

The Role of Allergy Evaluation in Adults With Eosinophilic Esophagitis

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Background: Allergy evaluation and skin prick testing for foods are recommended in all patients with eosinophilic esophagitis. However, the yield of allergy evaluation in adult eosinophilic esophagitis is not known.

Goals: To determine the yield of allergy evaluation in adults with eosinophilic esophagitis.

Study: All adult patients in the Cleveland Clinic eosinophilic esophagitis registry between January 2006 and April 2008 were identified. Diagnosis was based on clinical presentation and endoscopy with biopsies showing ≥ 15 eosinophils/hpf. From this group, all patients referred for allergy evaluation were identified. Allergy evaluation consisted of skin testing to foods in all patients. Selected patients underwent skin testing to inhalants based on the presence of concomitant allergic rhinitis and/or asthma. Immediate hypersensitivity skin testing was performed and scored by standard methodology. Patients were referred on an ad hoc basis by the gastroenterologist and not based on a priori identification of an allergic diathesis.

Results: Twenty-six out of 68 patients (38%) completed allergy evaluation. Thirteen out of 26 patients (50%) demonstrated a positive skin test to ≥ 1 food allergen. Of the 15 patients who underwent skin testing for inhalants, 14 (93%) had a positive skin test to 1 or more inhalants. In total 21/26 patients (81%) had ≥ 1 allergen identified, 16/26 (62%) had ≥ 5 allergens identified, and 4/26 (15%) had ≥ 10 allergens identified (range: 0 to 20 allergens identified). Peanut, egg white, soybean, cow's milk, and tree nuts were the most common food allergens identified.

Conclusions: Allergy evaluation has a high yield in adult eosinophilic esophagitis as 81% of referred patients had one or more allergens identified and 50% had one or more skin tests positive to foods. Allergy evaluation should be considered in adult patients with eosinophilic esophagitis.

Key Words: eosinophilic esophagitis, allergy, esophagitis

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Eosinophilic esophagitis is a clinicopathologic entity characterized by esophageal symptoms in association with a dense eosinophilic infiltrate currently defined as ≥ 15

eosinophils per high power field in the appropriate clinical context.¹ Eosinophilic esophagitis is increasingly recognized in both children and adults, and multiple studies document the rising prevalence of this disorder.^{2,3}

The etiology and natural history of eosinophilic esophagitis among adults is not well understood. However, the high prevalence of atopic diseases such as allergic rhinitis, atopic dermatitis, and asthma in both pediatric and adult eosinophilic esophagitis patients suggests an allergic response to one or more antigens that may provoke and perpetuate this condition.^{4–6} Food allergies have a clear role in pediatric eosinophilic esophagitis patients, especially in light of positive treatment trials with elemental and elimination diets.^{5,7–9} The recently published eosinophilic esophagitis consensus statement recommends complete evaluation by a well-informed allergist in conjunction with skin prick testing for foods and inhalants in all eosinophilic esophagitis patients.¹ However, the value of immediate hypersensitivity skin testing for inhalant and food allergy in adult eosinophilic esophagitis patients has not been established. Thus, the aim of this study was to assess the yield of allergy evaluation in adults with eosinophilic esophagitis.

MATERIALS AND METHODS

Patients

All adult patients with eosinophilic esophagitis were identified using the Cleveland Clinic eosinophilic esophagitis registry, which consists of all patients diagnosed with eosinophilic esophagitis at the Cleveland Clinic between January 2006 and April 2008. Patients were initially referred to the Department of Gastroenterology and Hepatology for evaluation of symptoms of recurrent dysphagia, recurrent food bolus impaction or heartburn refractory to at least a 2-month trial of proton pump inhibitor treatment. This study was approved by the Institutional Review Board of the Cleveland Clinic.

Endoscopy and Biopsy Protocol

All patients underwent upper endoscopy at the Cleveland Clinic with Olympus GIF 160 or GIF 180H standard or high definition endoscopes (Olympus America Inc, Center Valley, PA). All patients were placed on proton pump inhibitor therapy before upper endoscopy to decrease the likelihood of reflux related eosinophilic infiltration. The esophagus was carefully examined and any mucosal abnormalities such as multiple rings, linear furrows, and white exudates were identified. Biopsies were also obtained in the absence of endoscopic findings suspicious for eosinophilic esophagitis. A total of 6 biopsies were obtained from the distal, mid and proximal esophagus with

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a large capacity forceps (Radial Jaw 4, Boston Scientific, Natick, MA).

Pathology

Fixed, paraffin-embedded biopsy specimens were stained with hematoxylin and eosin and all slides were reviewed by a single experienced gastrointestinal pathologist (J.G.) using a 40× high-powered microscopic field. Eosinophils were evaluated by counting the number of eosinophils per high power field in the area where they seemed most dense. Eosinophilic esophagitis was defined as ≥15 intraepithelial eosinophils/hpf, typically with aggregation of eosinophils near the surface of the mucosa and/or the formation of eosinophilic microabscesses.

Allergy Evaluation

Patients were referred for evaluation on an ad hoc basis by the gastroenterologist managing their case and not based on a priori identification of an allergic diathesis. Allergy evaluation consisted of a detailed history including adverse reactions to foods and past or current respiratory or cutaneous symptoms consistent with immunoglobulin E (IgE) mediated disorders (atopy). Atopy was considered to be present in individuals with current or past symptoms consistent with allergic rhinitis, asthma or atopic dermatitis. Patients underwent immediate hypersensitivity skin testing to a standard panel of foods including egg white, cow's milk, soybean, peanut, English walnut, wheat, shrimp, and halibut. Further skin testing to other foods was on the basis of a clinical history of reaction to that food. Selected patients underwent skin testing to inhalants based on the presence of concomitant allergic rhinitis and/or asthma. Inhalant extracts included cat, dog, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, mold spores (*Alternaria*, *Aspergillus*, *Cladosporium*), tree mix, grass, weed mix, and ragweed. Patients who exhibited dermatographia underwent diagnostic evaluation using an in vitro method [radioallergoimmunosorbent testing (RAST)]. Quantification of total serum IgE levels was performed in selected patients.

Skin testing was performed with commercially available extracts (Greer Laboratories, Inc, Lenoir, NC). Testing was performed using conventional methodology,¹⁰ with prior omission of medication with antihistaminic properties and scoring of wheal/flare reaction using a 0 to 4+ scale.

Statistics and Analysis

Values are presented as mean ± standard deviation for age, median (25th, 75th percentiles) for number of positive skin tests and N (%) otherwise. Student *t* test for age and Fisher exact tests for all categorical factors were used to assess associations between presence of food allergens and subject characteristics. In addition, Wilcoxon rank sum tests were used to evaluate the association between number of food allergens and presence of symptoms of atopic status and endoscopic findings. A *P* < 0.05 was considered statistically significant. The SAS version 9.1 software (The SAS Institute, Cary, NC) was used to perform all analyses.

RESULTS

A total of 68 adult patients (20 to 74 y of age) were diagnosed with eosinophilic esophagitis during the study period. From this group, 28 patients were identified (41%) who were referred for allergy evaluation as shown in

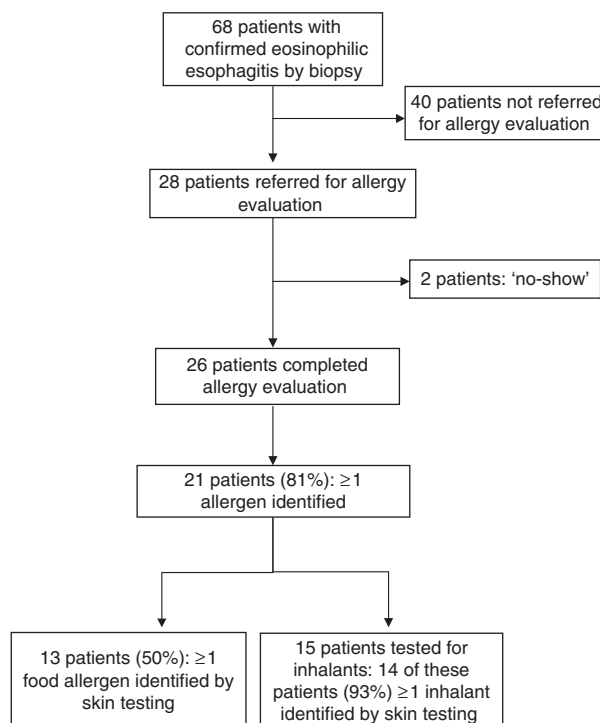


FIGURE 1. Flow chart of eosinophilic esophagitis patients undergoing allergy evaluation.

Figure 1. One patient cancelled the appointment and another patient did not attend, leaving a total of 26 adult patients who completed their allergy evaluation. Demographics of the study population are shown in Table 1.

Figure 1 summarizes the study findings. Twenty-one out of 26 patients (81%) had ≥1 food and/or inhalant

TABLE 1. Demographics of Study Population and Atopic Status (N = 26)

Gender	
Male/female (% male)	17/9 (65%)
White	25 (96%)
Mean age (SD) [range (y)]	41.4 ± 11.0 (20-74)
Presenting symptoms	
Dysphagia	23 (88%)
Heartburn	9 (35%)
Food impaction	7 (27%)
Endoscopic features (n = 25)*	
Rings	17 (68%)
Furrows	8 (32%)
White exudates	4 (16%)
Normal	6 (24%)
Concomitant atopic disorders	
Allergic rhinitis	24 (92%)
Asthma	9 (35%)
Atopic dermatitis	3 (12%)
Pollen-fruit syndrome†	7 (27%)

*One patient underwent upper endoscopy at an outside institution, the images of which were not available for review. None of the patients had endoscopic evidence of reflux esophagitis.

†A syndrome of IgE-mediated oropharyngeal pruritis caused by consumption of raw fruits and/or vegetables in patients with concomitant allergic rhinitis.

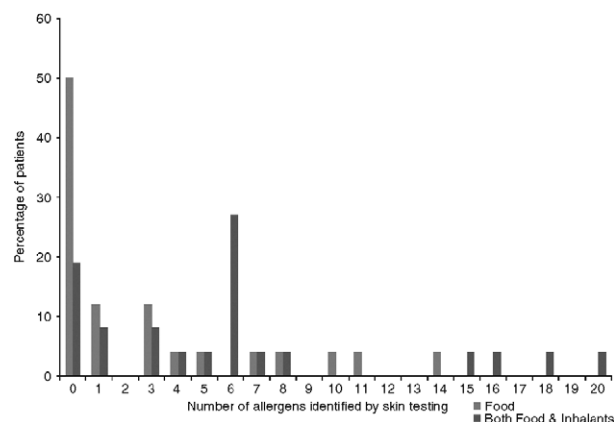


FIGURE 2. Percent of adult eosinophilic esophagitis patients with positive skin tests.

identified by skin testing (range: 0 to 20 allergens). Figure 2 shows the percent of patients with positive skin tests. The median (25th, 75th percentiles) number of positive skin tests (foods and/or inhalants) was 6.¹⁸ A total of 13/26 patients (50%) demonstrated a positive skin test to ≥ 1 food allergen. Peanut, egg white, soybean, cow's milk and tree nuts, including walnut, almond and Brazil nut, were the most common food allergens identified. The results of skin testing to foods are shown in Table 2.

Only 15 of 26 patients underwent skin testing for inhalants. Such testing was not based on the presence of positive skin tests to foods. Fourteen out of 15 patients (93%) were skin test positive to ≥ 1 inhalant. The median (25th, 75th percentiles) number of positive skin tests to inhalants among those patients tested was 6 (0, 9). The 11 patients who were not tested for inhalants either had no concurrent symptoms of allergic rhinitis (7 patients) or were previously evaluated for allergic rhinitis with skin testing at an outside institution before the diagnosis of eosinophilic esophagitis (4 patients). The results of such prior skin tests were not available for review. The most common inhalants identified were grass and weed pollens, including ragweed as shown in Table 3. One patient evaluated at an outside institution for symptoms of allergic rhinitis underwent RAST to inhalants which confirmed the presence of elevated levels of specific IgE to grasses, weeds, trees, dust mite, and animal danders.

Total serum IgE levels were not routinely quantified. IgE levels were checked in 6 of the 26 patients with 5 of those 6 patients demonstrating elevated IgE levels (> 150 U/mL, range: 154 to 1683 U/mL), which in cases of marked elevation likely reflected atopic dermatitis. Five out of 26 patients exhibited dermatographia during skin testing. For these 5 patients RAST was obtained, which confirmed elevated levels of specific IgE antibodies to

selected foods including peanut/tree nuts, soybean, wheat, egg white, fruits, and vegetables.

Table 4 stratifies demographic and clinical characteristics of adult eosinophilic esophagitis patients by wheal/flare reaction to foods on skin testing. No statistically significant results were obtained when stratifying demographic and clinical characteristics by number of positive skin tests.

DISCUSSION

Our study demonstrates that routine allergy evaluation has a high yield in adult eosinophilic esophagitis patients; 81% of the patients referred for an allergy evaluation had ≥ 1 allergen identified by skin testing. Fifty percent had ≥ 1 food allergen identified by skin testing and 93% of those tested had ≥ 1 inhalant identified. This group of patients also had a high prevalence of atopy with allergic rhinitis representing the most common atopic diathesis.

The recent eosinophilic esophagitis consensus statement recommended that patients with eosinophilic esophagitis should undergo a complete allergy evaluation.¹ However, these recommendations were based primarily on studies in the pediatric population and the value of routine referral of adult eosinophilic esophagitis patients has not been firmly established. Allergic potential to foods in pediatric patients with eosinophilic esophagitis ranges from 60% to 77% by either skin testing or RAST.^{5,9,11} The most common foods identified are milk, egg, peanut, soybean and wheat, a profile of foods very similar to those identified in this study.

Up to date, little is known about the role of routine allergy evaluation in adult patients with eosinophilic esophagitis. Prior studies have reported high rates of atopy among adult eosinophilic esophagitis patients.^{12–16} These reports have relied on symptoms of asthma, allergic rhinitis or atopic dermatitis or prior diagnosis of these conditions rather than objective testing. Recent work by Roy-Ghanta et al¹⁷ confirmed a high rate of allergic sensitization to both foods and inhalants in adult eosinophilic esophagitis patients by measuring serum specific IgE antibodies to common foods and inhalants. The authors found that 19/23 patients were positive to 1 or more allergens. Roy-Ghanta et al performed in vitro testing to a large number of foods, which may, in part, explain the relatively high rate of elevated IgE levels to foods found in their study. We elected to use skin testing in our patients for 2 reasons: (1) skin testing has a higher sensitivity than in vitro methods (eg, RAST)¹⁸; and (2) the recent eosinophilic esophagitis consensus statement recommends skin testing for allergy evaluation.¹ The results of skin testing in our study are comparable to the preliminary results of others.¹⁹

Interventions on the basis of results of allergy evaluation seem to be promising in children. Complete

TABLE 2. Number of Patients With Positive Skin Test Results to Food Allergens

	Food Allergens							
	Egg white	Cow's Milk	Peanut	Soybean	Walnut	Wheat	Shrimp	Other*
Positive skin test	7/26 (27%)	5/26 (19%)	10/26 (38%)	6/26 (23%)	5/26 (19%)	1/24 (4%)	1/25 (4%)	9/26 (35%)

*Further skin testing to food allergens on selected patients on the basis of clinical history. The most common food allergens identified from this category include almond, Brazil nut, pistachio, filbert nut, and cantaloupe. No patients had positive skin tests to fish.

TABLE 3. Number of Patients With Positive Skin Test Results to Inhalants

	Inhalants							
	Cat	Dog	Cockroach	Dust Mite	Molds	Trees	Grasses	Weeds*
Positive skin test	10/15 (67%)	8/15 (53%)	4/13 (31%)	9/13 (69%)	9/14 (64%)	11/15 (73%)	13/15 (87%)	14/15 (93%)

Select patients underwent allergy evaluation to inhalants based on presence of symptoms consistent with allergic rhinitis and/or asthma.

*Weeds category includes ragweed.

symptomatic and histologic improvement may be seen in children treated with an elemental diet.^{7,8,20,21} A 6 food elimination diet that excluded cow-milk protein, soy, egg, wheat, peanut/tree nuts, and fish led to significant histologic improvement in 74% of children with eosinophilic esophagitis.²⁰ However, elimination diets on the basis of results of skin testing or atopy patch testing have also demonstrated a high rate of histologic and clinical improvement, with 77% of children showing a decrease in esophageal eosinophilic infiltration after a 6-week diet that eliminated foods found on allergy evaluation.⁹ Subsequent reintroduction of the causative food led to an increase in the number of esophageal eosinophils in a subset of children. The importance of allergen avoidance is further exemplified by studies showing that pediatric patients with eosinophilic esophagitis and concomitant allergy do not respond as well to swallowed fluticasone compared with nonallergic patients.^{22,23} Thus, the effectiveness of such avoidance measures may allow patients to avoid the use of long-term topical steroid treatment with its associated local side-effects and high relapse rates.

Much less is known about the implications of allergy evaluation in adult patients with eosinophilic esophagitis, as suggested by the consensus statement.¹ No symptom improvement was noted in 6 adult eosinophilic esophagitis patients with skin tests positive to wheat and rye after an elimination diet avoiding wheat and rye for 6 weeks.²⁴ Preliminary results of an empiric 6 food elimination diet that excluded milk, egg, soy, wheat, nuts, and seafood in 18 adult patients revealed a significant improvement in histologic and endoscopic parameters in 78% of these patients.¹⁹ A subset of 6 patients in this study underwent

food reintroduction which reproduced symptoms, endoscopic features, and eosinophilic infiltration. The most common food triggers were milk and wheat followed by soy and egg. To our knowledge, there are no studies in adults that have examined the role of avoidance of foods identified on skin testing as a treatment option for eosinophilic esophagitis. There are also no studies to date that have compared an empiric 6-food elimination diet with a skin test guided elimination diet.

We found that 93% of selected patients were skin test positive to 1 or more inhalants. The role of inhalants as a cause of eosinophilic esophagitis is supported by a number of animal studies. Intranasal sensitization of mice with *Aspergillus fumigatus* produced esophageal eosinophilic infiltration whereas intragastric sensitization was not associated with such response.²⁵ It is conceivable that sensitized individuals may swallow inhaled allergens producing an IgE mediated reaction within the esophagus.⁴ The importance of inhaled aeroallergens is supported by the seasonal variation in diagnosis of eosinophilic esophagitis observed in both children and adults.^{26,27} Only patients with a concurrent or past history of allergic rhinitis and/or asthma underwent skin testing to inhalants in this study. It is not standard of care to perform skin testing to inhalants in patients who do not have rhinitis and/or asthma owing to the low positive predictive value in this setting.¹⁸ Additional investigation is required to assess the yield of skin testing to inhalants in adult eosinophilic esophagitis patients without allergic rhinitis or asthma.

Skin testing is recommended as the preferred screening test to confirm or rule out a diagnosis of IgE mediated potential to foods or inhalants.¹⁸ As mentioned above, skin

TABLE 4. Demographic and Clinical Characteristics of Adult Eosinophilic Esophagitis Patients in Association with Positive Skin Tests to Foods*

Factor	Food Allergy N = 13	No Food Allergy N = 13	OR (95% CI)
Male Sex	8 (61.5)	9 (69.2)	0.71 (0.14, 3.6)
White	12 (92.3)	13 (100.0)	
Age (y)	40.4 (11.7)	42.5 (10.7)	0.98 (0.91, 1.06)
Dysphagia	12 (92.3)	11 (84.6)	2.2 (0.17, 27.6)
Heartburn	5 (38.5)	4 (30.8)	1.4 (0.28, 7.1)
Food impaction	3 (23.1)	4 (30.8)	0.68 (0.12, 3.9)
Rings	11 (84.6)	6 (50.0)	5.5 (0.84, 36.2)
Furrows	3 (23.1)	5 (41.7)	0.42 (0.07, 2.4)
White exudates	2 (15.4)	2 (16.7)	0.91 (0.11, 7.7)
Normal endoscopic features	2 (15.4)	3 (27.3)	0.48 (0.07, 3.6)
Atopic dermatitis	2 (15.4)	1 (7.7)	2.2 (0.17, 27.6)
Allergic rhinitis	11 (84.6)	13 (100.0)	
Asthma	5 (38.5)	4 (30.8)	1.4 (0.28, 7.1)
Pollen-fruit syndrome	5 (38.5)	2 (15.4)	3.4 (0.53, 22.4)

Results are not statistically significant ($P > 0.05$).

*Values presented as mean (SD) for age and N (%) otherwise.

CI indicates confidence interval; OR odds ratio.

testing has greater sensitivity compared with in vitro methods. Emerging evidence supports the contention that the pathogenic mechanism underlying eosinophilic esophagitis is not simply confined to IgE or immediate hypersensitivity, but may also include T cell mediated inflammation.^{28–30} Atopy patch testing assesses the potential for delayed hypersensitivity whereas immediate hypersensitivity skin testing does not. Evidence suggests that a combination of skin testing and atopy patch testing for foods leads to an increased specificity compared with each test alone.²⁹ Patch testing was not performed in this study. Performance of atopy patch testing is controversial and is not recommended by the current eosinophilic esophagitis consensus statement.^{1,18}

We found pollen-fruit syndrome in 27% of our patients. Pollen-fruit syndrome is an IgE-mediated response caused by cross-reacting antigens in pollens and raw fruits, vegetables, and nuts. This condition is confined to the oral cavity and is typically diagnosed on the basis of oropharyngeal pruritis after the consumption of specific foods. Pollen-fruit syndrome was estimated to occur in 8% of adult patients with allergic rhinitis in a survey of allergists in the United States,³¹ but has been reported to occur more frequently in other studies.³² The true prevalence of this condition is unclear, owing to geographic variation in aerobiology and nutritional intake, as well as a tendency for under-diagnosis by physicians and under-reporting by patients.^{31,33} In addition, 5 patients (19%) exhibited dermatographia in our study and required in vitro testing. Simple dermatographism, a condition in which an erythematous wheal may be provoked by stroking of the skin, is estimated to occur in approximately 2% to 5% of the general population.³⁴ For patients with dermatographia, skin testing may be uninterpretable. The rates of both pollen-fruit syndrome and dermatographia, if confirmed in larger studies, may provide clues regarding factors important for development of eosinophilic esophagitis and thus warrants further study.

Our study has several limitations. Only a subset of our patients were referred for allergy evaluation. The majority of patients were referred before the consensus statement recommendations. A 100% referral pattern would have been ideal, although we feel that these results reflect a real life clinical practice scenario. Furthermore, allergy evaluation took place at the discretion of the treating physician and not as part of a systematic protocol. As such, there is the potential for referral bias as we do not know the allergy status of individuals who were not referred. Our results are consistent with previous observations, making this less likely. Not all patients were on twice daily proton pump inhibitor therapy before endoscopic biopsies. Again, this reflects management of adult eosinophilic esophagitis patients before the publication of the consensus statement recommendations. There was also no control group who underwent skin testing. However, 81% of patients with ≥ 1 allergen identified on skin testing in our study is substantially higher than the 54% overall prevalence of wheal/flare reaction to inhalants or peanut in the 10,863 healthy adults and children who participated in skin testing during NHANES III.³⁵ Thus, we believe that our findings offer a useful snapshot of what might be expected if allergy evaluation occurs in adults with eosinophilic esophagitis.

In summary, referral of adult eosinophilic esophagitis patients for allergy evaluation commonly identifies potentially relevant foods and inhalants. Eighty-one percent of

selected patients referred for allergy evaluation in this study had ≥ 1 allergen identified by skin testing. On the basis of these findings, allergy evaluation should be considered for all adult eosinophilic esophagitis patients. However, it remains unknown what role a skin test directed elimination diet might play in the treatment of adult eosinophilic esophagitis. Given the limited efficacy of current treatment options for eosinophilic esophagitis, this concept warrants further investigation.

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