies
Antihistamines/decongestants—no benefit
Antivirals—no benefit
Steroids—no benefit
Subcutaneous immunotherapy—no studies
Immune modulatory oligonucleotides—showed promise in animal model

allergic children with OME and from seven nonallergic control children undergoing stapedectomy.⁶³ All specimens were assayed for distribution of CD3 and major basic protein by immunohistochemistry staining and for IL-5 mRNA by *in situ* hybridization. These Th-2-type measures were increased in the biopsy specimens recovered from the allergic OME patients versus the control patients. A follow-up study showed similar findings in the middle ear effusions of allergic children with OME.⁶⁴ The investigators concluded that type I hypersensitivity (allergy) involving Th-2-type cytokine and cellular profiles may be a contributing factor in the persistence of OME in atopic children.

What Is the “Allergic Shock Organ”? If an allergic reaction is crucial for the development and/or persistence of OM, what is the site of the responsible allergic reaction (*i.e.*, the “allergic shock organ”)? As shown in Fig. 1, potential sites include the nasopharynx, the ET, and the middle ear itself. However, in all of the various animal and human models of OM, allergen exposure was capable of producing nasal and ET obstruction and middle ear underpressures (in some studies), but not OME. Indeed, monkeys sensitized to allergen and administered provocative intranasal allergen challenge⁶⁵ or direct middle ear allergen challenges (William J. Doyle, personal communication, 1990) did not develop OM. Because direct middle ear allergen challenge (bypassing the nasopharynx and ET) did not induce OM, these data suggest that the middle ear is not the “allergic shock organ.” Thus, the most likely responsible “allergic shock organ” is the ET because it reproducibly obstructs following allergen challenge in sensitized individuals and prolonged obstruction can lead to the development of OM.

Evidence from Controlled Clinical Trials (Human)

Early trials using antihistamines and decongestants in human models produced conflicting results with regard to effects on ET obstruction (Table 3). In the first such study, terfenadine significantly dampened the sneezing response during a provocative intranasal histamine challenge in allergic rhinitis subjects but had no

effect on the increasing ET obstructive responses to increasing histamine doses.⁶⁶ In the second study, the effect of an antihistamine/decongestant on nasal and ET function after intranasal ragweed pollen challenge was evaluated.⁶⁷ Not surprisingly, there were increasing levels of ET obstruction with increasing ragweed doses and active therapy significantly dampened but did not eliminate the ET obstructive responses.

A variety of allergy therapies has been tested in OM patients in controlled clinical trials, and the results have largely been negative for antihistamines and decongestants⁶⁸ and steroids.⁶⁹ However, none of these trials specifically enrolled the subset of OM patients with allergy and none of the more specific allergy therapies (*e.g.*, environmental controls and allergen immunotherapy) has been tested. Indeed, recent Cochrane Reviews concluded that there was insufficient evidence to support a role for antihistamines and decongestants, either alone or in combination, in the treatment of OME or acute OM in children.^{70,71}

One study on the role of food allergy in OM found a very high frequency (78%) of food allergy in children with recurrent SOM. Avoidance of the implicated food improved the SOM in most of the children and the SOM returned on rechallenge with the implicated food. However, the results have not been confirmed and do not support definitive conclusions on the role of food allergy in OM and the role of food avoidance in the treatment of OM.⁷²

The aforementioned results, among others, prompted the 2004 clinical practice guidelines on OM to conclude that no recommendations could be made for "...allergy management as a treatment for OME based on insufficient evidence of therapeutic efficacy or a causal relationship between allergy and OME".⁷³

Do Histamine and Leukotrienes Mediate Both Allergic Rhinitis and OM?

Histamine is a well-known mediator of allergic rhinitis, and based on the aforementioned results may be a mediator of OM as well (disease induced by direct middle ear application in an animal model). The same is true for cysteinyl leukotrienes, which also are well-characterized mediators of allergic rhinitis.⁷⁴ In studies, leukotrienes are present at the site (nasal) during viral upper respiratory infections that trigger OM,^{75,76} middle ear injection of leukotriene D₄ directly induces experimental OME in animals,⁷⁷ and a human controlled clinical trial yielded supportive results.⁷⁸ In the latter trial,⁷⁸ montelukast, added to antibiotic, reduced the duration of middle ear effusion after acute OM compared with placebo (percent with effusion at week 4).

ROLE OF VIRAL UPPER RESPIRATORY INFECTIONS

Most evidence shows that the majority of new OM episodes are a complication of a viral upper respiratory tract infection.⁷⁹ Indeed, ET obstruction has been observed after experimental intranasal challenge with rhinovirus, influenza, and respiratory syncytial virus^{80–82} (see Table 2). Even more importantly, the development of experimental OM was clearly shown in adults challenged intranasally with influenza virus.⁸³ Interestingly, elevations of histamine metabolites were observed in urine during such infections as well. Moreover, controlled clinical trials of some⁸⁴ but not all⁸⁵ antihistamines in adults with common colds showed benefit for certain cold symptoms. Taken together with the aforementioned results, histamine may be a contributing inflammatory mediator to the pathogenesis of two of the major risk factors of OM (allergy and viral upper respiratory tract infection) as well as OM directly. Disappointingly, no beneficial effect of antiviral therapy on the ET obstructive response to influenza virus challenge was shown.⁸⁶

IMPLICATIONS FOR DIAGNOSIS AND TREATMENT

Given the strong likelihood of allergy as a risk factor for OM, allergic rhinitis patients should be evaluated for OM and patients with OME should be considered for an allergy evaluation. If significant allergic rhinitis is diagnosed in a patient with OME, it should be treated aggressively (as in any case of moderate to severe allergic rhinitis) until further studies are conducted.

FUTURE DIRECTIONS

Future studies will undoubtedly focus on identification of the "at-risk" population based on genetics and environment and on new therapeutic approaches. An at-risk group may then potentially benefit from as yet undefined preventative strategies. Indeed, cytokine genotypes have been used to help identify those at risk of OM. In that line of investigation, Patel *et al.* provided data suggesting that tumor necrosis factor α (–308) and IL-6 (–174) polymorphisms are associated with increased risk for OM susceptibility and placement of tympanostomy tubes and that environmental factors such as breast-feeding may modify the risk for OM susceptibility in polymorphic individuals.⁸⁷

Also, immune modulatory oligonucleotides have shown promise therapeutically in animal models. Blanks *et al.*^{88,89} concluded that immune modulatory oligonucleotides, *via* transtympanic application, can prevent and treat allergy-induced ET dysfunction in rats and that immune modulatory oligonucleotides may offer substantial promise in the future manage-

Table 4 Summary

Allergic rhinitis and OM are strongly linked epidemiologically and mechanistically. Evidence supports a role for histamine in both conditions. A causal relationship between the two conditions has not been proven. Therapeutic trials using common allergy therapies have either not been conducted or showed no benefit. Allergic rhinitis is likely a risk factor for OM. Diagnostically, allergic rhinitis patients should be checked for OM and patients with OME should be considered for an allergy evaluation. Therapeutically, allergic rhinitis should be treated aggressively in patients with both allergic rhinitis and OM until further studies are conducted. No definitive conclusions about a role for food allergy in causing or treating OM can be made.

OM = otitis media.

ment of OME. Clearly, studies in humans will be needed in the future.

SUMMARY

In summary of the previous discussion (Table 4), allergy and OM are both very common conditions and are linked epidemiologically and mechanistically.¹⁸ If allergy is causal in OM development, the requirements likely include nasal allergy in a child or adult with marginal constitutive ET function and long duration exposure to a relevant allergen. In that context, the nasal inflammation provoked by allergen exposure would downgrade the preexisting marginal ET function and increase the rate of middle ear underpressure development *via* increased middle ear blood flow. This would effectively shift the middle ear gas supply/demand balance to favor demand with consequent OME development. As mentioned previously, past studies in adults with allergic rhinitis support the first component of this model, because ET obstruction developed after intranasal challenge with or natural exposure to relevant allergens. However, the second component has been identified in animal studies but has not been evaluated in humans. In the previous contexts, viral and allergen interactions in promoting such outcomes are feasible and even likely, given overlapping seasons of exposure.

Research supports a causal relationship between the allergy and OM conditions, but conclusive proof is lacking. If there is causality, histamine and possibly leukotrienes are likely to be involved. Clearly, more studies are needed to examine the relationship between allergy, inflammatory mediators, and OM.

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