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Review Article

The Middle Ear: A Major Target of Upper Respiratory Tract Allergic Disease

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Background

Chronic otitis media with effusion (OME) describes a prevalent inflammatory process within the middle-ear space that is generally associated with the accumulation of fluid. OME is associated clinically with hearing loss, subsequent delayed speech development, and permanent middle-ear damage with mucosal changes. Sequela of this chronic disease are leading causes of hearing loss and speech difficulties, leading to impaired educational performance in children. Untreated progression leads to mastoid disease with more irreparable dysfunction. Therefore, OME is a major health problem throughout the world.

The diagnosis and treatment of chronic otitis media with effusion (OME) has been a long-standing conundrum in medical practices. Why? The medical literature dating back to 1931, as reported through 21 studies of 2326 patients by Proetz, Shambaugh, Zhang, Draper, Doyle, Pelikan, Ojala, McMahan, Tomonaga, Nsouli, Lasisi, Nguyen, Tian, Sobol, Smirnova, Shim, Smirnova, Luong, and Hurst [1] support the allergic causes of otitis media with effusion (OME) and that "ETD responds best to immunotherapy"(Table 1) [1]. Yet while hay fever, asthma, dermatitis, etc, respond to the traditional anti-allergic medicines and antihistamines, OME itself shows little benefit from these treatments. Persistence and/or recurrence of fluid in the middle ear leaves the surgeon to rely on repeated myringotomy and placement of tympanostomy tubes(M&T) in order to remove the fluid and provide aeration so as to restore hearing and avoid the long-term consequences of hearing loss and mastoid disease. Unfortunately, surgical approaches such as repeated M&T, as well as eustachian tube dilatation, do not address the underlying etiology and the possibility of recurrence.

Table 1: 21 Studies of 2326 OME Patients with Allergy Confirmed by Skin Testing [1].

Year	Author	# Patients	% Atopic	Resolution
'42	Dohlman67	178	56%	
'42	Mao68		29%	of pathologically
				deaf children
			2%	of normal children
'49	Jordan	123	74%	98%
'58	Solow	50	72%	
'61	Lecks	82	88%	
'65	Fernandez	113	55%	95%
'65	Whitcomb	38	100%	87%
'67	Draper	340	53%	
'81	Hall	92	100%	
'81	McMahan	119	93%	86%
'86	Sanz	20	30%	
'88	Tomonaga	259	72%	of OME
'90	Hurst	20	100%	0% non-atopic
'91	Becker	35	34%	SPT
'94	Nsouli	104	78%	86%
'94	Corey8	89	61%	
'96	Hurst	73	87%	
'98	Psifidis	148	59%	78%
'04	Doner	22	38%	SPT
'08	Lasisi	80	80%	SPT
'08	Hurst	89	100%	89% resolve
	21 Studies	2326 total	Ave 68%	0% of Controls
		Patients	7 > 87%	

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What have we learned over the past 100 years? The middle ear is essentially a fifth sinus that happens to harbor the organ of hearing. It is an extension of the upper respiratory tract and is aerated via a narrow orifice, similar to the paranasal sinuses. We contend that the middle ear behaves like the rest of the respiratory tract and that what has been learned about the atopic response in mucosa of the sinuses and lungs may be applied to the ear to help in understanding OME.

Unfortunately, surgical approaches such as repeated M&T, as well as eustachian tube dilatation, do not address the underlying etiology. Identification of factors involved in the chronicity of otitis media is an essential step in the treatment and ultimate prevention of chronic disease.

Pathophysiology

Allergy or atopy, for current purposes, can be defined as a genetically transmitted, T-cell-mediated, cytokine-driven, eosinophil-affected inflammation.

Despite years of clinical suspicion that OME was related to allergy, confirmation has been lacking, and therefore, the relation of otitis media with effusion (OME) to allergy remains controversial. Partly, because of the poor sensitivity of earlier methodology for determining atopy, which has hindered an impetus for further investigation. However, technological advances over the years have allowed the identification of various components of inflammatory responses throughout the body. Thus, during the past 40 years, evaluation of middle ear effusion fluid has made astonishing advances in understanding what is occurring in the middle ear to cause the effusion. It is essential to characterize the cellular constituents and their degree of activity in the diseased middle ear. This report will summarize those advances.

Clinical studies have shown that patients with OME have allergies that can be diagnosed by standardized intradermal (IDT) or Skin Prick Testing (SPT) and *in vitro* testing [2-4]. When these allergies are properly treated, the patient's effusion will resolve [3-6] and recurrence is rare. The association of OME with allergy does not prove causality.

Finding both mast cells and their mediator, tryptase, in the middle ear fluid confirmed that a Th2-driven immune response was present in a majority of ears that had chronic effusion. These findings support the hypothesis that the middle ear mucosa is capable of an allergic response and that the inflammation within the middle ear of most OME patients is allergic.8

Immunologic studies have confirmed OME to be an immune-mediated disease [7]. However, despite reports of the presence in middle ear fluid of various mediators of an allergic response, including histamine, leukotrienes, prostaglandins, and various cytokines, few otologists credit allergy with a direct role in the pathophysiology of middle ear disease, possibly due to the lack of instruction regarding allergic mechanisms during surgical training [7] and physicians are certainly further handicapped by patients conflicting responsiveness to existing diagnostic allergy testing measures.

Clinical evidence

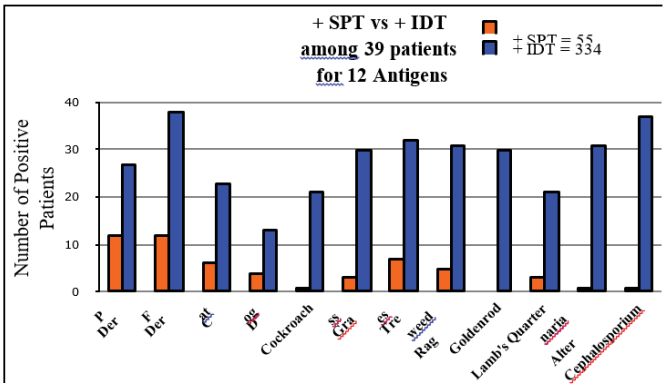
In order to characterize the relation of allergy or infection to OME, we measured ECP, MPO, and tryptase in effusion from 97 patients (Tables 2,3). Thirty-six pre-school children (age 14 months to 6 years), 41 children of school age (6-18 years), and 20 adults were selected in a consecutive, prospective manner [8]. All had documented hearing loss, flat tympanograms, and effusion of a minimum of 3 months duration unresponsive to

Table 2: Mean mediator levels in 116 middle-ear effusions from 97 patients with OME [8].

	Non-atopic	Atopic	Total
Effusion			
No. of Ears	21	95	116
Mean ECP	3.38	165.82	
Standard Deviation (SD)	3.5	240.26	
±(SEM)	0.76	24.65	
$p < 0.0001$			
Effusion MPO			
No. of Ears	18	51	69
Mean MPO	115.96	6231	
Standard Deviation (SD)	125.32	8018	
Standard Error of Mean (SEM)	29.54	1122	
$p < 0.0001$			
Effusion Tryptase			
No. of Ears	8	49	57
Mean Tryptase	1.34	4.78	
Standard Deviation (SD)	0.39	5.09	
Standard Error of Mean (SEM)	0.14	0.73	
$p = 0.009$			

Comparison of effusion ECP, MPO and Tryptase (in µg/l) from 97 atopic and non-atopic patients' ears. SD = Standard Deviation; SEM = Standard Error of Mean; 28 allergens tested at 1:20 prick, 8 by intradermal.

Table 3: Direct comparison of results of 1:20 Skin Prick (SPT) *vs.* Intradermal (IDT) Testing of 39 Patients by both a General Allergist and an ENT Allergist [17].
Comparisons of allergen detection by both SPT and IDT. Number of positive skin-test reactions by SPT and IDT to each of 12 allergens among 39 patients tested by both methods. Comparing tests for the same 12 allergens, SPT was found to detect only 16% of allergens found by IDT.
Prick testing MISSED: Dust F, Cat, Dog, Cockroach, Grass, Goldenrod, and all molds as all were below the sensitivity of prick testing. The ENT allergist found the same patient positive to 14 of 17 allergens by intradermal testing.



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antibiotic and/ or decongestant therapy. Ear effusions were collected at the time patients underwent routine M&T.

Age: Infants and young children 14 months to 6 years of age presented as a mixture of both PUR-OME and OME. Fewer than 20% of patients older than 6 years present with infection (PUR-OME). All patients over 6 years old had allergies. Both Gates, et al. [9] and Yellon, et al. [10] observed that older children typically tend to have more chronic OME, have different levels of cytokines in their effusion, and need repeated myringotomy and tympanostomy.

The appearance of mast cells in airway epithelium is an indication of disease and not a normal feature [11]. Initial reports of mast cells in humans had been limited to cadaver temporal bones, in which the number of mast cells was significantly increased in chronic inflammatory reactions [12,13]. In the initial stages of serous otitis, mast cells have been found in the lamina propria and the pars flaccida [14,15]. Histopathologic examination of effusion demonstrates that both eosinophils and neutrophils are integral components in these secretions [16]. Mast cells were thought to "play an important role in the pathogenesis of chronic otitis media through the release of their active biochemical mediators [16]. The atopic status of that author's patients was not determined.

Clinical studies have shown that patients with OME have allergies that can be diagnosed by standardized intradermal (IDT)or Skin Prick Testing (SPT) and *in vitro* testing [9-11]. When these allergies are properly treated, the patient's effusion will resolve [3,4,10,11]. Adding IDT testing to SPT discovers 54% more allergens (Figure 1) [12,17].

Effusion subjects: We measured tryptase and ECP in middle ear effusions from 38 individuals (i.e., 44 ears, including 6 pairs) who presented with refractory OME to a solo community-based otolaryngologist [16]. Subjects included 18 children (age 32 months to 6 years) and 15 children of school age (6-18 years) selected in a random, prospective manner. Five adults (age 55 to 69) with eustachian tube dysfunction served as controls. None were immunodeficient nor exhibited congenital malformations. All had documented hearing loss, flat tympanograms, and effusion of a minimum of 2 months duration unresponsive to antibiotic and/or decongestant therapy. Among the 33 diseased patients were several children with no known antecedent infections who presented after failing a school hearing test. Serum and MEE were collected at the time patients underwent routine myringotomy and placement of tympanostomy tubes (M&T) [16].

A second cohort of five children with 8 diseased ears (ages 5.2 to 16 years) was selected randomly for biopsy. All 5 patients had serum ELISA testing. Four other patients who had no signs of effusion or infection but were undergoing routine tympanoplasty for dry perforations served as controls. Biopsies from both normal and diseased patients were taken from the promontory of the middle ear following approval of the Franklin Memorial Hospital (Farmington, Maine) Committee on Ethics and Human Experimentation and with patient or parental consent. Working through the myringotomy incision, a 2 mm diameter sample of mucosa was elevated with a microcurette and removed using a microcup forceps (Figure 2) [16].

To avoid bias, but 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. All were assessed in an identical manner by history, otologic exam, pneumatic otoscopy, audiometry, and tympanometry, and offered the same treatment options. 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 their tonsils and/or adenoids removed, are listed in Table 4. 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 [18]. Table 4: Demographics of treatment and control cohorts [18].

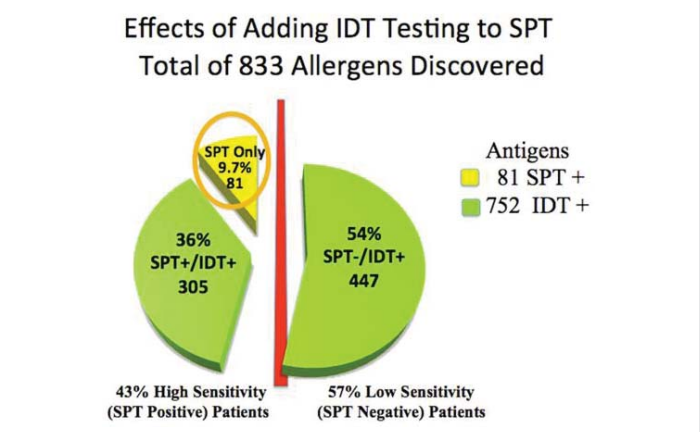

Figure 1: Effect of adding IDT testing to SPT [17].

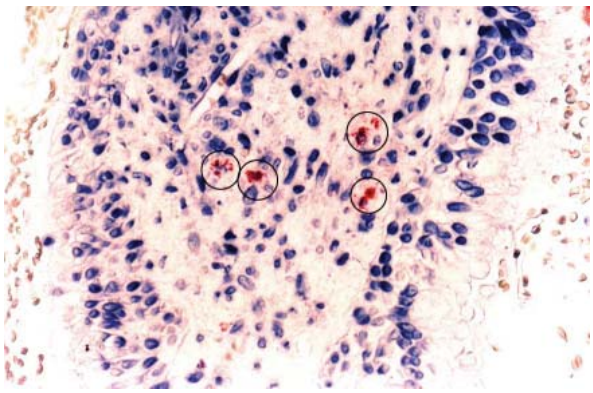

Figure 2: Anti-tryptase antibody (AA1) staining of mast cells (circled) [16] (Adopted from: Hurst DS, Amin K, Sevéus L, Venge P. Evidence of mast cell activity in the middle ear of children with otitis media with fusion. Laryngoscope. 1999;109:471-°©-477; with permission From Lippincott Williams & Wilkins, Inc.)

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Table 4: Demographics Demographics of treatment and control cohorts.

Number of Patients	Treatment	Control	Total	*p* Value
Atopic No. (%)	68	21	89	
	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				
Adenooidectomy 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 + only A	25 (36.8)	8 (38.0)	33 (37.0)	0.3 = ns
Mean no. + allergies by IDT	10.16	13.0		

Intervention consisted of immunotherapy according to AAOA criteria. All patients in both treatment and control groups were found to be atopic. The sex, age, and number of tubes or adenoid surgeries in the two groups were compared (Table 4). No statistical difference was found between the treatment and control cohorts for any parameter other than the apparent excess number of 51-70 year 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. Ten patients served as their control. Although they became free of effusion or drainage on initial IT, their effusion recurred when their shots were discontinued prematurely.

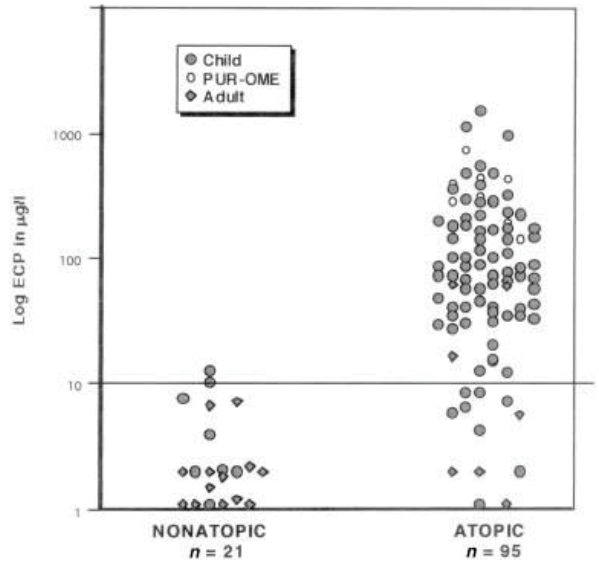
The author's reputation as having a particular interest in allergy and chronic middle-ear disease might have led to a referral bias with a higher incidence of atopy than found in the community at large, although 40% had no associated allergic symptoms to prompt referral on those grounds. Secondly, it has been documented that by the natural progression of the disease, 1/4 of ''all'' OME patients might be expected to resolve spontaneously [19]. 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 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 [18].

The surprising finding that 100% of patients in this study were atopic by objective testing implies selection bias. This is more likely a result of the marked increase in sensitivity of IDT *vs.* either prick (sensitivity < 45%) or RAST testing [20], especially in patients with low total IgE levels. It is for this reason that practice parameters of the AAAAI [21] and AAOA [22] 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).

Diagnostic studies involving serum skin testing for allergy have shown little consistent results, partly due to the significant difference between intradermal (IDT) and skin prick testing (SPT), wherein the general allergists prefer SPT vs otolaryngologists (Figure 2) who prefer intradermal testing as being twice as sensitive (Table 5) [17,23,24].

To avoid bias, ears that typify episodes of recurrent acute otitis media, which quickly resolve between infections, were excluded from the study. Patients designated as having OME were those who maintained effusion beyond 2 months. The biopsy samples were fixed in acetone [16], which had been precooled to -20°C. The fixative included the proteinase inhibitors phenyl methyl sulfonyl fluoride (2 mM) and iodoacetamide (20 mM). Tryptase in the effusion was measured

Table 5: Characteristics of 116 Patients with Otitis Media with Effusion [8]. ECP and tryptase in middle ear effusions. Results measured in diluted samples (6 or 7:1) are expressed as means = +/- SEM. Serum IgE an ELISA drawn at the time of middle ear sampling. +AE = atopy with effusion noted; -AE = no atopy with effusion noted; AE/NR = atopy not related.



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by a double antibody radioimmunoassay (Tryptase, Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) using a monoclonal antibody marked with radioactive I.

The dilution of the effusion specimens in this study is an important consideration. Assuming an average volume of 0.3 mL of effusion diluted during collection with 2 mL of saline to wash the thick mucoid samples removed during M&T from the 20 French suction tube, the absolute tryptase concentration in those middle ears in which tryptase was measurable (mean 6.46 µg/l) was 6 to 7 times greater than that recorded in Table 2 and represents a mean of 38.8 - 45.2 µg/l.

Mast cells as well as their chief mediator, tryptase, were present in the mucosal biopsies of 6 of 9 ears from 8 patients with chronic effusion, all of whom were atopic to an average of 10 allergens. Mast cells were present in the mucosa [16] and submucosa in allergics but absent in controls. The diseased ears demonstrated granulocytes in the mucosa, which stained positive for ECP, indicating the presence of eosinophils [16].

To further characterize the relation of allergy or infection to OME we measured ECP, MPO, and tryptase in effusion from an additional 97 patients [8] (Tables 2,3). Thirty-six children (age 14 months to 6 years), 41 children of school age (6-18 years), and 20 adults were selected in a consecutive, prospective manner. All had documented hearing loss, flat tympanograms, and effusion of a minimum of 3 months duration unresponsive to antibiotic and/or decongestant therapy. Ear effusions were collected at the time patients underwent routine M&T. Atopic Status: Eighty-one percent of this second group of 97 OME patients (79/97) were atopic [23]. Among the children, 93% (72/77) were atopic [23].

Mediator levels in effusions: The inflammatory response by eosinophils, neutrophils, and mast cells in the middle ear was distinctly different depending on the patient's atopic status ($p < 0.001$) [8]. ECP was elevated (> 10 µg/L) in 86.1% (68/79) of ears of atopic patients (mean 165.8 µg/L). Tryptase was elevated (mean 4.8 µg/L) in the effusion from 64% (23/36) of atopic patients. Tryptase was below 2µg/L in all 7 non-atopic patients as well as in 1 PUR-OME and 12 atopic patients. There was no correlation of tryptase to either MPO or ECP (Spearman $p > 0.05$). The highest levels of MPO were found in ears that had a superimposed infection at the time of myringotomy (PUR-OME). Neutrophils were significantly active in all atopic ears, producing mean MPO levels 53 times higher than those measured in non-atopic ears. The inflammatory response by eosinophils, neutrophils, and mast cells in the middle ear [8] was distinctly different depending on the patient's atopic status ($p < 0.001$) [23].

Conclusion

Our observations add to the body of evidence demonstrating that the cells and cytokines essential to the production of a Th2 immune-mediated hypersensitivity reaction (atopy) are present in the majority of ears that have chronic effusion. This study confirms at a cellular level that mast cell mediators measured in the effusion of atopic patients arise from actively degranulating mast cells identified in the local tissue lining the middle ear cleft. Neither tryptase nor ECP levels were elevated if the patient was not a topic (Table 5) [8].

Immunohistochemical staining of biopsy material from normal ears showed no evidence of either mast cells or eosinophils but did demonstrate both cells to be present within the mucosa of 80% of ears from atopic children with OME.

The inflammatory response by eosinophils, neutrophils, and mast cells in the middle ear is distinctly different between atopic and non-atopic patients ($p < 0.001$) [16]. These findings provide further evidence that eosinophils and mast cells, both essential to a Th-2 driven immune response, are active in the majority of ears from atopics with chronic OME and support the hypothesis that: middle ear mucosa, similar to that of the rest of the upper respirator tract, is capable of an allergic response [19,24-26]. The surprising finding that 100% of patients in this study were atopic by objective testing implies selection bias. This is more likely a result of the marked increase in sensitivity of IDT *vs.* either prick (sensitivity < 45%) or RAST testing [17], especially in patients with low total IgE levels. It is for this reason that practice parameters of the AAAAI [20] and AAOA [21] suggest that, in the face of a negative prick test, intradermal testing may be the only practical way to determine sensitivity.

Implications

This study documents 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. 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 ($p < 0.001$).

Take away

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.

Thus, it is apparent that any child or adult considered for a second set of PE Tubes should also be evaluated for allergies as the underlying cause of their chronic middle ear disease, as immunotherapy offers the best opportunity for and the most long-lasting resolution of OME [1,10,14]. 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.

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