

Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis

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Background: Although associated allergies are common and the mechanism may include long-term exposure to allergens, measurement of serum specific IgE levels has not been studied in pediatric eosinophilic esophagitis (EE).

Objective: To compare the results of serum IgE testing, patch testing, and epicutaneous skin testing to measure allergic sensitization in pediatric patients with EE.

Methods: In a cross-sectional study of 53 pediatric patients with EE, relevant history was obtained by questionnaire, and patch testing to foods was performed. Food and inhalant sensitivities were also assessed using skin prick testing and serum specific IgE measurement. Streptavidin CAP was used to measure specific IgE to cross-reactive carbohydrate determinants and *Helicobacter pylori*.

Results: The overall prevalence of food and inhalant sensitization was 80%, with higher total IgE levels in sensitized vs nonsensitized patients (median, 150 vs 13 IU/mL; $P < .001$). For foods, serum IgE measurement detected more positive results than did skin prick testing. Specific IgE to milk was most common (43%). Inhalants were implicated as frequently as were foods. In keeping with this, 32% of patients had a cluster of multiple sensitivities that included pollens, soy, grains, peanut, and tree nuts and had higher total IgE levels ($P = .001$). Patch test results were interpreted as positive in 39% of patients (rye, wheat, and soy were the most common).

Conclusions: Most, but not all, patients with EE are highly atopic individuals with frequent allergic sensitivities. Thus, serum IgE measurement of low-titer IgE antibody may be useful in identifying relevant food sensitivities and in distinguishing subgroups of patients with EE, making a more directed approach to food avoidance possible.

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INTRODUCTION

Eosinophilic esophagitis (EE) is an increasingly recognized disorder characterized by an abnormal accumulation of eosinophils in the esophageal mucosa in patients with symptoms of refractory gastroesophageal reflux and dysphagia.¹ Although its pathogenesis remains unknown, initial studies^{2,3} in mice exposed to the aeroallergen *Aspergillus fumigatus* suggested a role for T cells and interleukin 5. A recent study⁴ of RNA in human biopsy specimens suggested a role for interleukin 13 and eotaxin-3 in the recruitment of eosinophils. Once present, eosinophils may act in an autocrine manner to perpetuate inflammation and decrease epithelial barrier func-

tion.⁵ An allergic trigger for this inflammation is suspected because a large proportion of patients have identifiable allergic sensitivities.^{6,7} Despite the high prevalence of specific allergic sensitivities and associated atopic diagnoses frequently found in patients with EE, the relationship between EE and allergic sensitization is not straightforward.

The role of allergic sensitization in EE seems to mimic that seen in atopic dermatitis and asthma rather than in traditional food allergy. To start with, the inciting food or inhaled allergen cannot be identified from the patient's history. Individuals with EE who have IgE antibody to food allergens do not usually report immediate symptoms, such as oral allergy syndrome, urticaria, or anaphylaxis. Although seasonal fluctuations in symptoms and eosinophil counts have been observed, the role of inhalant allergic triggers remains less clear.^{8,9} The mechanism of EE may not be a result of preformed mediator release from cross-linking of mast cell-bound IgE antibodies, and food (and inhalant) sensitivities have not been found in some patients. However, almost all patients have been shown to improve with complete dietary avoidance.^{10,11} This makes the proper identification of allergic triggers highly desirable.

Typically, serum IgE antibody measurements have not been used in the measurement of food sensitivities in pediatric patients with EE.¹ The objective of the present study was

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to characterize the allergic sensitization found in pediatric patients with EE by measuring specific IgE antibodies to common food and inhalant allergens (using CAP-FEIA [Phadia, Uppsala, Sweden]) and comparing the results with those of patch testing to foods and standard epicutaneous skin tests to foods and inhalants.

METHODS

Between January 15, 2007, and June 29, 2009, patients referred to the Allergy Clinic at Nationwide Children's Hospital with positive biopsy findings for EE, defined as at least 15 eosinophils per high-power field (eos/hpf), were randomly approached for participation in a cross-sectional study. All the parents (and patients) ($n = 55$) agreed to participate; however, blood could not be collected from 2 patients, so they were not included in the analysis. This study was approved by the institutional review board of Nationwide Children's Hospital, and all the parents (and participants) provided written informed consent (and assent).

Questionnaires were administered to document EE symptoms and treatment and associated allergic diagnoses. Standard epicutaneous allergy skin prick tests (SPTs) were performed to a panel of 16 foods (egg, milk, wheat, soy, peanut, cashew, shrimp, beef, chicken, pork, rye, oat, corn, peas, tomato, and potato) and 38 common inhalant allergens using Sharp-Test Applicators (Panatex, Placentia, California).¹¹ A wheal response at least 3 mm (in greatest diameter) larger than the negative control with surrounding erythema was considered positive. Total IgE and specific IgE antibodies to the 8 most common foods identified by testing (egg, milk, wheat, soy, peanut, cashew, beef, and rye) and 8 inhalant allergens (dust mite, cat, dog, mold mix, birch, timothy, weed mix, and ragweed) were measured using CAP-FEIA. Milk proteins (α -lactalbumin, β -lactoglobulin, and casein), bromelain, Bet v 2 (profilin), and *Candida albicans* were also measured. Levels of specific IgE to cross-reactive carbohydrate determinants (CCDs) and *Helicobacter pylori* were measured using streptavidin CAP.¹² Specific IgE measurements greater than 0.35 IU/mL were classified as positive.

At a separate visit, patch testing to foods was performed regardless of the results of SPTs and serum IgE measurements ($n = 44$). Patch testing materials were prepared using approximately 2 g of dry food in 2 mL of saline (milk, soy, egg, peanut, wheat, corn, oat, rice, rye, white potato, chicken, beef, pork, and lamb).¹³ Single-ingredient baby food vegetables and fruits were used undiluted. The semisolid food preparations were placed in 12-mm Finn Chambers (Allergan Laboratories Inc, Phoenix, Arizona) secured on the patient's back for 48 hours. Skin responses were read at 72 hours (the same investigator [E.A.E.] interpreted all of the tests). The results were graded incrementally based on the presence (or absence) of erythema and the number of papules observed at each site. For this study, a response that included papules was considered positive.

The outcome of interest was evidence of sensitization based on the results of SPTs, CAP-FEIA, and patch tests.

Sensitization was classified as IgE mediated if either SPT or CAP-FEIA results were positive. A positive patch test result was considered a non-IgE-mediated sensitization. Geometric mean titers of specific IgE to foods were measured and compared using analysis of variance. The correlation between total IgE level and titers of specific IgE was evaluated using the Spearman rank correlation. The Kruskal-Wallis χ^2 test was used to evaluate the relationships between age, esophageal eosinophil counts, peripheral blood eosinophil counts, and total IgE levels in the subgroups of patients we identified (ie, non-IgE-sensitized patients, cow's milk-sensitized patients, and those with multiple food and pollen sensitivities). Statistical analyses were performed using SPSS version 17 (SPSS Inc, Chicago, Illinois).

RESULTS

The demographic profile of the pediatric patients with EE included in this analysis is similar to that reported in other groups.¹⁴ Patients ranged in age from 7 months to 18 years, with a median age at diagnosis of 9.0 years. A predilection for male sex was observed (75%), and a history of allergy medication use or a diagnosis of asthma was reported in 70% of patients. The most frequently observed EE symptoms were dysphagia (51%), abdominal pain (45%), and vomiting (45%). Food impaction was reported by 36% of patients. Esophageal eosinophil counts ranged from 15 to 230/HPF (median, 50/HPF). The median peripheral blood eosinophil count was 390/mm³ (Table 1).

We evaluated IgE responses to food by using SPT and serum specific IgE antibody measurement. Serum assays compared with SPT detected more positive results, particularly regarding milk, wheat, soy, and egg (Fig 1). Overall, serum IgE measurements identified previously undiagnosed food sensitivity in 42% of patients. The additional sensitivity most frequently recognized with serum assays was milk (36%). The prevalence of milk sensitivity identified by using both testing methods was 43%. The geometric mean titer of specific IgE to each food was low, with egg at 2.4 IU/mL, milk at 1.2 IU/mL, wheat at 1.3 IU/mL, soy at 1.5 IU/mL, and peanut at 5.5 IU/mL. However, in some cases, SPT results were negative, and the titer of specific IgE measured was high (Fig 2). Furthermore, specific IgE titers were high relative to total IgE levels, and for wheat, soy, and peanut, specific IgE level was related to total IgE level (Spearman $r = 0.45, 0.57, \text{ and } 0.61$, respectively; $P < .01$ for each).

Inhalant sensitivities were measured using SPTs and a screening panel of specific IgE tests. Even in this pediatric population, inhalant sensitivity was found as frequently as was food sensitivity (Fig 3). In keeping with that, multiple sensitizations were common; the mean number of IgE-mediated sensitivities per individual was 3.5. Despite the finding of frequent multiple sensitivities, levels of total IgE for the whole group were not markedly elevated (median, 64 IU/mL). Seventeen patients (32%) had a cluster of multiple sensitivities (≥ 4) that included pollens, soy, grains, peanut, and tree nuts. Compared with the non-IgE-sensitized and

Table 1. Comparisons of Atopic Variables in 3 Different Phenotypic Groups of Pediatric Patients With EE^a

	Overall (n = 53)	Patient group ^b			P value ^d
		Non-IgE sensitized (n = 15)	Cow's milk sensitized (n = 22) ^c	Multiple sensitivities (n = 17) ^c	
Age, y	9 (2.9–13.6)	9 (1.9–14)	4.5 (2.2–11)	13 (8.5–16)	.01
Esophageal eosinophil count, eos/hpf	50 (35–80)	36 (30–89)	50 (41–71)	55 (41–71)	.6
Peripheral blood eosinophil count, /mm ³	390 (200–690)	350 (130–530)	460 (240–730)	300 (200–540)	.3
Total IgE, IU/mL	64 (22–230)	13 (6.8–28)	120 (32–250)	230 (150–480)	.001
Presented with obstruction, No.	19	7	5	6	

Abbreviations: EE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field.

^a Data are given as median (interquartile range).

^b Five patients did not fit any classification group. They had specific IgE to 1 or 2 foods or inhalants only. For this group, median age was 4.6 years; median esophageal eosinophils, 85/HPF; median peripheral blood eosinophils, 483 mm³; and median total IgE level, 49 IU/mL; and 1 patient presented with obstructive symptoms.

^c Six patients had both specific IgE to cow's milk and multiple sensitivities. They were included in the number of patients shown for each group but were not included in the statistical analysis for comparison among groups.

^d Statistical comparisons were made using the Kruskal-Wallis χ^2 test.

cow's milk-sensitized groups, patients with multiple pollen and food sensitivities tended to be older and to have higher total IgE levels (Kruskal-Wallis χ^2 , $P = .01$ and $P < .001$, respectively) (Table 1).

Because of recent evidence that IgE antibody to plant- and mammalian-derived CCDs can give rise to positive serum assay results with negative skin test results, we also tested the sera for specific IgE to CCDs. The sera were tested for MUXF3 (using bromelain), galactose- α -1,3-galactose (using cetuximab), and *N*-glycolylneuraminic acid. Two different patients had specific IgE to bromelain, and only 1 patient had specific IgE to galactose- α -1,3-galactose (Table 2).

Patch testing was performed to identify non-IgE-mediated food sensitivities. The results did not correlate with those

found using skin or serum testing. Overall, patch test results were interpreted as positive in 17 of 44 patients (39%). The most common sensitivities noted by patch testing were rye ($n = 7$), wheat ($n = 6$), and soy ($n = 6$). Other grains and meats were occasionally positive (Fig 1). Five patients who were otherwise nonsensitized had at least 1 positive patch test result. Patients who were food sensitive by patch test(s) only (9%) were classified with patients who had neither food nor inhalant sensitivities (19%) as non-IgE sensitized. Total IgE levels in non-IgE-sensitized patients were significantly lower (median, 13 IU/mL) than those of patients who had positive skin test or serum IgE assay results (median, 150 IU/mL; Mann-Whitney, $P < .001$).

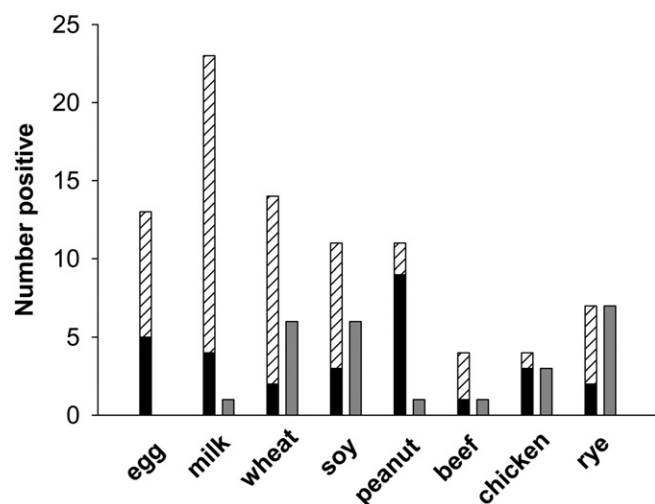


Figure 1. Food sensitivity as identified using different testing methods. For milk, egg, wheat and soy, serum specific IgE measurement (hatched bars) detected more positives than skin prick testing (black bars) or patch testing (gray bars). Note that for each of the foods milk, soy, and peanut there was one patient who had a positive skin test but specific IgE <0.35 IU/mL.

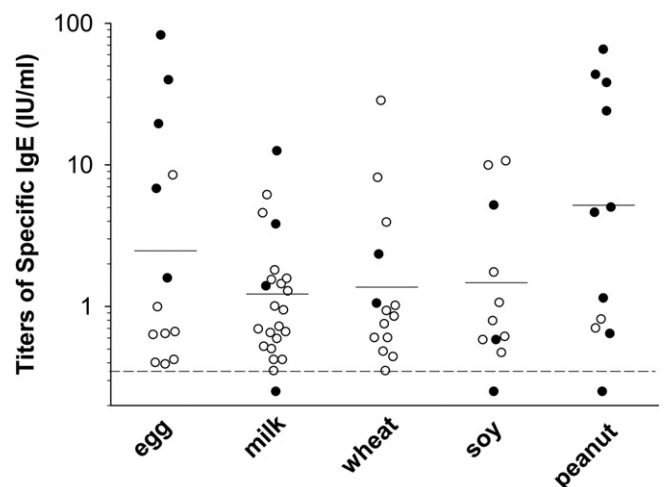


Figure 2. Titers of specific IgE to common food allergens. Serum measurements in patients with positive skin tests are represented by filled circles. In the cases of milk, wheat, and soy, some patients with high titers of specific IgE had negative skin test results (open circles). Horizontal lines indicate geometric mean titers of specific IgE. The dashed line is the level of detection used for specific IgE.

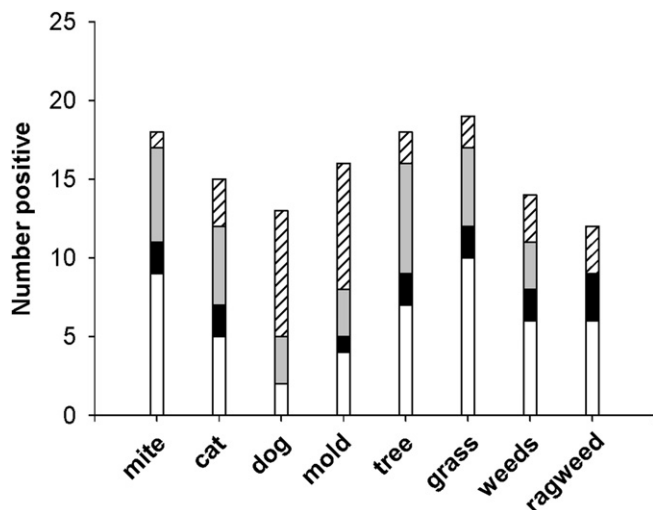


Figure 3. All patients had skin testing to inhalants. Serum measurements were tested in a subgroup (black bars are skin test positive/serum negative, light gray bars are skin test positive/serum positive, and hatched bars are skin test negative/serum positive). White bars indicate that no serum measurement was performed. The number of positives detected by each testing technique varied by allergen.

Because of continuing confusion about the causes of EE and the presence of children without identifiable sensitization, we assayed sera for specific IgE to common commensal agents of the gastrointestinal tract. We selected *C albicans* because it is a common organism in the esophagus and because application of corticosteroids to the esophagus is a known cause of increased candidal growth. We also included *H pylori* because of the high prevalence of *H pylori* infection in patients with gastritis.¹⁵ Two sera were positive for specific IgE to *H pylori*, and 5 sera were positive for specific IgE to *C albicans* (Table 2). None of the non-IgE-sensitized patients had a positive test result to either agent.

This was not designed as a treatment study; however, after finding a high prevalence of specific IgE to milk, clinical significance was examined retrospectively. For patients with milk sensitivity, medical records were reviewed for treatment recommendations and for response to therapy (Table 3). Dietary avoidance of milk was recommended in 13 patients who had specific IgE to milk. Nine of these patients/parents reported clinical improvement and attributed it to the removal of milk from the diet. Repeated endoscopy and biopsy revealed fewer than 15 eos/hpf in 5 of 7 patients and showed improvement in 6 of 7 patients. Confounding factors included the common finding of multiple allergic sensitivities and concurrent use of medications.

DISCUSSION

As a group, patients with EE have an atopic phenotype with associated allergic rhinitis, asthma, or both and frequent allergic sensitivities.^{1,6,7,16} Some investigators have suggested the importance of food triggers and others inhalants.^{2,9,16} The

results of this study emphasize that a large proportion of pediatric patients with EE have specific IgE to milk and that subgroups of patients with EE can be identified and distinguished based on IgE responses. In this cohort of pediatric patients, 3 clinical groups were observed: non-IgE-sensitized patients, milk-sensitized patients, and those with multiple sensitivities (ie, molds, pollens, grains, and legumes). Serum specific IgE measurements were helpful in detecting additional food sensitivities. However, even with extension of the battery of tests to foods, inhalants, CCDs, and commensal organisms, there was a significant group of patients (20%-30%) with no detectable sensitivity.

Serum specific IgE measurement as performed using CAP-FEIA detected low levels of specific IgE to milk in 36% of patients studied. Furthermore, in all the serum samples with levels of IgE to milk greater than 0.35 IU/mL that were tested, specific IgE to 2 or more individual milk proteins (ie, α -lactalbumin, β -lactoglobulin, and casein) was found. In contrast, only 4 patients had a positive standard SPT result to milk. By using SPT and patch testing, cow's milk sensitivity as a cause of symptoms has been difficult to exclude in other groups of patients with EE. A negative predictive value of only 41% was reported when using the combination of SPT and patch testing to diagnose milk sensitivity.¹⁷ Serum IgE measurement improves the detection of milk sensitization. In the present patients, levels of specific IgE to milk ranged from 0.42 to 12.5 IU/mL. Clinically relevant titers in EE are not known; however, low levels of specific IgE to milk have been found to be relevant in patients with typical IgE-mediated food hypersensitivity.¹⁸ Only for levels of specific IgE antibody to milk less than 0.8 IU/mL was the negative pre-

Table 2. Prevalence of Specific IgE to Cross-reactive Carbohydrate Determinants (CCDs) and Infectious Agents of the Gastrointestinal Tract

	Patient group, No. ^a		
	Non-IgE sensitized	Cow's milk sensitized ^b	Multiple sensitivities ^c
CCD ^d			
MUXF3 (bromelain)	0	1	1 (1)
Galactose- α -1,3-galactose (cetuximab)	0	0	1 (1)
<i>Helicobacter pylori</i>	0	2 (2)	1 (1)
<i>Candida albicans</i>	0	1 (1)	4 (1)

^a Numbers in brackets indicate the number of patients with positive results having a serum IgE measurement of class 2 or higher.

^b Seven serum samples with specific IgE to milk (>0.35 IU/mL) were tested for specific IgE to individual milk proteins (α -lactalbumin, β -lactoglobulin, and casein). All 7 samples had measurable IgE to 2 or 3 proteins.

^c In 7 patients with multiple pollen sensitivities, specific IgE to profilin was measured and was negative.

^d IgE antibody to *N*-glycolylneuraminic acid was also measured. No positive results were found.

Table 3. Characteristics of 13 Patients With Serum IgE Antibody to Milk in Whom a Milk Elimination Diet Was Attempted^a

Patient No.	Specific IgE, IU/mL (SPT, mm) ^b	Other allergic sensitivities ^c	Treatments		Previous biopsy/repeated biopsy, eos/hpf
			Inhaled corticosteroid ^d	Clinical response to milk avoidance	
1	12.5 (4)	>5 Foods and inhalants	Yes	No change	ND
2	6.12	>5 Foods and inhalants	Yes	Symptoms better	ND
3	4.56	Beef, dust mite	No	No change	ND
4	3.8 (6)	Soy	No	No change	ND
5	1.54	Egg	Yes (stopped)	Symptoms better	60/0
6	1.44	None	Yes	Symptoms better	26/11
7	1.39 (3)	Cat	No	Symptoms better	ND
8	1.28	Egg, wheat, rye	Yes	Symptoms better	150/1
9	1	>5 Inhalants	No	Symptoms better	160/11
10	0.94	Cat	Yes	Symptoms better	40/25
11	0.59	Cat, grass	Yes	No change	ND
12	0.52	>5 Foods and inhalants	Yes	Symptoms better	55/50
13	0.42	None	Yes	Symptoms better	75/0

Abbreviation: eos/hpf, eosinophils per high-power field; ND, not done; SPT, skin prick test.

^a Eight patients had levels of serum IgE to milk greater than 0.35 IU/mL; however, milk elimination was not attempted. These patients are not included in this table.

^b Skin prick test response in patients with a positive result (mm of wheal in greatest diameter).

^c Other sensitivities identified by positive skin test or serum specific IgE results.

^d Inhaled corticosteroid was administered without a spacer, and patients were instructed to swallow the medication.

dictive value for having a clinical reaction greater than 95%. This study was not designed to evaluate the response to treatment. However, most patients who instituted a milk avoidance diet as a result of serum IgE measurement stated that this decreased their symptoms. Biopsy improvement was confirmed in most patients who underwent endoscopy. These data suggest that serum IgE antibody measurement may be helpful in the diagnosis of cow's milk sensitivity in patients with EE and that a subsequent trial of cow's milk avoidance may provide clinical benefit.

As in studies of adults with EE, many of the present patients with sensitivity to pollen by SPT also had low levels of specific IgE to wheat and soy.¹⁹ Although a small study²⁰ in adults suggested that a 6-week elimination diet of grains (wheat and rye) did not result in decreased frequency of EE symptoms, the significance of these low levels remains unclear. It is possible that the low levels that we found using specific IgE measurement are consistent with existing data that suggest that most patients, even those without detected allergic sensitivities, respond to a strict elimination diet or a 6-food elimination diet that includes the foods most frequently associated with sensitization.^{8,21} It is also possible that low levels of serum specific IgE may be a reflection of local production of IgE in EE. There is now accumulating evidence for local production of IgE in tissues. Vicario et al²² detected mature IgE messenger RNA using reverse transcriptase–polymerase chain reaction on esophageal biopsies from patients with EE. Recently, it has been observed that B-cell isotype switching can occur independent of interaction with CD40L.²³ The molecule B-cell activating factor, which is from the tumor necrosis factor superfamily and is produced

by a variety of cells, including epithelial cells and dendritic cells, can act as a second signal for class switching in the absence of CD40L interaction. Up-regulation of B-cell activating factor has been measured in bronchoalveolar lavage fluid of asthmatic and allergic patients in response to allergen challenge.²⁴ In the same study,²⁴ eosinophils were the cells that accumulated most after challenge.

One-third of the present patients had multiple pollen and mold sensitivities that were often associated with grain and legume sensitivity. This could not be explained by nonspecific binding as a result of elevated total IgE levels. In fact, total IgE levels were only moderate, as in an earlier study of allergic rhinitis.²⁵ Despite the relatively unimpressive total IgE measurements in this population with EE, total IgE level was useful for distinguishing the subgroup of individuals without IgE-mediated sensitization (they had significantly lower levels). Furthermore, the predominance of inhalant sensitivities to molds and pollens in itself is striking. Studies^{26,27} of asthma have shown dust mite and cat to be the relevant associated allergic sensitivities. In contrast, pollen and mold sensitivities are more frequently associated with allergic rhinitis. In this group of patients with EE living in the Midwest with exposure to a variety of inhalant allergens, including dust mite, pets, molds, and pollens, the prevalence of mold and pollen sensitivity is high compared with sensitivity to indoor allergens.

The consistent pattern of multiple associated sensitivities suggested that cross-reactive carbohydrate IgE antibodies to foods and inhalants could be relevant in patients with EE. Carbohydrate specific IgE has been reported for 2 basic types of glycans: N-linked and O-linked.²⁸ N-glycans consist of a

core that includes 2 *N*-acetylglucosamines and a mannose with additional possible linkages of $\alpha(1,3)$ -fucose and $\beta(1,2)$ -xylose. These nonmammalian substitutions are highly immunogenic in humans, and their presence in a variety of plants and invertebrates leads to a high degree of cross reactivity. Clinically, a subset of grass pollen-allergic patients has been found to have IgE to peanut attributed to CCDs.²⁹ Specific IgE to CCDs was not a common feature in the present patients (only 3 patients had detectable levels). We measured levels of IgE to several plant N-linked glycans and to the nonprimate galactose- α -1,3-galactose linkage.³⁰ Specific IgE to galactose- α -1,3-galactose has been linked to anaphylaxis and delayed responses to mammalian-derived food allergens.³¹ In the absence of specific IgE to CCDs in this population, alternative explanations for the multiple associated sensitivities would be IgE antibody to cross-reacting proteins or the independent development of IgE antibodies to many different epitopes. None of the 7 serum samples taken from patients with multiple sensitizations that we tested had specific IgE to profilin.

One limitation of this study, and most other studies of EE, is that food challenges were not performed to evaluate the eosinophilic response to food. Such an approach would be difficult for a variety of reasons. First, because patients with EE often have a delayed response to foods, it would be hard to predict the timing of a response to food challenge. Another related issue is that a patient would have to be controlled (symptom free) to isolate a response to a single food. Furthermore, most patients had multiple food sensitivities and would require numerous procedures to assess individual food responses. Even the alternative of using skin biopsy after patch tests, commonly used with the atopy patch test in adults, has been considered too invasive in children.

EE is a mixed model of allergic disease that shares some features of atopic dermatitis and asthma and some features of allergic rhinitis. Similar to patients with allergic rhinitis, patients with EE have total IgE levels usually within the reference range and frequent pollen and mold sensitivities. On the other hand, the delayed response to allergen exposure and suspected barrier defect are more consistent with atopic dermatitis and asthma. The results of this study suggest that a more directed approach to food avoidance may be beneficial. This could be accomplished by the addition of serum specific IgE testing to standard SPT to obtain a full sensitivity profile. Once obtained, classification of an individual patient into the appropriate allergic grouping could be used to guide initial treatment recommendations.

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