



Efficacy of allergy immunotherapy as a treatment for patients with chronic otitis media with effusion[☆]

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KEYWORDS

Allergy;
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Summary

Objective: Controversy persists over the significance of allergy as it might relate to chronic middle-ear disease as no controlled study of the efficacy of allergy immunotherapy has been published. The aim of this study was (1) to evaluate the atopic status of patients with intractable chronic otitis media with effusion or drainage from their middle ear and (2) to determine in this select population the efficacy of specific allergy immunotherapy in preventing or limiting the duration of their chronic middle-ear disease.

Methods: This was a prospective, cohort study of patients cared for in a private community practice. History, examination, audiogram, tympanometry and recurrence of effusion/infection were recorded on 89 patients (52 children <15 years old, 37 adults) referred with (1) effusion found to warrant myringotomy and ventilation tubes, or (2) chronic drainage from a perforation or tube. All were evaluated for allergy by intradermal skin testing according to criteria of the American Academy of Otolaryngic Allergy. A control cohort of 21 patients who refused therapy was included. Intervention consisted of immunotherapy for dust, pollen, and molds. Recurrence or persistence of fluid or drainage following 2–8 years of therapy was compared to the patient's pretreatment status.

Results: All 89 OME patients proved to be atopic. Most were allergic to dust (94%), animals (44%) and molds (88%) while 9% were allergic only to seasonal pollens. Associated allergic diseases included asthma (21%) and allergic rhinitis/sinusitis (63%). Otitis was the sole symptom among 37%. Immunotherapy provided complete resolution of effusion or drainage in 85% of 127 ears.

Conclusion: Intradermal testing proved all 89 patients with intractable middle-ear disease in this study who presented with chronic effusion or chronic draining perforations or tubes to be atopic. Specific allergy immunotherapy significantly improved

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5.5% and completely resolved 85% of chronic otitis media with effusion in these ears. None of the controls resolved spontaneously ($p < 0.001$). This supports the hypothesis that in many, otitis media with effusion is an immune mediated allergic disease and suggests that these patients deserve consideration for aggressive evaluation and allergy treatment, as most respond to immunotherapy.

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1. Introduction

Otitis media with effusion (OME) describes an inflammatory process within the middle-ear space that is generally associated with accumulation of fluid. OME is associated clinically with hearing loss, subsequent delayed speech development and permanent middle-ear damage with mucosal changes. The cause of OME has been the source of much controversy, generating numerous studies in an effort to clarify the issue. Chronic middle-ear disease likely represents an entity with multiple etiologic factors such as genetic predisposition, endogenous and exogenous factors. It is heterogeneous in its presentation. Its categorization depends on the length of time effusion persists, presence of purulence and whether the tympanic membrane is intact, perforated, or draining.

Atopy has been defined as the sensitization or predisposition to hyperreactivity to a normally non-reactive antigen. Allergic patients are considered to be those who express symptoms related to exposure and are not merely sensitized [1].

Despite studies in China, Japan, USA, Canada, and Sweden demonstrating that all the mediators required for a Th-2 inflammatory response, including eosinophil cationic protein, tryptase, and/or IL-5 mRNA cells, CD3+ T cells [2], eosinophils [3], mast cells [4], Rantes [5], prostaglandins [6] and IgE [7] are present in the majority of ears with chronic effusion, a role of allergy with clinical applicability to chronic middle-ear disease is not embraced by most otologists. A recent clinical practice discussion and literature review states that "the relation between allergy and OME will remain controversial until well-controlled clinical studies are conducted documenting that in select populations anti-allergy therapy is efficacious in preventing or limiting the duration of OME" [8]. The aim of this study was to examine that premise.

It has been shown that "there are no substantial differences in Eustachian Tube (ET) function between ears that develop OME recurrence and ears that do not" [9]. It is also a commonly held myth that the eustachian tube will grow to normal size as children mature despite evidence that there is no difference in the size of either the isthmus or pharyngeal portion of the ET in children with OME vs.

normals [10]. This suggests that our understanding of ET dysfunction as a reflection of a pathophysiologic manifestation of significant mucosal disease may be incomplete. A direct effect of allergy on ET dysfunction is conjecture, though supported by some mice studies [11]. This clinical study is an attempt to establish indirect evidence of such a relationship. The question being asked is: if a patient has documented allergies, will conventional immunotherapy directed at those specific allergens alter the course of their disease?

2. Methods

Lacking the milieu to conduct an ideal randomized, double blind placebo-controlled (DBPC) study, we designed a prospective, cohort study to assess both the atopic status of patients with intractable chronic OME or drainage from the middle-ear using intradermal skin testing (IDT) as well as the efficacy of allergy immunotherapy (IT) as a treatment intervention. All patients over 4 years of age presenting to a solo-practitioner, community-based otolaryngologist from 9/95 to 12/05 with any of the variations of intractable chronic middle-ear disease were enrolled prospectively; follow up continued to 12/07. All were assessed in an identical manner by history, otologic exam, pneumatic otoscopy, audiometry and tympanometry and offered the same treatment options. Any patient with (A) chronic OME >6 months during a 1-year period and no previous myringotomy and tubes (M&T) or OME >3 months warranting a second M&T, and/or (B) chronic suppurative otitis media (CSOM) with persistent drainage from a perforation or tympanostomy tube which had been otherwise unresponsive to oral and/or topical antibiotics was included. Patients with cranial facial abnormalities, muscular dystrophy, or a history of previous cholesteatoma, mastoidectomy or autoimmune disorders were excluded. Selection for myringotomy with placement of pressure equalization tubes was based on standard criteria including persistent middle-ear effusion (MEE), abnormal tympanogram and a conductive hearing loss greater than 15-dB. IDT for specific allergens was performed on all patients following approval of the Franklin Memorial Hospital (Farmington, Me) Committee on Ethics and Human Experi-

mentation plus signed patient or parental consent for both testing and treatment. A total of 89 patients, 45 male and 44 female were enrolled. Fourteen additional patients were identified but lost to follow up and not included in the reported data. Demographics including age, number of tubes and patients who had had their tonsils and/or adenoids removed are listed in Table 1. Among the 138 ears in the treatment cohort, 8 normal ears and 1 with a cholesteatoma were excluded, leaving 127 diseased ears. Among 21 patients whose families refused to initiate or maintain IT, 3 had unilateral disease, leaving 39 diseased ears as controls.

Testing was performed for a battery of 11 inhalants and 4 molds (dust mites der P and der F, cat, dog, cockroach, Timothy and Meadow Fescue grass, long and short ragweed, birch, oak, *Alternaria*, *Hormodendrum*, *Mucor*, and *Fusarium*). Intradermal test injections consisted of an allergenic extract in volumes of 0.01 ml to produce a 4-mm wheal according to American Academy of Otolaryngic Allergy (AAOA) guidelines. The skin tests were performed with 1:500 wt. vol and successive serial five-fold weaker dilutions of the allergenic extracts. For each challenge results were considered positive

when a wheal of 7 mm or larger was observed that was at least 2 mm larger than the wheal of a glycerin control of the same dilution strength, all measured after 10 min. A separate staff of trained allergy nurses performed testing. Patients were categorized as atopic if they reacted positively to at least two allergens at a class 2 (1:500) dilution or greater. This definition was designed to intentionally exclude borderline atopic patients. Twenty-one individuals self-selected to be a "control cohort" by choosing for a variety of reasons not to proceed with IT. Selection criteria for these patients had been identical to that for the treatment cohort. Reasons for non-participation included lack of insurance, discontinuation of therapy in less than 1 years time, moving, or simply refusing allergy immunotherapy injections.

Intervention consisted of immunotherapy according to AAOA criteria. IT dosage for those antigens eliciting a reaction at class 2 or greater was administered at the maximum tolerated dosage. Injections were maintained weekly throughout the first year and advanced until the patient could maintain a symptom free state while on a 3-week dosage interval for a year, after which therapy was discon-

Table 1 Demographics of treatment and control cohorts

	Treatment	Control	Total	<i>p</i> -Value
Number of patients	68	21	89	
Atopic, no. (%)	68 (100)	21 (100)	89 (100)	ns
Sex, no. (%)				
Male	34 (50.0)	11 (52.4)		ns
Female	34 (50.0)	10 (47.6)		ns
Age in years, no. (%)				
4–15	37 (54.4)	15 (71.4)	52 (58.4)	0.19 = ns
16–51	18 (26.4)	5 (23.8)	23 (25.8)	0.85 = ns
51–70	13 (19.1)	1 (4.7)	14 (15.8)	
Mean age of children 4–15	9.3	8.5		ns
Mean age of all patients	26.6	18.7		
Number of sets of tubes per patient including those inserted during the study				
No tube	11	1	12 (13.4)	
One tube	19	4	23 (25.8)	
Two tubes	15	9	24 (26.9)	
Three tubes	11	4	15 (16.8)	
Four tubes	8	1	9 (10.1)	
Five to ten tubes	3	2	5 (5.6)	
Mean # tubes/patient	1.94	2.29		0.3 = ns
Total # patients with tubes	57 (83.8)	18 (85.7)	75 (84.2)	ns
Surgical interventions				
Adenoidectomy only	16 (23.5)	5 (23.8)	21 (23.6)	
Or T&A	9 (13.2)	3 (14.2)	12 (13.4)	
Total T&A + A	25 (36.8)	8 (38.0)	33 (37.0)	0.3 = ns
Mean no. + allergens by IDT	10.16	13.0		

no. (%): number (%); T&A: tonsillectomy and adenoidectomy; A: adenoidectomy; *p*: Mann–Whitney *p*-value.

tinued. Mean dosage time was 4 years. Patients were all seen initially at 4 months after initiation of therapy. They were reexamined on a 6-month schedule throughout the study interval to evaluate presence of fluid, history of interim treatment for drainage or infection, compliance with therapy and status of other allergy symptoms.

At the conclusion of the study period treatment patients included here had been followed for 2–8 years and most tympanostomy tubes had extruded. Determination of exacerbations was assessed and noted. Patients were categorized as having complete resolution (no evidence of effusion, normal hearing and normal pneumatic otoscopy and/or tympanometry), partial resolution or treatment failures after a minimum of 1 year on therapy. Each reported exacerbation which required any intervention, yet cleared within a month or less, whether with topical antibiotic ear drops, antihistamines, and/or a prednisone taper of 30 mg over 10–15 days was recorded. Any patient with up to two episodes during any follow up year of recurrent drainage or effusion (reported or observed) regardless of cause was defined as “partial resolution.” Patients with persistent disease similar to their pretreatment status lasting more than 2 months or recurring three or more times a year were defined as treatment failures. Any patient requiring replacement of a tympanostomy tube while on immunotherapy was considered a failure. Follow up of controls was more sporadic and depended on treatment of recurrent problems. The Mann–Whitney *U*-test with Bonferroni’s correction was used to compare the different groups. Statistical calculations were performed by means of the statistical package, Instat[®] (Graphpad Software, San Diego, CA).

3. Results

All patients in both treatment and control groups were found to be atopic. The sex, age, number with

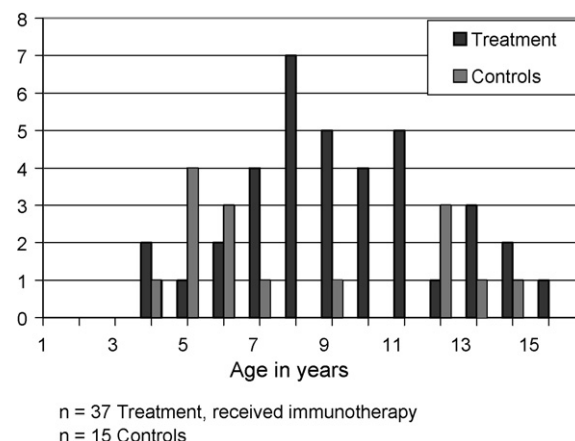


Fig. 1 Distribution of the number of patients by age among 52 children presenting with OME. Treatment, received immunotherapy ($n = 37$); controls ($n = 15$).

tubes or adenoid surgery in the two groups were compared (Table 1). The mean number of sets of tubes, including those inserted during the study, was similar in the two groups (2.58, 2.40). No statistical difference was found between the treatment and control cohorts for any parameter other than the apparent excess number of 51–70 years olds in the treatment group. This suggests that overall there was a relative absence of departure from baseline balance in the selection of the patients for either group in all other parameters (Table 1). The distribution by age of 52 children in both groups is presented in Fig. 1. The numbers who had chronic effusion, eventually required tympanostomy tubes, presented with retraction or atelectasis as well as those with drainage from a tube, or perforation are listed in Table 2.

Most (85.7%) patients were panallergic to an average of 9 allergens including dust (94%), animals (47%), ragweed (67%), and molds (88%). Nine were allergic only to seasonal pollens. A similar number of patients in both groups also had associated allergy

Table 2 Classification of individual ear disease among 89 patients on initial presentation

Problem at presentation	Treatment ears	% Atopic	Control ears	% Atopic
Normal (unilateral)	8 ^a		3 ^a	
cholesteotoma	1 ^a			
TM retraction + effusion	16 (12.6)		5 (12.8)	
Atelectasis + effusion	7 (5.5)		3 (7.7)	
Subtotal	23 (18.1)	100	8 (20.5)	100
Chronic OME, no tube	57 (44.9)	100	14 (35.9)	100
Requiring tubes	22 (17.3)		8 (20.5)	
Drainage from tube	14 (11.0)		9 (23.1)	
From perforation	11 (8.7)		3 (7.7)	
Total OME ears ^a	127	100	39	100

^a Normal and cholesteotoma ears excluded.

Table 3 Response of 68 patients to immunotherapy vs. 21 controls from presentation to completion of immunotherapy

	Treatment group		Complete resolution	Partial resolution	Failed
	Patient age	# Patients			
	4–15	37	34 (92.2)	3 (7.8)	0
	16–50	18	15 (83.3)	2 (13.3)	1 (4.1)
	51–70	13	6 (46.2)		7 (53.8)
Total		68	55 (80.9)	5 (7.4)	8 (11.8)
Controls	4–59	21	0	0	21 (100)

symptoms at time of presentation including asthma (21%, 13%) and allergic rhinitis (63%, 53%). Importantly, over a third in both groups (37%, 48%) presented with otitis as their only allergic symptom. Surprisingly, allergic otitis presented as unilateral disease in 13%.

Results are tabulated by both patient (Table 3) and individual ear response (Table 4). Initial improvement as seen by reduction of effusion, pressure sensation, drainage and/or hearing improvement among our treatment cohort typically was observed within 4 months of beginning IT. Most, 108 of 127 (85.0%) ears became and remained free of effusion or drainage within a year on IT, while seven additional ears (5.5%) experienced one or two exacerbations and were considered to be partially resolved for the duration of their treatment. More than half of the study patients, having completed the 4–5 years necessary for adequate therapy, have been able to discontinue their shots and continue to remain disease free, as is typical of the experience in treating allergic rhinitis by IT. Some have required continual immunotherapy up to 8 years to control their asthma, yet their ears have remained free of effusion. None of the controls resolved spontaneously ($p < 0.001$).

Half of the ears presenting with effusion and atelectasis and half of those with effusion and myringostapedopexy failed to return to a normal

position, though the effusion itself had often cleared. Twelve ears (9.5%) from eight patients (11.8%) failed. Seven (87.5%) of the failures were patients who were over age 50 when first seen. Three of these failures had subsequent eustachian tube endoscopy according to methods described by Dr. Dennis Poe in his recent publication [12]. No pathology was found to explain their OME. None of the children <15 years old failed nor did any require tube replacement.

One ear with a perforation (following a welding slag injury) which had drained 3–6 times a year for 20 years and had developed a secondary fungal external otitis became totally dry within 4 months of initiating allergy IT for molds. His perforation has since closed and the ear has remained free of effusion for over 2 years. Overall four of the 11 perforations closed spontaneously. One woman in her early seventies had bilateral 50 dB sensorineural hearing loss and perforations which had been draining for years, making it nearly impossible to wear her hearing aids. Her ears became dry within 2 months of initiation of IT and have remained completely dry for over 2 years.

Ten patients served as their own control. Although they became free of effusion or drainage on initial IT, their effusion recurred when their shots were discontinued prematurely. All have since resumed therapy and nine resolved. Eleven others

Table 4 Response to immunotherapy by individual diseased ear from presentation to completion of immunotherapy

	Problem at presentation			
	#Ears	Complete resolution	Partial resolution	Failure
Chronic OME, no tube	57	48	4	5
requiring tube	22	21	1	0
TM retraction + effusion	16	14	1	1
Adhesions + effusion	7	6	1	0
Drainage from tube	14	9		5
from perforation	11	10		1
Number on immunotherapy ^a	127	108 (85.0)	7 (5.5)	12 (9.5)
Control cohort ^a	39	0 (0)		39 (100)

^a Excludes normal and cholesteotoma ears.

had been tested, found to be atopic but either refused IT outright or could not maintain IT for the minimum of 12 months required to determine treatment efficacy. Within 2–9 years these patients had all returned with a history and signs of persistent effusion or drainage.

3.1. Comment

This study is the first to our knowledge to document that in a select population anti-allergy therapy is efficacious in preventing or limiting the duration of OME while comparing treatment patients to a control cohort. Direct proof that allergy contributes to chronic OME and/or other manifestations of chronic middle-ear disease is best done by a randomized, DBPC trial. None have been published. Objective information on the allergic status of OME patients is lacking in available databases [13] making the true incidence of allergy unknown. For lack of objective studies, the allergy connection to middle-ear disease has been discounted for 30 years. Despite the inherent limitations of a clinical study in a community practice, the implications of these results should not be dismissed out of hand. Rather, they raise the question of whether treatment using immunotherapy, an established, conventional modality recognized to be effective in treating and reversing allergic rhinitis and asthma, is worth considering for those patients with this type of otherwise seemingly intractable middle-ear disease.

Proof of the hypothesis that chronic OME is an immune mediated allergic disease requires several steps. First, establish a relevant, associated, objective diagnosis of atopy in patients with persistent effusion or middle-ear drainage. This was done in 100% of both the treatment and control cohorts. Other investigators using objective intradermal and in-vitro testing have similarly demonstrated that 72–93% of the children with otitis media with effusion are atopic: Tomonaga (72%) [14], Nsouli (78%) [15], Hurst (81%) [3], Hall (100%) [16], McMahan (93%) [17]. Secondly, establish an association of allergic immune-mediated histochemical reactivity within the effusion itself. Recent guidelines from otologists, pediatricians and allergists support the hypothesis that there is a relation of atopy to chronic OME. The evidence is conclusive enough for them to state that the middle-ear epithelium of atopics has all the components required to behave in a manner similar to that of the rest of the upper respiratory system, and that “like other parts of respiratory mucosa, the mucosa lining the middle-ear cleft is capable of an allergic response” [18]. Finally, one must demonstrate a dose response curve and consistency of results. This study found

that allergy immunotherapy directed at those allergens specifically identified by intradermal skin testing proved effective in completely controlling OME in 80.9% of patients. None of the control cohort resolved spontaneously ($p < 0.005$ by Fischer’s Exact Test). These findings are in keeping with other studies which, though lacking a control group, have also demonstrated that when a patient’s allergies are properly treated with IT and/or diet elimination, their effusion resolves in the majority of patients: McMahan (98%) [17], Nsouli (86%) [15], Hurst (100%) [19], Psifidis (78%) [20].

Although 100% of both control and treatment cohort patients in this study were atopic it does not prove that all patients with OME are atopic. All were not tested, only those who fit the criteria. The author’s reputation as having a particular interest in allergy and chronic middle-ear disease might have led to a referral bias with a higher incidence of atopy than found in the community at large, although 40% had no associated allergic symptoms to prompt referral on those grounds. Secondly, it has been documented that by the natural progression of the disease 1/4 of “all” OME patients might be expected to resolve spontaneously [21]. This group might have been excluded by our patient selection criteria whereby only those with persistent disease were included. Thirdly, it is possible that the 14 “lost” individuals had all simply recovered. Including them in the control cohort would then alter the results so as to have 35 controls. The resulting ratio of resolved:failed among controls of 14:21 as compared to the ratio for the treatment cohort of 60:8 would still support a significant difference by Fischer’s exact test of $p < 0.001$ in favor of IT.

The age of this patient group seems skewed towards older children because we evaluate children aged 1–5 using in vitro (RAST or micro-ELISA (THABEST-IgE[®], Molecular Medicine, Inc., Denville, NJ, USA) testing. They are treated with sublingual therapy and often for foods, thus did not meet the criteria for inclusion. Our previous report [16] of 91 consecutive OME patients more accurately reflects the age distribution of OME in the practice, with 37.1% age 14 months to 6 years, 42.3% age 6–18 years and 20.6% adults, of whom 81% were atopic. Yet the current study population seems to be fairly representative of the typical range of OME patients as 34 (38%) presented with no previous M&T, 12 not needing tubes (Table 1) and 22 initially requiring tubes at the onset of the study (Table 2). Others presented with more refractory disease, having already had 3 to 10 sets of tubes (Table 1).

The surprising finding that 100% of patients in this study were atopic by objective testing implies selec-

tion bias. This more likely is a result of the marked increase in sensitivity of IDT vs. either prick (sensitivity <45%) or RAST testing [22], especially in patients with low total IgE levels. It is for this reason that practice parameters of the AAAAI [23] and AAOA [24] suggest that in the face of a negative prick test, intradermal testing may be the only practical way to determine sensitivity. The concern of a false positive IDT resulting from this increased sensitivity was addressed by requiring two positive tests. The average OME patient proved to be sensitive to nine allergens (range 4–15). Since chronic otitis has been shown to be a low level IgE mediated disease similar to allergic rhinitis, with 2/3 of OME patients having a serum IgE < 100 (mean 93.8 μ g/L) [3], we therefore chose intradermal testing for its greater sensitivity and reproducibility as the test for atopy.

Immunotherapy was chosen to treat the underlying allergy because it has been shown to have a long lasting effect on T lymphocytes, acts in the earliest stages of immunologic response, and can revert an atopic from a Th-2 response back to being a normal Th-1 responder [25]. This has been documented in cases of asthma, allergic sinusitis, and now clinically in chronic OME, all of which are diseases of atopics involving hyper-reactive mucous membrane lining various aspects of the respiratory tract [6].

OME is a multifactorial disease, of which symptoms of respiratory allergy, otitis heritability and IgE sensitization are all independently associated [26]. Allergy adds unique co-morbidity. Thus a child who gets an episode of acute otitis media is up to three times more likely to develop OME if that same child is also allergic [27]. For this reason each of the past five International Symposia on Otitis Media have called for outcome based studies of allergy therapy. This is the first to do so with a control cohort.

It is important to make a distinction between acute otitis media and chronic otitis media, either of which may also present as an acute episode of otorrhea through a perforation or tympanostomy tube. These are two distinct diseases. Acute otitis media will clear in 80% of cases in 3 days. Only 17% of AOM patients remain otitis prone. Spontaneous resolution rates of OME are reported to be 25% (95% CI: 13–39%) within 6 months. The median duration of untreated OME is reported to be a staggering 6.1–7.8 years [21]. This study focused on only the group who remained unresolved at 6 months. Although OME is predominantly a disease of children, it may extend into adulthood. Many of the older patients reported having had tubes and/or drainage before age 15.

It seems essential in the short term to remove the fluid from an ear with chronic effusion so as to return hearing to normal. This also serves to physically remove a host of very potent inflammatory mediators (ECP, IL-4 and 5, tryptase, myeloperoxidase) that are known to perpetuate chronic inflammation.

Chronic OME and CSOM may be manifestations of the same middle-ear pathology. Patients initially assigned to groups A or B differed only in the duration of their disease and the integrity of the tympanic membrane; i.e. intact, perforation or tube. Our data (Table 4) showing that 19 of 25 (76%) ears with chronic otorrhea from a perforation or tube resolved and remained dry for years suggests that more studies are needed to find the true incidence and relation of allergy as a risk or perhaps contributing factor in cases of recurrent otorrhea and thereby lead to more specific therapeutic modalities. Certainly allergy puts a patient at risk for recurrent sinus infections as it adds to conditions which can lead to an environment that is suitable for mucous stasis, bacterial overgrowth, and chronic inflammation [28]. The middle ear, which is identical in its mucosal lining to a sinus, would be expected to behave similarly as a part of a unified airway [6]. That allergy is a confounding factor in the development of asthma is well established [29] and it is beginning to be considered so in otitis media [8].

Why 54% of the 51–70-year old group did not respond to IT is unknown. The number in this group is too small to analyze. Their failure may be a reflection of the duration that these individuals had chronic middle-ear disease, or they may prove to be a significantly different subset.

The purpose of this study was to evaluate the efficacy of immunotherapy in reducing chronic middle-ear effusion and drainage in a community practice setting. Further affirmation that desensitization therapy can be effective in managing chronic OME would be to have the otologists truly blinded as to which patients were receiving allergy therapy. The use of a placebo agent was not considered due to ethical considerations in dealing with insurance billing. This work supports previous suggestions that the middle ear may serve as a target organ for allergic reactions [8,18] in that patients with OME were almost universally atopic and resolved with immunotherapy. It suggests that the association between allergy and OME deserves to be re-examined, applying the advances in knowledge of inflammation which have been discovered this past quarter century as regards other chronic mucosal inflammatory respiratory tract diseases (i.e. asthma and sinusitis) to the study of the middle ear. In chronic otitis media, as in

chronic sinusitis, it is the host's *immunologic status* that appears to hold the key to understanding the underlying mucosal response of that individual to the bacteria, viruses or biofilms that initiate the immunologic processes that lead to his/her sinusitis, asthma or middle-ear disease.

4. Conclusion

Intradermal testing proved all 89 patients (100%) with intractable middle-ear disease in this study who presented with chronic effusion or chronic draining perforations or tubes to be atopic. Specific allergy immunotherapy significantly improved 5.5% and completely resolved 85% of chronic otitis OME in these diseased ears. All children <15 and most adults resolved within 4 months and have remained free of disease while on allergy IT for 2 or more years of follow up. None of the controls resolved spontaneously ($p < 0.001$). This data suggests that many patients with intractable, refractory middle-ear disease appear to be atopic and deserve consideration for an aggressive allergy evaluation, as most respond to immunotherapy.

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