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Pediatric eosinophilic esophagitis: the Vanderbilt experience

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ABSTRACT

Background: Eosinophilic esophagitis (EoE) is a chronic allergic disease of the esophagus unresponsive to treatment with proton pump inhibitors. A combination of immediate, IgE-mediated and delayed, and non-IgE-mediated immune reactions to foods and aeroallergens is thought to contribute to disease pathogenesis. Optimal methods to assess for food allergen sensitization have been debated. Patients with EoE often have comorbid atopic diseases.

Objective: To characterize pediatric patients diagnosed with EoE at a single institution within the southeastern United States.

Methods: A retrospective study was conducted to evaluate 211 pediatric patients with EoE at Vanderbilt University Medical Center. Aeroallergen and food sensitization profiles obtained by skin prick testing (SPT), atopy patch testing (APT), and history of associated atopic diseases were analyzed.

Results: Older patients with EoE showed greater aeroallergen sensitization; the most common allergens were pollens and dust mite. Younger patients showed greater sensitization to foods by SPT and APT. The most common foods identified by SPT were peanut, egg, and soy. The most common foods identified by APT were potato, pork, and wheat. Comorbid atopic disease was common. Patients with atopic dermatitis did not show significantly greater sensitization to foods by SPT or APT compared with patients without atopic dermatitis.

Conclusion: In pediatric patients with EoE, sensitization to aeroallergens increases with age, whereas sensitization to foods decreases with age. Concomitant atopic disease is common. APT is useful to identify additional food allergens not detected by SPT. A history of atopic dermatitis does not appear to be associated with nonspecific positivity by SPT or APT.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic disease of the esophagus that is often confused with gastroesophageal reflux disease but is unresponsive to treatment with proton pump inhibitors (PPIs). According to the 2011 updated consensus recommendations, EoE is “characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation.”^{1,2}

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Diagnosis requires a minimum density of 15 eosinophils per 400× high-power field (HPF) in at least 1 biopsy specimen.¹ Endoscopic and histologic esophageal abnormalities have been associated with, but none are pathognomonic for, EoE.¹ Clinical presentation varies significantly with age; young children are more likely to present with nonspecific gastrointestinal complaints, such as feeding difficulties or vomiting, whereas specific symptoms of dysphagia and food impaction occur more commonly in adolescents and adults.^{3,4} Previous studies have shown a white male predominance, although disease does occur in females and in all races.² Personal and family histories of atopic disorders are common.¹ Most studies have indicated increasing incidence and prevalence of EoE, which do not appear to be due entirely to increased disease recognition.

Although the exact pathogenic mechanisms are unknown, a combination of immediate, IgE-mediated and delayed, and non-IgE-mediated immune reactions to foods and aeroallergens is thought to contribute to disease pathogenesis.⁵ Support for food as a definite

trigger for EoE has been shown with improvement clinically and histologically in patients after elimination diets.^{5–7} Optimal methods to assess for food allergen sensitization have been debated.^{8–11} In a retrospective analysis of 941 pediatric patients with EoE, Spergel et al⁶ found that the negative predictive value for the combination of skin prick testing (SPT) and atopy patch testing (APT) to identify causative foods averaged 92%, with the exception of milk at 44%. The positive predictive value was lower at 44%. Of those patients who followed a guided elimination diet based on results of combined testing plus the empiric elimination of milk, 77% had resolution of esophageal eosinophilia.⁶ Use of APT in EoE has been criticized for its lack of standardization and difficulty in interpretation of results, particularly in patients with atopic dermatitis (AD), in whom irritant reactions are more common.¹⁰

Rates of aeroallergen sensitization have been reported to be as high as food sensitization rates in some patients² and seasonality to the diagnosis of EoE has been documented, supporting a role for aeroallergens in disease pathogenesis.^{12–16} Retrospective studies have shown increased diagnosis in spring, summer, and autumn compared with winter months,^{14–16} and correlations have been made between diagnosis and levels of pollen.¹³ Geographic variation in disease frequency also has been reported, with the highest rates occurring in the cold and arid climate zones. It has been postulated that different geographic and climate patterns may aid in the identification of potential disease-triggering antigens.¹⁷

To the authors' knowledge, no published studies have analyzed the pediatric population with EoE from a single institution within the southeastern United States. This retrospective study aimed to characterize a group of pediatric patients evaluated for EoE at Vanderbilt University Medical Center (VUMC; Nashville, Tennessee) from January 1, 2009 through June 30, 2012. Information regarding demographic variables, presenting symptoms, personal and family histories of atopy, endoscopic and histologic findings, seasonality of diagnosis, and food and aeroallergen sensitization profiles was investigated. Potential differences between patients with and those without atopy were analyzed.

Methods

Study Design and Data Collection

A retrospective chart review was performed of all pediatric patients (0–20 years old) who were evaluated at the VUMC Pediatric Gastroenterology and/or Pediatric Allergy/Immunology Clinics for EoE from January 1, 2009 through June 30, 2012. Charts were identified through the electronic medical record database at VUMC using keywords *eosinophilic esophagitis*. Each chart was analyzed by a single physician to determine whether the patient met diagnostic criteria for EoE. Clinical data, including demographics (date of birth, race, sex), personal and family histories of atopic diseases (asthma, allergic rhinitis, AD, food allergy, EoE), presenting symptoms, date of diagnosis, gross endoscopic appearance of the esophagus, histologic features of esophageal biopsies, and results of allergy testing (SPT to aeroallergens and SPT and APT to foods), were collected and stored in a password-protected database. Data collection was approved by the VUMC institutional review board.

Diagnosis of EoE

The diagnosis of EoE was made in patients presenting with at least 1 of the following clinical symptoms of esophageal dysfunction: feeding difficulties, failure to thrive, weight loss, gastroesophageal reflux disease (including symptoms of heartburn, acid brash, and/or reflux), vomiting, abdominal pain, chest pain, dysphagia, or food impaction. Diagnosis was confirmed with esophagogastroduodenoscopy (EGD) by obtaining biopsy specimens from the esophagus, stomach, and duodenum. In some cases,

biopsy findings were reported only for proximal or distal portions of the esophagus, not both. Biopsies were reviewed under a 400× HPF by a board-certified pathologist. Patients met criteria for diagnosis if they had at least 15 eosinophils per HPF (peak value) in the esophagus after treatment with a PPI. In some cases, patients were not initially on PPI therapy at the time of biopsy but were included in the analysis if they subsequently met the histologic criteria at a later date while on PPI therapy. Patients who had initial biopsies performed at outside institutions often had esophageal eosinophil counts reported in ranges (eg, >50/HPF), and those numbers were withheld from the analysis of median eosinophil counts in the proximal and distal esophagus.

Skin Prick Testing

Skin prick testing was performed for food and environmental allergens using commercial extracts (Greer Laboratories, Lenoir, North Carolina; Hollister-Stier, Spokane, Washington) applied to the skin using a puncture technique with QUINTEST and QUINTIP devices (Hollister-Stier). Positive histamine and negative saline controls were used. Reactions were recorded after 15 minutes by measuring the largest diameter of the wheal and flare in millimeters. Testing was considered positive if the wheal measured 3 mm larger than the negative control.

Skin prick testing for food allergens was performed using a standard panel, including peanut mix, fish mix, shellfish, egg, corn, cow's milk, soybean, wheat, almond, cashew, pecan, walnut, chicken, turkey, pork, beef, lamb, barley, oat, rice, rye, navy bean, string bean, carrot, pea, white potato, apple, peach, and mustard. Additional extracts were tested if there was clinical suspicion of a different offending food.

Skin prick testing for inhalant allergens was performed using a standard panel, including cat, dog, dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cockroach, and mold mix and regional mixes of grass pollen, weed pollen, and tree pollen.

Atopy Patch Testing

Atopy patch testing was performed by mixing 1 mL of sterile water with 1 teaspoon of dry powdered foods for egg, soy, wheat, rice, corn, oat, barley, potato (Barry Farm Foods, Wapakoneta, Ohio), and peanut (Byrd Mill, Ashland, Virginia). Dry powdered milk (Barry Farm Foods) was reconstituted using fresh milk instead of sterile water. Single-ingredient commercially prepared pureed baby foods were used to test beef, chicken, ham, turkey, peas, green beans, carrot, peach, and apple. Reconstituted dry foods and undiluted baby foods were loaded into 8-mm Finn chambers on Scanpore tape (Actavis AS, Norway/Norgesplaster) and taped in place on the patient's back. Reconstituted dehydrated cow's milk was loaded into a 12-mm Finn chamber and was similarly placed. Patches were removed at 48 hours and read at 72 hours after initial application, similar to methods described by Spergel et al.⁹ Results were interpreted based on the classification proposed by Heine et al¹⁸ in 2006.

Of note, patients were instructed to discontinue use of systemic steroids or other immunosuppressants 1 month before testing and topical immunosuppressants at the application site 1 week before testing. APT was not performed on foods for which the patient exhibited positive reactions to SPT.

Statistical Analysis

Descriptive statistics were calculated as the median with interquartile range for continuous variables. For categorical variables, frequencies and percentages were presented. Wilcoxon rank-sum test and Pearson χ^2 test were used to compare differences between patients with AD and those without and between those with a history of atopy and those without. All tests were 2-tailed, with a

Table 1
Demographics and history of allergy (N = 211)

Age (y)	
Median	7.0
Interquartile range	2.0–11.0
Age (y), % (n)	
0–4	35 (73)
5–9	30 (64)
10–14	25 (53)
>15	10 (21)
Sex, % (n)	
Female	28 (59)
Male	72 (152)
Race, % (n)	
Caucasian	78 (164)
African American	11 (24)
Hispanic	1 (3)
Asian	0 (1)
Other	9 (19)
Personal history of atopy, % (n)	
Yes	86 (181)
No	14 (30)
Family history of atopy, % (n)	
Yes	66 (139)
No	18 (39)
Unknown	16 (33)

significance level of 5%. All statistical analyses were performed using open source R 3.0.2 statistical software (Vienna, Austria).

Results

Three hundred eleven pediatric patients with EoE evaluated at VUMC from January 1, 2009 through June 30, 2012 were identified. Among the 311 patients, 138 were on PPI therapy at initial EGD. Of the 173 who had not received PPI therapy at initial EGD, 73 underwent subsequent biopsy examination on treatment (topical steroids, dietary modification, or a combination of the 2) that included a PPI and met the diagnostic criteria for EoE. Sixty-three patients who had not received PPI therapy at initial EGD did not

undergo follow-up biopsy examination and were excluded from analysis. The remaining 37 patients who had not received PPIs initially underwent subsequent biopsy examination at treatment that included a PPI and no longer met the diagnostic criteria for EoE. These patients may represent a group with PPI-responsive esophageal eosinophilia but were excluded from analysis. The final study group included 211 patients, including the 138 who were on a PPI at initial diagnosis and the 73 who were not but who met the diagnostic criteria at treatment with a PPI at follow-up.

Demographics and Presenting Symptoms

The median age of patients was 7 years, with the largest number of patients 0 to 4 years old (Table 1). The youngest patient was 6 months and the oldest was 18 years. Most were boys (72%), with a male-to-female ratio of 2.6:1. Seventy-eight percent of patients were white compared with only 11% African American and 1% Asian races. Eighty-six percent of patients had a personal history of atopy; allergic rhinitis (67%) and asthma (42%) were the most common diagnoses. A family history of atopy was present in 66% of patients; however, only 7% reported a history of EoE or esophageal dilation in a family member.

The diverse range of clinical symptoms in this pediatric population with EoE is presented in Figure 1. The most common presenting symptoms overall were vomiting (54%), gastroesophageal reflux (53%), and abdominal pain (45%); however, presenting symptoms varied based on age of the patient. Failure to thrive and feeding difficulties were more common in children younger than 7 years, whereas weight loss and food impaction were more common in those older than 9 years. Many patients of all ages complained of multiple symptoms on initial presentation.

Initial EGD Findings and Seasonality of Diagnosis

Linear furrowing (48%) and white papules or plaques (25%) were the most common abnormal findings at initial EGD. However, nearly one third of patients had a normal-appearing esophagus despite evidence of significant esophageal eosinophilia at biopsy.

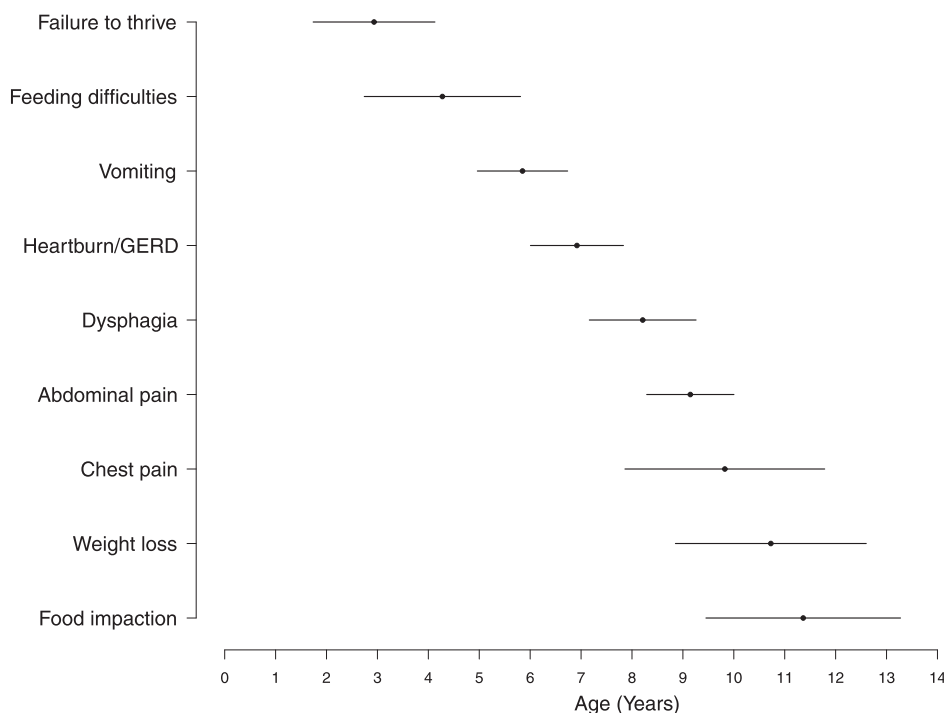


Figure 1. Age distribution of presenting symptoms of eosinophilic esophagitis. GERD, gastroesophageal reflux disease.

Table 2

Seasonal variation to the diagnosis of eosinophilic esophagitis in patients with atopy vs those without^a

Season	No atopy (n = 30)	Yes atopy (n = 181)	All patients (N = 211)
Winter	20% (6)	24% (44)	24% (50)
Spring	27% (8)	24% (44)	25% (52)
Summer	37% (11)	28% (50)	29% (61)
Fall	17% (5)	24% (43)	23% (48)

^aNumbers within parentheses are frequencies.

When stratified by age, esophageal rings and strictures occurred more frequently in children older than 9 years, whereas younger children were more likely to exhibit a grossly normal appearance. The most common histologic findings proximally and distally were increased intraepithelial eosinophils, basilar hyperplasia, and spongiosis. No patterns emerged when stratifying biopsy appearance by age. The median numbers of proximal and distal eosinophils were 54.5 and 56, respectively.

No seasonal pattern emerged when analyzing the entire group or when comparing those with a history of atopy with those without a history of atopic disease (Table 2).

Allergen Sensitization Profiles

Ninety-one percent of patients were evaluated by an allergist to assess for potential disease triggers. SPT to aeroallergens was performed in 162 patients, largely based on a clinical history suggestive of seasonal rhinitis symptoms. One hundred four patients (64%) had positive reactions, often to more than 1 extract. The most common aeroallergens identified were tree pollen (41%), grass pollen (39%), weed pollen (38%), and dust mite (36%; Fig 2). Sensitization to aeroallergens increased with age; only 53% of patients 0 to 4 years old were sensitized to an aeroallergen compared with 77% of patients at least 15 years old (Fig 3).

Skin prick testing to foods was performed in 192 patients, 120 (65%) of whom had a positive reaction to at least 1 food. The most

common foods identified across all age groups were peanut (31%), egg (30%), soy (25%), pea (19%), and almond (19%). However, food sensitization profiles differed when stratified by age. For instance, egg and cow's milk produced the most commonly positive reactions in the 0- to 4-year-old group, yet only 1 patient older than 14 years exhibited positivity to either of these foods. The most common food reactions overall by SPT and stratified by age are listed in order of decreasing frequency in Table 3. In contrast with aeroallergen sensitization, food sensitization decreased with age. Seventy-four percent of patients 0 to 4 years old exhibited positivity to foods by SPT compared with 50% of patients at least 15 years old (Fig 3).

Atopy patch testing to foods was performed in 62 patients, 48 (77%) of whom had at least 1 positive reaction. The most common foods identified by APT across all age groups were potato (26%), pork (26%), wheat (24%), peanut (21%), chicken (21%), turkey (21%), and pea (21%). Similar to findings at SPT, sensitization profiles to foods by APT differed when stratified by age. Milk and egg were uncommon allergens after 4 years of age. The most common foods overall by APT and stratified by age are listed in order of decreasing frequency in Table 4. Like food sensitization by SPT, sensitization to foods by APT also decreased with age. Eighty-six percent of patients 0 to 4 years old exhibited positivity to foods by APT compared with 40% of those at least 15 years old (Fig 3).

Among all 211 patients, 54 (25.6%) had comorbid AD. The number of positive reactions by each skin testing method did not differ significantly between those patients with AD and those without AD (Table 5).

Discussion

Examination of a database of pediatric patients with confirmed EoE from a single institution in the southeastern United States showed several similarities to other large-scale descriptive studies performed in other regions of the country, including disease predominance in white male patients and an association with personal and family histories of atopy.^{1,3,4,16,19} Significant variation in clinical

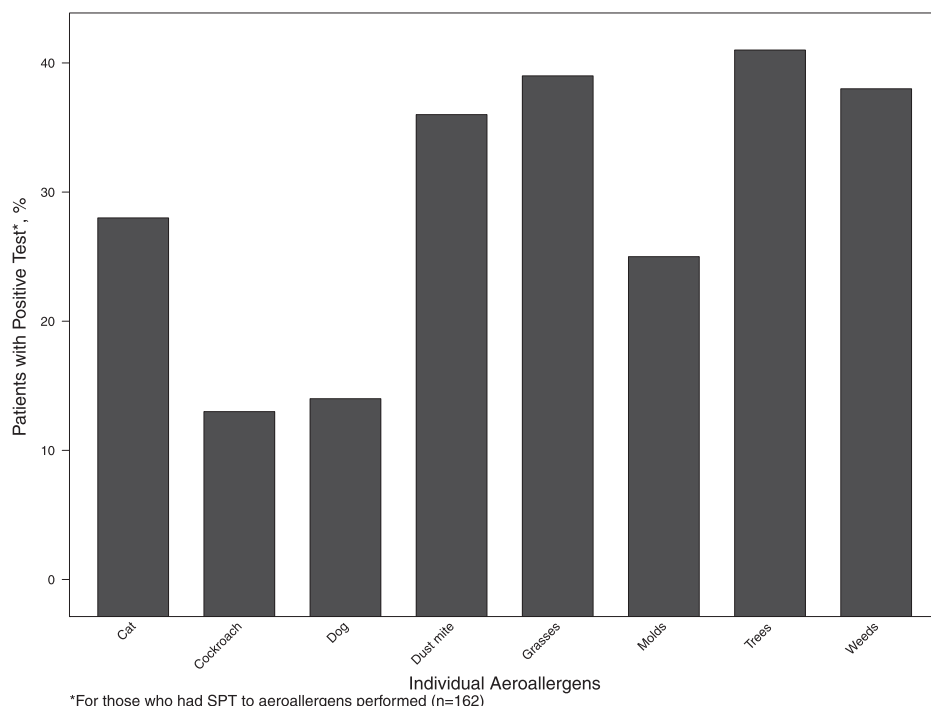


Figure 2. Percentage of patients with positive skin prick test reactions to specific aeroallergens when skin prick testing to aeroallergens was performed (n = 162). Patients may have more than 1 positive test reaction.

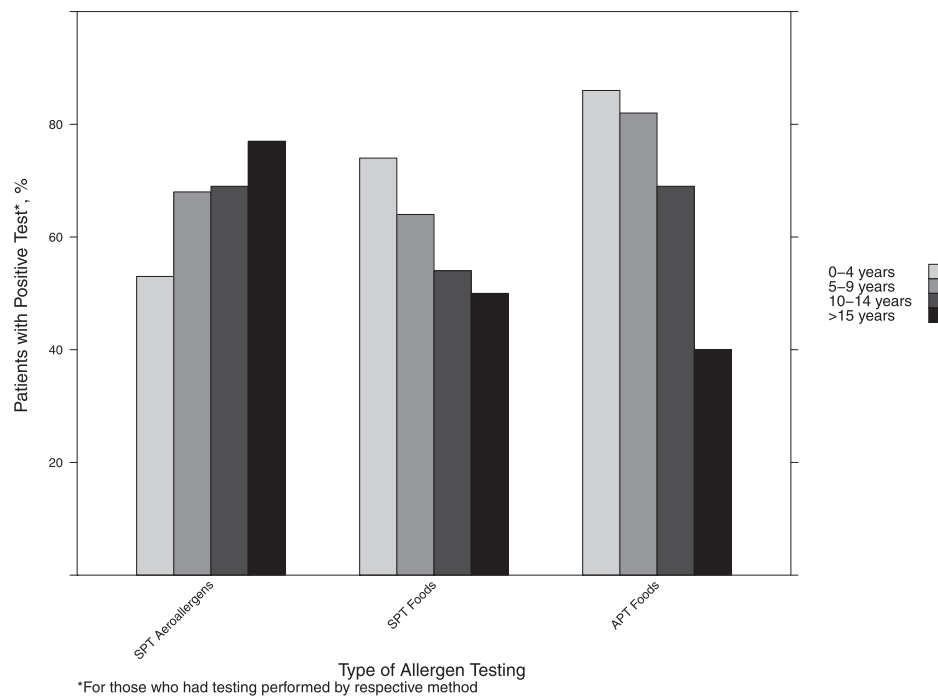


Figure 3. Percentage of patients with positive allergen test reactions, stratified by age and testing method, for those who had respective testing performed. Patients may have undergone more than 1 type of testing. APT, atopy patch testing; SPT, skin prick testing

presentation based on age highlights the importance of consideration of EoE in the differential diagnosis of nonspecific gastrointestinal complaints that are unresponsive to acid suppression therapy with PPIs.

Several endoscopic features and histologic findings are consistent with a diagnosis of EoE in the appropriate clinical setting; however, none are pathognomonic because they have been described in association with other disease processes. The most common gross abnormalities in the present study were linear furrowing and the presence of white papules or plaques on esophageal mucosa. Twenty-seven percent of patients had an endoscopically normal-appearing esophagus in the setting of histologic eosinophilic inflammation, highlighting the importance of obtaining multiple biopsies from all portions of the esophagus to increase diagnostic sensitivity.²⁰

Seasonal variations^{4,13–16,21} and increases in diagnosis paralleling elevations in pollen counts¹³ have been documented in previous studies, suggesting a possible role for aeroallergens in disease pathogenesis. Exposure to perennial allergens, such as *Aspergillus* species, dust mite, and cockroach, also has been shown to induce

esophageal eosinophilia in experimental murine models.^{22,23} Sixty-four percent of the present patients who underwent SPT to aeroallergens had a positive reaction to at least 1 allergen, the most common being tree pollen, followed by grass pollen, weed pollen, and dust mite. Unlike previous studies, the authors were unable to find an obvious seasonality to diagnosis, which may reflect high sensitization rates to aeroallergens prevalent in all seasons. These findings also may be more reflective of timing of endoscopy, because the procedure is often delayed for ease of scheduling for the patient or provider or based on need for urgency. If timing of endoscopy is based on symptom onset or worsening, a different seasonal pattern may emerge. When comparing patients with atopy with those without atopy, the nonatopic group trended toward more new diagnoses in the spring and summer (63%) than in the autumn and winter (37%). Sensitization to aeroallergens increased with age in the present population. Similarly, increasing aeroallergen sensitization has been correlated with increasing age in an Australian cohort of 45 pediatric patients with EoE.²⁴ These findings have important implications for treatment of this disease. Allergen avoidance measures and adequate treatment of allergic

Table 3
Most common food allergens by skin prick testing^a

0–4 y old (n = 70)	5–9 y old (n = 56)	10–14 y old (n = 46)	>15 y old (n = 14)	Overall (n = 186)
egg (47)	soybean (32)	peanut (28)	soybean (29)	peanut (31)
peanut (36)	peanut (29)	soybean (17)	almond (29)	egg (30)
milk (27)	egg (29)	almond (17)	pea (29)	soybean (25)
soybean (24)	corn (25)	shellfish (15)	peanut (21)	almond (19)
beef (24)	walnut (23)	corn (15)	corn (14)	pea (19)
pea (19)	pea (21)	pea (15)	cashew (14)	milk (18)
almond (17)	milk (20)	egg (11)	pecan (14)	corn (16)
chicken (17)	almond (20)	wheat (11)	navy bean (14)	beef (14)
pork (17)	shellfish (16)	walnut (9)	mustard (14)	walnut (13)
turkey (16)	navy bean (16)	oat (9)	shellfish (7)	shellfish (12)

^aNumbers within parentheses are percentages per age group. Patients may have more than 1 positive test reaction.

Table 4
Most common food allergens by atopy patch testing^a

0–4 y old (n = 22)	5–9 y old (n = 22)	10–14 y old (n = 13)	>15 y old (n = 5)	Overall (n = 62)
milk (32)	potato (41)	wheat (15)	turkey (40)	potato (26)
wheat (32)	pork (41)	oat (15)	soy (20)	pork (26)
barley (27)	peanut (36)	pork (15)	wheat (20)	wheat (24)
egg (23)	beef (32)	carrot (15)	oat (20)	peanut (21)
potato (23)	chicken (32)	milk (8)	barley (20)	chicken (21)
turkey (23)	turkey (27)	peanut (8)	potato (20)	turkey (21)
pea (23)	pea (27)	rice (8)	chicken (20)	pea (21)
peanut (18)	soy (23)	corn (8)	pork (20)	barley (19)
corn (18)	wheat (23)	potato (8)	pea (20)	beef (19)
beef (18)	barley (23)	beef (8)		milk (18)

^aNumbers within parentheses are percentages per age group. Patients may have more than 1 positive test reaction.

Table 5

Median number of positive test results per patient based on presence or absence of atopic dermatitis^a

Testing method (n)	With AD	Without AD	P values ^b
SPT aeroallergens (162)	2 (0–4)	2 (0–4)	.976
SPT foods (186)	2 (0–7)	1 (0–5)	.080
APT foods (62)	4 (2–5)	2 (0–4)	.120

Abbreviations: AD, atopic dermatitis; APT, atopy patch testing; SPT, skin prick testing.

^aNumbers represent median (lower quartile–upper quartile).

^bBy Wilcoxon rank-sum test.

rhinitis through the use of intranasal corticosteroids and oral antihistamines may complement other treatment modalities, such as dietary elimination and topical corticosteroids, for maximal control of upper airway and esophageal allergic inflammation. This may be more important for adolescents and those without overt sensitization to food antigens.

The role of food allergens as a trigger of EoE for many patients has been established; however, the optimal method of testing remains controversial. SPT is used to detect the presence of IgE-mediated hypersensitivity to foods and APT can be used to detect delayed, cell-mediated reactions to foods. Spergel et al.⁶ reported poor positive predictive values, ranging from 17% to 82%, for the combination of APT and SPT to identify causative foods. However, negative predicative values were much higher, averaging greater than 96% for all foods except milk (44%), egg (93%), and wheat (88%).⁶ Debate regarding the use of APT stems from the fact it is not a standardized procedure for foods and concern over whether it might produce irritant reactions in individuals with concomitant AD. The present group of patients showed a high sensitivity to foods by SPT (65% of those tested) and APT (77% of those tested). Sensitization to foods decreased with age by these 2 methods, similar to the results of the Australian cohort described by Sugnam et al.²⁴ Patients with AD did not show increased positivity by either method of testing compared with patients without AD. The risk of nonspecific positivity and irritant reactions does not appear to be increased in patients with AD who have APT performed on skin that is not flared.

Within the present group, the most common foods identified by SPT overall were peanut, egg, soy, pea, and almond. The most common foods identified by APT overall were potato, pork, and wheat. Food sensitization patterns varied for these 2 methods when stratified by age. Milk and egg rarely produced positive reactions after 9 years of age. This is in stark contrast to findings of previous studies showing milk and egg to produce the most frequently positive reactions by SPT and wheat by APT.^{3,8} Differences in findings may be secondary to geographic and cultural influences on eating patterns and food exposures. Given that roughly three fourths of patients had positive reactions by APT, this test may be a useful adjunct to SPT to help identify potential food triggers, because patients were only patch tested to those foods that showed negative reactions by SPT. Further studies in this population are needed to identify which foods are causative, requiring evidence of resolution of esophageal eosinophilia on elimination of the food and recurrence at reintroduction.

Limitations of the present study were largely related to its retrospective design. In some instances, it was difficult to decipher exact presenting symptoms and their duration before diagnosis. Knowledge of seasonal variation of symptoms and relating this to allergen sensitization profiles would have been helpful in determining whether a relation exists between aeroallergens and disease exacerbations; however, seasonal worsening of symptoms was documented in only 4 cases. Another potential limitation was that biopsy specimens were obtained and the diagnosis of EoE was

made by multiple gastroenterologists at the authors' center. Not all physicians obtained biopsy specimens from multiple levels of the esophagus, and some based EoE diagnosis solely on histopathologic evidence of eosinophilic inflammation without prior treatment with PPIs. Thirty-seven of 100 patients excluded from analysis responded to PPI therapy alone, indicating a false diagnosis rate higher than 30% in that group. This highlights the importance of adherence to current diagnostic guidelines before establishing a definitive diagnosis.¹ The authors attempted to minimize the risk of including patients with gastroesophageal reflux disease or PPI-responsive esophageal eosinophilia by including only patients who were treated with PPIs at initial biopsy or those who received PPIs alone or with another therapy at follow-up EGD and continued to meet criteria for diagnosis (≥ 15 eosinophils/HPF).

In conclusion, EoE can have a diverse presentation that varies with age and should be entertained as a diagnosis when patients present with gastrointestinal complaints that are unresponsive to treatment with PPIs. Concomitant atopic disease is common, as is a family history of atopy. In pediatric patients with EoE, sensitization to aeroallergens increases with age, whereas sensitization to foods decreases with age. APT is a useful adjunct to identify potential food triggers not detected by SPT. A history of AD does not appear to be associated with nonspecific positivity by SPT or APT.

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