



Role of food and aeroallergen sensitization in eosinophilic esophagitis in adults

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ARTICLE INFO

Article history:

Received for publication May 19, 2016.

Received in revised form July 2, 2016.

Accepted for publication August 8, 2016.

ABSTRACT

Background: Evaluation of IgE-mediated food sensitivity is frequently performed for patients with eosinophilic esophagitis (EoE). However, the clinical relevance of identifying IgE-mediated sensitivity to foods in adults is unclear.

Objective: To determine whether EoE associated with food or aeroallergen sensitivity represents a phenotype of EoE with distinct clinical or biological features.

Methods: A medical record review identified 257 patients with a diagnosis of EoE evaluated in the adult allergy clinic at the University of Wisconsin Hospital and Clinics from 2008 to 2013. Patient records were reviewed to capture measures of disease severity, endoscopy results, pathology reports, allergy testing, medical management and patient-reported outcomes.

Results: Evaluation of food sensitization with skin prick testing and/or serum IgE was performed for 93% of patients. Sensitization to at least 1 food was identified in 54% of patients who were more likely to report concomitant asthma, allergic rhinitis, eczema, and/or food allergy compared with nonfood sensitive patients. Aeroallergen sensitivity was identified in 87% of patients tested. Clinical characteristics, including EoE symptoms, disease severity, endoscopic findings, peripheral eosinophilia, and patient-reported outcomes, did not differ between food sensitive and non-food sensitive patients. However, on endoscopy, aeroallergen sensitive patients were more likely to have strictures and less likely to exhibit felonization compared with non-aeroallergen sensitized patients.

Conclusion: Adults with EoE and IgE-mediated food sensitivity are not phenotypically different than non-food sensitive patients. There is no clear clinical utility in identifying food sensitivity in adults with EoE. Further studies are needed to determine whether aeroallergen sensitivity represents a distinct phenotype of EoE.

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Introduction

Eosinophilic esophagitis (EoE) is an emerging chronic inflammatory disease that affects both children and adults.¹ The disease is characterized by signs and symptoms of esophageal dysmotility from underlying chronic inflammation of the esophagus.

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Disclosures: Dr Mathur reports holding the office of president for the Wisconsin Allergy Society and is principal investigator for the National Institutes of Health funding. No other disclosures were reported.

Funding Sources: This study was funded by grants P01 HL088594, R21 AI122103, and T32 GM008692 from the National Institutes of Health.

<http://dx.doi.org/10.1016/j.anai.2016.08.008>

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Histologically, EoE is characterized by eosinophilic infiltration into the esophagus that persists after a proton pump inhibitor (PPI) trial. Chronic inflammation leads to histologic remodeling of the esophagus inclusive of fibrosis, rings, linear furrows, and stricture formation.² Symptoms vary between children and adults. Whereas children tend to present with vomiting, abdominal pain, and/or failure to thrive, adults often have dysphagia, food impaction, and heartburn.

The hypothesis that foods are triggers for EoE has been supported by the success of various food elimination diets. Since the first description of a successful food elimination diet in 1995,³ many additional studies have validated these findings. EoE resolution rates in children treated with an amino acid-based diet are 96% or higher.^{4–6} An elemental diet also improves endoscopic and histologic features of EoE in 72% of adults.⁷ Empiric 4- or 6-food

elimination diets also lead to resolution of EoE in more than 70% of adults,^{8–10} and sequential reintroduction of foods is able to uncover specific trigger foods of EoE. Although efficacious, empiric elimination diets are also often cumbersome, time-consuming, costly, and unpalatable (particularly an elemental diet) and may induce iatrogenic nutritional deficiencies. Thus, more targeted approaches to food elimination have been sought.

Although IgE-mediated skin testing does not appear to be an accurate predictor of EoE food triggers in adults,^{2,5,11–13} we sought to determine whether the identification of food and/or aeroallergen sensitivity in patients with EoE may provide other significant clinical information about the patient and/or their disease. More specifically, does the presence of food or aeroallergen sensitivity identify a distinct phenotype of EoE in adults? To address this question, we performed a retrospective medical record review on adults with EoE within our University of Wisconsin Health System clinics. With these data, we examined whether food allergen sensitivity or aeroallergen sensitivity identify distinct clinical phenotypes of EoE.

Methods

We performed an institutional review board–approved retrospective medical record review of patients with a diagnosis of EoE (based on *International Classification of Diseases, Ninth Revision* codes) seen at the University of Wisconsin Hospital and Clinics during the years 2008 to 2013. Of the total 724 patients, 257 were seen in a University of Wisconsin Hospital and Clinics adult allergy clinic. All 257 patient records were accessed to capture demographics, atopic history, disease severity, endoscopy results, pathology reports, allergy test results, medical management, and patient-reported outcomes.

Patient demographic information included age at presentation, ethnicity, race, and sex. History of atopic diseases was based on patient report and/or physician diagnosis as documented in the medical record. Disease severity was assessed by duration of EoE symptoms, history of emergency department visits for EoE symptoms, and need for procedural interventions for EoE complications. Peripheral eosinophilia was defined as a peripheral eosinophil count of greater than 500 per high-power field (HPF). Endoscopy findings were obtained from a patient's initial diagnostic upper endoscopy procedure note. Eosinophils per HPF were recorded based on patient endoscopic esophageal pathology report. If multiple eosinophil counts were recorded, the highest number was used. If the report stated a count of "greater than x," it was recorded as such. A patient's medical management for EoE was based on documentation from the initial visit in the allergy clinic and included medications for EoE, food avoidance strategies, and procedural interventions. The preallergy management was based on the allergist's documentation of management before the initial allergy clinic visit. Postallergy visit medical management was based on the allergist's documentation of recommendations at the initial encounter visit. Patient outcomes were determined by patient symptom report at a subsequent follow-up visit with either a gastroenterologist or allergist. Outcomes were categorized based on subjective evaluation of the clinic visit note as complete improvement, partial improvement, no change, or worse. There were a number of patients that did not return to either the gastroenterology or allergy clinics after their initial evaluation and were listed as lost to follow-up. If any specific information was not available for a patient, then unknown was recorded for that entry.

Skin prick test (SPT) results were obtained from the patient's medical record. A positive SPT result was recorded if there was any skin reaction to testing, which included trace reactions. For those patients with indeterminate SPT results attributable to a blunted histamine reaction or positive saline reaction, indeterminate was

recorded. In these cases, serum specific IgE results for foods and/or aeroallergens were recorded instead, if available. If no SPT was completed, but serum specific IgE tests to foods and/or aeroallergens were performed, then results of the serum specific IgE were recorded. Any serum specific IgE level greater than 0.35 kU/mL was considered a positive result. Patients were categorized as either food sensitive or non–food sensitive based on food SPT and/or serum IgE test results.

For statistical analyses, the χ^2 test for association was used to compare categorical characteristics or outcomes by food sensitization status and aeroallergen sensitization status. Unknowns were included in the analysis. Because eosinophil counts per HPF were often recorded as "greater than x" and were thus right censored, they were compared between groups using a parametric lognormal survival regression model. $P < .05$ was regarded as statistically significant.

Results

Of the total 257 patients seen at a University of Wisconsin Hospital and Clinics adult allergy clinic, 155 patients (60%) were male and 102 patients (40%) were female. The mean patient age was 38 years (range, 13–83 years). Four patients (2%) self identified as being of Hispanic/Latino ethnicity. The remainder of the patients who reported an ethnicity identified themselves as non-Hispanic. Most patients (97%) identified their race as white, followed by black (1%) and Hawaiian/Pacific Islander (1 patient). Most patients (84%) had concurrent atopic diseases, such as asthma (43%), allergic rhinitis (79%), food allergy (21%), and atopic dermatitis (9%). In regard to reported food allergy, peanut/tree nut allergy was most common (35%), followed by fish/shellfish allergy (32%).

As reported in Table 1, the most commonly reported symptoms of EoE included dysphagia (81%), food impaction (58%), and symptoms of gastroesophageal reflux disease (47%). In patients whose medical records documented duration of EoE symptoms, almost 90% had EoE symptoms for more than 1 year. Emergency department visits for EoE symptoms, emergency procedures for food impaction, and dilations were seen in 28%, 18%, and 39% of patients, respectively. Most patients whose records documented a peripheral eosinophil count did not have peripheral eosinophilia (76%). Common esophageal endoscopy findings included esophageal rings (56%), linear furrows (35%), and strictures (40%). The most common recommended treatment for EoE was swallowed steroid (74%) followed by PPI (70%). Food avoidance was recommended in 40% of cases, although we did not capture whether the food elimination was based on targeted recommendations from the food allergy testing or empiric elimination. Food avoidance was also often recommended in addition to other medical therapies. Food avoidance as the sole treatment recommendation was only recommended in 10 patients. A total of 32 patients were advised to try food avoidance in addition to a PPI. In the patients with known outcomes, regardless of recommended treatment, there were no significant differences in the reports of complete improvement, partial improvement, or no change in symptoms (eFig 1).

IgE-mediated testing to foods, by SPT and/or serum specific IgE tests, was completed for 238 of the 257 adults with EoE (92%). Food SPT was performed for 224 patients (87%), with 9 patients having uninterpretable results attributable to blunted histamine response or dermatographism. Of these 9 patients, 7 had food specific serum IgE testing completed in addition to the SPT, and the remaining 2 patients had no additional testing performed. Excluding these 2 patients without interpretable results, there were a total of 236 patients with results in the form of SPT and/or serum specific IgE. A total of 56 patients (22%) had food specific serum IgE results: 42 patients had food specific IgE testing performed in combination

Table 1
Clinical Characteristics of the Patients With EOE

Clinical characteristic	No. (%) of patients (N = 257)
Symptoms	
Dysphagia	209 (81)
Food impaction	148 (58)
GERD	212 (82)
Nausea or vomiting	22 (9)
Abdominal pain	12 (5)
Regurgitation	16 (6)
Chest pain	17 (7)
Choking	18 (7)
Other	19 (7)
Duration of symptoms, y	
<1	29 (11)
1–5	72 (28)
5–10	30 (12)
>10	75 (29)
Unknown	50 (49)
Severity	
ED visit	71 (28)
Procedure-FI	46 (18)
Dilation	100 (39)
Peripheral eosinophils, per HPF	
≥500	43 (17)
<500	137 (53)
Unknown	77 (30)
Endoscopic findings	
Rings	143 (56)
Furrows	89 (35)
Strictures	102 (40)
Treatment recommendation	
PPI	179 (70)
Histamine ₂ -blocker	27 (10)
Swallowed steroid	189 (74)
Oral prednisone (Entocort)	12 (5)
Montelukast	11 (4)
None	4 (2)
Food avoidance total (with or without other treatments)	103 (40)
Food avoidance only	10 (4)
Food avoidance and PPI only	32 (12)
PPI and swallowed steroid	133 (52)
Any combination of >1 medicine	150 (58)
Reported outcomes	
Partial improvement	39 (15)
Complete improvement	118 (46)
Worse	4 (2)
No change	23 (9)
Unknown	73 (28)

Abbreviations: ED, emergency department; FI, food impaction; GERD, gastroesophageal disease; HPF, high-power field; PPI, proton pump inhibitor.

with food SPT, and 14 patients had food specific IgE tested only performed.

Of the 236 patients with interpretable IgE-mediated testing, 128 (54%) had a positive result to at least one food. As shown in Figure 1, of the 6 foods most commonly tested, peanut sensitivity was the most prevalent (51%), followed by soy (35%). Cod was the least common food sensitivity (8%). A complete list of food sensitivities is provided in the online supplement (eTable 1).

A summary of aeroallergen sensitivity results is shown in Figure 2. SPT to aeroallergens was completed for 181 of the 257 adults with EoE (70%) of whom 5 had noninterpretable results. Of the 5 patients with noninterpretable SPT results, 2 had aeroallergen serum specific IgE testing completed, and 3 patients did not undergo any additional testing. An additional 2 patients had serum aeroallergen specific IgE testing performed without any SPT. Of the 180 patients with interpretable aeroallergen test results, 157 (87%) were sensitized to at least 1 aeroallergen. Tree, dust mite, and pet (cat and/or dog) sensitivities were the most common, affecting 70%, 69%, and 66% of the patients, respectively.

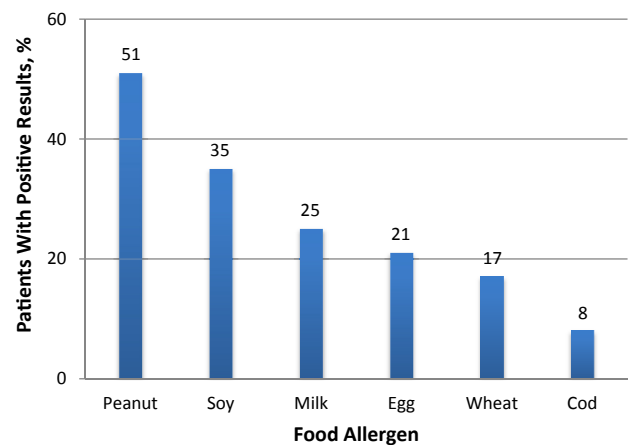


Figure 1. Percentage of patients who exhibited a positive skin prick test or serum IgE test result for the specified food allergens.

To determine whether patient allergic sensitivities affect the clinical or biological characteristics of EoE, patients were stratified as food sensitive vs non-food sensitive based on food IgE-mediated testing (SPT and/or serum specific IgE) and stratified as aeroallergen sensitive vs non-aeroallergen sensitive based on aeroallergen IgE-mediated testing. As indicated in Table 2, a total of 128 patients were sensitized to at least 1 food, and 108 patients had no food sensitivities. Patient characteristics did not differ between groups, except food sensitive patients were more likely to report concomitant asthma ($P = .01$), allergic rhinitis ($P = .02$), food allergy ($P < .001$), or atopic dermatitis ($P = .03$) compared with non-food sensitive patients. Patient-reported EoE symptoms and duration of symptoms did not significantly differ between groups. Number of patients requiring emergency department visits for EoE signs or symptoms, emergency endoscopy for food impaction, and esophageal dilations did not significantly differ between the groups. Additional analyses were performed to compare patients with 1 or more food sensitivities with a history of a true IgE-mediated food allergy and patients with food sensitivities without a history of a correlating IgE-mediated food allergy (eTable 2). There were no statistically significant differences in patient clinical characteristics between these 2 groups.

When patients were stratified by aeroallergen sensitivity, 157 patients were sensitized to at least 1 aeroallergen, and 23 patients had no aeroallergen sensitivities (Table 2). Patient characteristics did not differ between groups, except aeroallergen sensitive

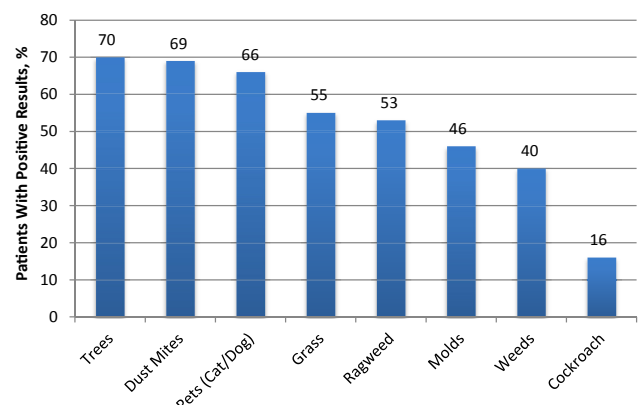


Figure 2. Percentage of patients who exhibited a positive skin prick test or serum IgE test result for the specified aeroallergens.

Table 2

Comparison of Clinical Characteristics Stratified by Allergen Sensitivity

Patient characteristic	No. (%) of food sensitive patients		No. (%) of aeroallergen sensitive patients	
	Yes (n = 128)	No (n = 108)	Yes (n = 157)	No (n = 23)
Symptoms				
Dysphagia	101 (79)	90 (83)	128 (82)	21 (91)
Food impaction	69 (54)	68 (63)	86 (55)	17 (74)
GERD	66 (52)	43 (40)	79 (50)	10 (43)
Nausea or vomiting	12 (9)	9 (8)	12 (8)	2 (9)
Abdominal pain	6 (5)	4 (4)	10 (6)	1 (4)
Regurgitation	11 (9)	5 (5)	10 (6)	2 (9)
Chest pain	10 (8)	8 (7)	10 (6)	2 (9)
Choking	10 (8)	3 (3)	10 (6)	0 (0)
Other	20 (16)	10 (9)	22 (14)	4 (17)
Duration of symptoms, y				
<1	13 (10)	13 (12)	13 (8)	4 (17)
1–5	29 (23)	37 (34)	42 (27)	6 (26)
5–10	15 (12)	14 (13)	21 (13)	3 (13)
>10	43 (34)	27 (25)	50 (32)	4 (17)
Unknown	27 (21)	17 (16)	30 (19)	6 (26)
Patient-reported history of atopic disease				
Allergic rhinitis	107 (84) ^a	76 (70)	155 (99) ^b	11 (48)
Asthma	66 (52) ^a	37 (34)	80 (51) ^a	5 (22)
Food allergy	41 (32%) ^b	12 (11)	41 (26)	4 (17)
Atopic dermatitis	16 (12) ^a	4 (4)	17 (11)	0 (0)
Disease severity				
Dilation (at any time)	57 (44)	39 (36)	64 (41)	5 (22)
ED	32 (25)	37 (34)	35 (22)	19 (39)
Procedure for food impaction removal	24 (19)	20 (18)	26 (17)	5 (22)

Abbreviations: ED, emergency department; GERD, gastroesophageal disease.

^a*P* < .05.^b*P* < .01.

patients were more likely to report concomitant asthma (*P* = .02) and allergic rhinitis (*P* < .001) compared with non-aeroallergen sensitive patients.

The distribution of peripheral eosinophil counts was comparable regardless of food or aeroallergen sensitivity (Table 3). The endoscopy findings of esophageal rings and linear furrows were commonly observed in all patient groups (51%–61% and 28%–35%, respectively). Strictures were noted more often in aeroallergen sensitive patients (*P* = .02). In contrast, esophageal felinization was observed more often in non-aeroallergen sensitive patients (*P* = .003).

As indicated in Table 4, allergist treatment recommendations consisted primarily of PPI and/or swallowed steroid. As expected, food avoidance was recommended significantly more often for food sensitive patients compared with non-food sensitive patients (77% vs 9%, *P* < .001). Most patients reported symptomatic improvement at a subsequent follow-up visit, and this did not significantly differ between the groups of food sensitive and non-food sensitive patients. In addition, the recommendation of food avoidance for those patients who were food sensitive did not lead to differences in patient-reported outcomes (eFig 1).

Table 3

Comparison of Patient Laboratory and Endoscopic Findings Stratified by Allergen Sensitivity

Patient characteristic	No. (%) of food sensitive patients		No. (%) of aeroallergen sensitive patients	
	Yes (n = 128)	No (n = 108)	Yes (n = 157)	No (n = 23)
Peripheral eosinophil count, per HPF				
≥500	19 (15)	21 (19)	29 (18)	2 (9)
<500	78 (61)	50 (46)	84 (54)	11 (48)
Unknown	31 (24)	37 (34)	44 (28)	10 (43)
Endoscopic findings				
Gastritis or duodenitis	17 (13)	8 (7)	13 (8)	4 (17)
Esophageal inflammation	14 (11)	7 (6)	10 (6)	2 (9)
Plaques	12 (9)	6 (6)	10 (6)	3 (13)
Erosions or ulcers	10 (8)	10 (9)	8 (5)	3 (13)
Erythema	3 (2)	2 (2)	3 (2)	0 (0)
Hiatal hernia	16 (12)	20 (18)	26 (17)	3 (13)
Fibrosis or thickening	5 (4)	1 (1)	6 (4)	1 (4)
Rings	68 (53)	66 (61)	80 (51)	12 (52)
Linear furrows	42 (33)	38 (35)	45 (29)	8 (35)
Felinization	7 (6)	5 (5)	1 (1)	3 (13) ^b
Schatzki ring	11 (9)	8 (7)	13 (8)	0 (0)
Stricture	59 (46)	37 (34)	71 (45) ^a	4 (17)
None of the above	21 (16)	15 (14)	15 (10)	2 (9)
Unknown	15 (12)	11 (10)	22 (14)	2 (9)

Abbreviation: HPF, high-power field.

^a*P* < .05.^b*P* < .01.

Table 4

Comparison of Patient Treatment Recommendations and Reported Outcomes Stratified by Allergen Sensitivity

Patient characteristic	No. (%) of food sensitive patients		No. (%) of aeroallergen sensitive patients	
	Yes (n = 128)	No (n = 108)	Yes (n = 157)	No (n = 23)
Allergy recommended treatment				
Swallowed steroid	87 (68)	85 (79)	118 (75)	19 (82)
PPI	93 (73)	73 (68)	107 (68)	16 (69)
Histamine ₂ -blocker	12 (9)	8 (7)	17 (11)	4 (17)
Prednisone (Entocort)	8 (6)	4 (4)	7 (4)	1 (4)
Montelukast	5 (4)	5 (5)	7 (4)	0 (0)
No Treatment	1 (1)	3 (3)	2 (1)	0 (0)
PPI and swallowed steroid	66 (52)	57 (53)	81 (52)	14 (61)
Combination of medications	73 (57)	63 (58)	92 (59)	15 (69)
Food avoidance	98 (77) ^a	10 (9)	76 (48)	6 (65)
Patient-reported outcomes				
No change	10 (8)	11 (10)	16 (10)	1 (4)
Partial improvement	18 (14)	11 (10)	27 (17)	3 (13)
Complete improvement	66 (52)	46 (43)	75 (48)	10 (43)
Worse	1 (1)	2 (2)	2 (1)	1 (4)
Unknown	33 (26)	37 (34)	37 (24)	8 (35)

Abbreviation: PPI, proton pump inhibitor.

^aP < .01.

Esophageal biopsy eosinophils per HPF were analyzed with a parametric lognormal survival regression model. Eosinophil counts did not differ between food sensitive and non-food sensitive individuals (Fig 3A) or between aeroallergen sensitive and non-aeroallergen sensitive individuals (Fig 3B). However, a few patients in each group had biopsy eosinophil counts of 15 per HPF. These patients were still considered to have EoE per their gastroenterologist because of other classic endoscopy findings consistent with the disease (rings, linear furrows).

Discussion

Our findings are consistent with previously published reports that suggest that identification of IgE-mediated food sensitivities do not necessarily predict EoE trigger foods.^{11,12} We sought to further address whether there was another benefit to performing IgE-based testing in adults with EoE, specifically identifying a different clinical phenotype of EoE in adults. To this end, we examined clinical and pathophysiologic features of EoE to

determine whether patients with food or aeroallergen sensitivity exhibited differences compared with patients without sensitivity.

Our study has several limitations. A notable limitation to this study is the retrospective design without a standardized evaluation of patients with EoE. There are now validated instruments for endoscopic and symptom scoring that would be essential for future prospective evaluations of EoE.^{14,15} Because of the retrospective nature of this study, we were unable to determine whether patients were treated with a PPI before their endoscopic diagnosis. We recognize that this is a significant limitation because this is now part of the diagnostic criteria for EoE. Likewise, our medical record review was unable to establish why some patients did not have IgE-mediated food and/or aeroallergen testing performed. This is likely because there is no standardized allergy evaluation in adult EoE and the decision to perform allergy testing is based on provider discretion. An additional limitation is that our study reflects only the characteristics of patients with EoE seen in an allergy clinic. It is our experience that the decision to refer a patient with EoE to an allergist is specific to individuals health care professionals.

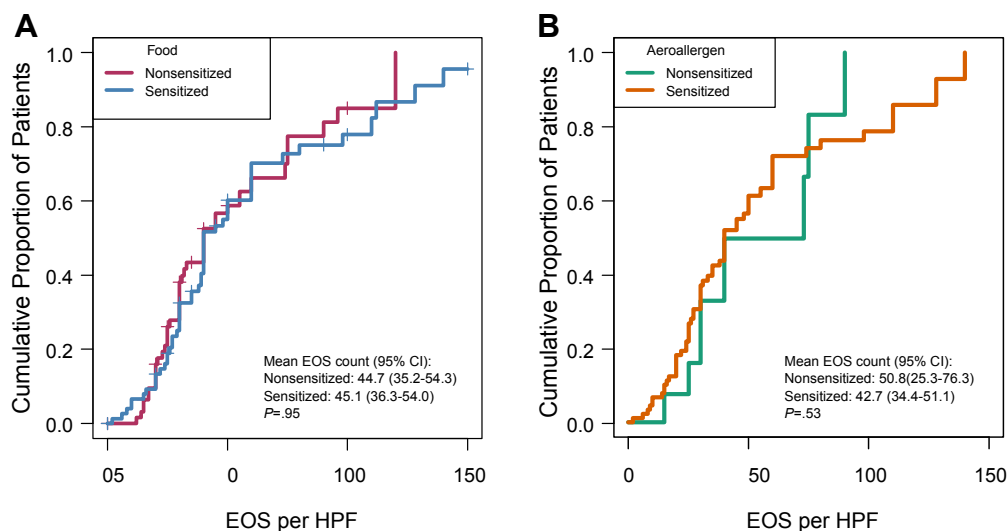


Figure 3. Eosinophil (EOS) levels on esophageal biopsy. The EOS count per high-power field (HPF) is represented as a cumulative proportion of patients who have smaller EOS counts per HPF listed. A, The food allergen sensitive (blue) and non-food allergen sensitive (red) patients were compared. B, The aeroallergen sensitive (orange) and non-aeroallergen sensitive (green) patients were compared.

However, our results reflect a subgroup of adults with EoE and therefore might not apply to all adults with EoE. It is possible that a more distinct phenotype of the disease would have been apparent had all the patients with EoE been studied.

Our data indicate that identification of IgE-mediated food sensitivity does reveal a patient population that is in general more atopic but otherwise does not distinguish a distinct clinical phenotypic of adult EoE. There were no significant clinical differences in patient demographics, patient-reported symptoms, duration of symptoms, severity of disease, endoscopic findings, esophageal pathologic findings, treatment, or patient-reported outcomes when comparing food sensitive and non-food sensitive patients. We acknowledge that patient outcomes were subjective and did not include validated tools to assess follow-up endoscopy, histologic examination, or patient-related outcome measures.^{14–16}

Similarly, the identification of IgE-mediated aeroallergen sensitivity revealed no significant clinical differences in patient demographics, patient-reported symptoms, duration of symptoms, severity of disease, esophageal pathologic findings, treatment, or patient-reported outcomes. A significant finding was that the endoscopy in aeroallergen sensitive patients more often revealed strictures. It is intriguing to consider whether this finding suggests differences in fibrotic vs inflammatory processes in the esophageal tissue. It is also notable that felinization was found less often in patients with aeroallergen sensitization, but this finding was relatively rare overall.

The role of targeted elimination diets based on allergy skin testing is unclear. Earlier studies found success rates in children of 53% and 65% by using allergen patch testing and skin testing, respectively, to identify culprit foods.^{4,17} Recent studies demonstrated sensitization to food allergens in 50% to 82% of adults with EoE.^{18,19} The most commonly identified food allergens were peanut, soy, egg, milk, and tree nuts,²⁰ as well as wheat, tomato, carrots, and onions.¹⁹ Although adults with EoE commonly have a high rate of food sensitization, this sensitization rarely connotes actual food allergy or correctly identifies a causative agent for EoE.⁵ In a study by Straumann et al,² 29% of adults had sensitization to milk, egg, fish, or seafood, but this finding was clinically relevant in only 1 patient. Molina-Infante et al¹¹ treated 15 adults with EoE with a targeted elimination diet, and only 5 of 15 had complete or partial histologic resolution of their EoE. Gonsalves et al¹² found that retrospectively SPTs would have predicted only 13% of trigger foods in adults with EoE undergoing empiric elimination diets. A recent systematic review of the various elimination diets reinforced the increasing evidence that allergy testing-directed elimination diets are among the least successful elimination diets in adults, with an overall effectiveness of 32%.¹³ Our study also failed to identify any clinical phenotypic difference associated with IgE-mediated food sensitivity.

EoE is considered an atopic disease and is commonly associated with other allergic diseases, such as allergic rhinitis, asthma, and atopic dermatitis.^{21,22} The pathogenesis of EoE is similar to that of other atopic conditions, primarily involving T_H2 inflammation, resulting in esophageal tissue expression of mediators, such as eotaxin-3, interleukin (IL) 13, and IL-5.^{23–25} Experimentally, EoE can also be induced in a mouse model by intrinsic T_H2 cytokines, such as IL-13 and IL-5.^{26,27} Studies have found seasonal peaks of EoE symptoms and diagnosis, correlating with pollen seasons, suggesting a potential role of aeroallergens in the pathogenesis of EoE.^{28–30} Prior studies have found aeroallergen sensitization in 86% to 93% of adults with EoE.^{18,19} Experimentally, EoE has been induced by intranasal exposure to aeroallergens in mice.³¹ In addition, experimental epicutaneous allergen sensitization may potentially prime the body for respiratory allergen-induced EoE.³² In a study of 63% of adults with EoE exhibiting IgE-mediated food sensitization, most patients were sensitized to foods that

cross-react with the pollens.²¹ Most notably, these adults were sensitized to wheat and rye, which is cross-reactive with grass pollen. However, an elimination diet of wheat and rye failed to improve EoE symptoms in sensitized patients.³³

Our data confirm that there is no utility in identifying food IgE-mediated sensitivity for EoE in adults. The most notable finding from this study regarding potential phenotypes of EoE was the differing prevalence of strictures and felinization noted on endoscopy in aeroallergen sensitive vs non-aeroallergen sensitive subjects. This observation coupled with the findings of aeroallergen involvement in EoE in humans and mouse models suggest that evaluation for aeroallergen sensitivity could be important as a phenotypic distinction in EoE. Future prospective studies are needed to determine whether aeroallergen sensitivity truly defines a distinct phenotype of EoE, whether there are differences in the pathophysiologic mechanisms of EoE, and whether there is clinical relevance to the identification of aeroallergen sensitive EoE.

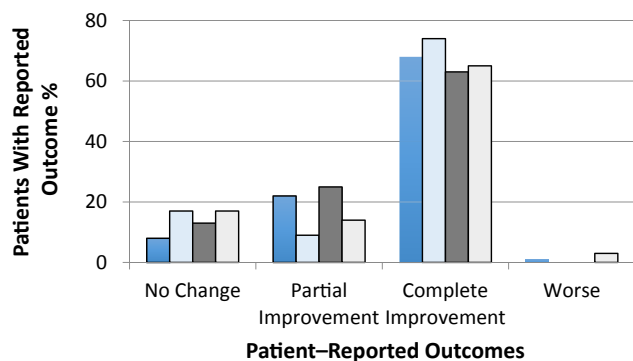
Supplemental Data

Supplemental data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.08.008>.

References

- Aceves SS. Eosinophilic esophagitis. *Immunol Allergy Clin North Am*. 2015;35:145–159.
- Straumann A, Aceves SS, Blanchard C, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy*. 2012;67:477–490.
- Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109:1503–1512.
- Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012;130:461–467.e5.
- Aceves SS. Food allergy testing in eosinophilic esophagitis: what the gastroenterologist needs to know. *Clin Gastroenterol Hepatol*. 2014;12:1216–1223.
- Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol*. 2003;98:777–782.
- Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol*. 2013;108:759–766.
- Rodriguez-Sanchez J, Gomez Torrijos E, Lopez Viedma B, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic esophagitis. *Allergy*. 2014;69:936–942.
- Molina-Infante J, Arias A, Barrio J, Rodriguez-Sanchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. *J Allergy Clin Immunol*. 2014;134:1093–1099.e1.
- Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006;4:1097–1102.
- Molina-Infante J, Martin-Noguero E, Alvarado-Arenas M, Porcel-Carreno SL, Jimenez-Timon S, Hernandez-Arbeiza FJ. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. *J Allergy Clin Immunol*. 2012;130:1200–1202.
- Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology*. 2012;142:1451–1459.e1. quiz e14–e15.
- Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146:1639–1648.
- Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology*. 2014;147:1255–1266.
- Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut*. 2013;62:489–495.
- Azzawi M, Bradley B, Jeffery PK, et al. Identification of activated T lymphocytes and eosinophils in bronchial biopsies in stable atopic asthma. *Am Rev Respir Dis*. 1990;142:1407–1413.
- Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol*. 2012;129:1570–1578.

- [18] Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2008;6:531–535.
- [19] Penfield JD, Lang DM, Goldblum JR, Lopez R, Falk GW. The role of allergy evaluation in adults with eosinophilic esophagitis. *J Clin Gastroenterol*. 2010;44:22–27.
- [20] Dominguez-Ortega J, Perez-Bedmar J, Rodriguez-Jimenez B, Butron M, Kindelan C, Ledesma A. Eosinophilic esophagitis due to profilin allergy. *J Investig Allergol Clin Immunol*. 2009;19:338–339.
- [21] Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol*. 2005;115:1090–1092.
- [22] Simon D, Straumann A, Simon HU. Eosinophilic esophagitis and allergy. *Dig Dis*. 2014;32:30–33.
- [23] Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol*. 2007;120:1292–1300.
- [24] Wechsler JB, Bryce PJ. Allergic mechanisms in eosinophilic esophagitis. *Gastroenterol Clin North Am*. 2014;43:281–296.
- [25] Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol*. 2001;108:954–961.
- [26] Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology*. 2003;125:1419–1427.
- [27] Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol*. 2002;168:2464–2469.
- [28] Almansa C, Krishna M, Buchner AM, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol*. 2003;104:828–833.
- [29] Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol*. 2003;112:796–797.
- [30] Moawad FJ, Veerappan GR, Lake JM, et al. Correlation between eosinophilic oesophagitis and aeroallergens. *Alimentary Pharmacol Ther*. 2010;31:509–515.
- [31] Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest*. 2001;107:83–90.
- [32] Akei HS, Mishra A, Blanchard C, Rothenberg ME. Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. *Gastroenterology*. 2005;129:985–994.
- [33] Simon D, Straumann A, Wenk A, Spichtin H, Simon HU, Braathen LR. Eosinophilic esophagitis in adults: no clinical relevance of wheat and rye sensitizations. *Allergy*. 2006;61:1480–1483.



eFigure 1. Patient-reported outcomes with food avoidance. The categories of outcomes are no change, partial improvement, complete improvement, and worse. The patients were grouped by food sensitive status and whether they included food avoidance in their treatment plan: food sensitive patients who did perform food avoidance (dark blue bars, $n = 72$), food sensitive patients not avoiding foods (light blue bars, $n = 23$), non-food sensitive patients who avoided foods (dark green bars, $n = 8$), and non-food sensitive patients not avoiding foods (light green bars, $n = 63$).

eTable 1

Food Sensitivities

Food	No. (%) of patients with positive test results
Peanut	65 (51)
Soy	45 (35)
Milk	32 (25)
Egg	27 (21)
Wheat	22 (17)
Green Pea	22 (17)
Tree nuts	21 (17)
Barley	21 (17)
Corn	21 (17)
Rye	17 (14)
Chicken	16 (13)
Carrot	15 (12)
Oat	14 (11)
Rice	12 (10)
Beef	11 (9)
Potato	11 (9)
Cod	10 (8)
Shellfish	10 (8)
Turkey	9 (7)
Fruit	9 (7)
Sesame seed	5 (4)
Tomato	4 (3)
Banana	4 (3)
Onion	3 (2)
Malt	3 (2)
Cantaloupe	3 (2)
Celery	2 (2)
Beans	2 (2)
Sunflower seed	2 (2)
Green bean	2 (2)
Garlic	2 (2)
Pork	2 (2)
Lettuce	1 (1)
Asparagus	1 (1)
Poppy Seed	1 (1)
Yeast	1 (1)
Lamb	1 (1)
Other fruits	1 (1)

eTable 2

Comparison of Food Sensitive Patients With a History of IgE-Mediated Food Allergy to Patient With Food Sensitivities Without a History of IgE-Mediated Food Allergy

Clinical characteristics	No. (%) of food sensitive patients with history of IgE-mediated food allergy (n = 41)	No. (%) of food sensitive patients without history of IgE-mediated food allergy (n = 87)
Symptoms		
Dysphagia	33 (80)	68 (78)
Food Impaction	21 (51)	48 (55)
GERD	19 (46)	47 (54)
Nausea or vomiting	1 (2)	11 (13)
Abdominal pain	1 (2)	5 (6)
Regurgitation	3 (7)	8 (9)
Chest pain	4 (10)	6 (7)
Choking	4 (10)	6 (7)
Other	6 (15)	14 (16)
Duration of symptoms, y		
<1	4 (10)	9 (10)
1–5	9 (22)	20 (23)
5–10	6 (15)	9 (10)
>10	14 (34)	29 (33)
Unknown	8 (20)	20 (23)
Patient-reported history of atopic disease		
Allergic rhinitis	38 (93)	69 (79)
Asthma	21 (51)	45 (52)
Food allergy	41 (100)	0 (0) ^a
Atopic dermatitis	6 (15)	10 (11)
Disease severity		
Dilation (at any time)	21 (51)	36 (41)
ED	12 (29)	20 (23)
Procedure for food impaction removal	10 (24)	14 (16)
Peripheral eosinophil count, per HPF		
≥500	3 (7)	16 (18)
<500	26 (63)	52 (60)
Unknown	12 (29)	19 (22)
Endoscopic findings		
Gastritis or duodenitis	5 (12)	12 (14)
Esophageal inflammation	5 (12)	9 (10)
Plaques	1 (2)	11 (13)
Erosions or ulcers	2 (5)	8 (9)
Erythema	1 (2)	2 (2)
Hiatal hernia	2 (5)	14 (16)
Fibrosis or thickening	1 (2)	4 (5)
Rings	21 (51)	47 (54)
Linear furrows	11 (27)	31 (36)
Felination	1 (2)	6 (7)
Schatzki ring	3 (7)	8 (9)
Stricture	19 (46)	40 (46)
None of the above	9 (22)	12 (14)
Unknown	5 (12)	10 (11)
Allergy recommended treatment		
Swallowed steroid	29 (71)	58 (67)
PPI	32 (78)	61 (70)
Histamine ₂ -blocker	4 (10)	8 (9)
Prednisone (Entocort)	5 (12)	3 (3)
Montelukast	3 (7)	2 (2)
No treatment	0 (0)	1 (1)
PPI and swallowed steroid	22 (54)	44 (51)
Combination of medications	25 (61)	48 (55)
Food avoidance	35 (85)	63 (72)
Patient-reported outcomes		
No change	2 (5)	8 (9)
Partial improvement	6 (15)	12 (14)
Complete improvement	24 (59)	42 (48)
Worse	0 (0)	1 (1)
Unknown	9 (22)	24 (28)

Abbreviations: ED, emergency department; GERD, gastroesophageal disease; HPF, high-power field; PPI, proton pump inhibitor.

^aP < .01.