

Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet

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Background: Eosinophilic esophagitis (EoE) is a chronic inflammatory disease with isolated eosinophils in the esophagus predominantly triggered by foods. The optimal testing to identify inciting foods remains unclear.

Objectives: We sought to determine the effectiveness of allergy testing-directed diets in patients with EoE.

Methods: A retrospective analysis of all children with EoE seen at the Children's Hospital of Philadelphia between 2000 and 2011 identified 941 patients with EoE. Skin prick tests (SPTs) and atopy patch tests (APT) were conducted, and predictive values were calculated. IgE-mediated food reactions were also identified. A food was considered to cause EoE if its elimination led to resolution of esophageal eosinophilia or reintroduction led to reoccurrence of EoE. The effectiveness of the various elimination diets was compared with targeted food antigen elimination.

Results: Definitive foods causing EoE were identified, with milk, egg, wheat, and soy as the most common foods in 319 patients. IgE-mediated reactions (urticaria and anaphylaxis) were seen in 15%. The negative predictive value for the combination of SPTs and APTs averaged 92%, with the exception of milk at 44%, and the positive predictive value averaged 44%. An empiric 6-food elimination diet or removal of positive foods on allergy testing (SPTs/APTs) both had a histologic success rate of 53%.

Removal of foods identified on SPTs/APTs plus empiric elimination of milk leads to resolution in 77% of patients.

Conclusion: An elimination diet based on SPT/APT results leads to resolution of esophageal eosinophilia in a similar proportion of patients as empiric removal of foods but required that fewer foods be removed. These observations suggest that both methods are acceptable options. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Eosinophilic esophagitis, food allergy, atopy patch testing, skin prick testing

Eosinophilic esophagitis (EoE) is characterized by an isolated infiltration of the esophagus with eosinophils without infiltration in other parts of the gastrointestinal tract. The symptoms of EoE are similar to those of gastrointestinal reflux disease and include vomiting, abdominal pain, regurgitation, and dysphagia. The number of esophageal eosinophils per high-power field (hpf) is required as part of the clinicopathologic diagnosis, which is defined as 15 or more eosinophils per hpf in a patient receiving a proton pump inhibitor.¹

Patients with EoE often have a history of atopy, such as increased serum IgE levels, peripheral eosinophilia, allergic diseases (including asthma, atopic dermatitis, or allergic rhinitis), and sensitization to foods and aeroallergens, as demonstrated by a positive skin test result.²⁻⁴ In addition, a high rate of IgE-mediated food allergies was reported in patients with EoE.⁵ We and others have reported improvement in symptoms and biopsy results after a trial of food avoidance, indicating that food allergy plays a key role in the pathogenesis of EoE.⁶⁻⁹ Although it is now accepted that foods are major antigenic triggers for EoE in children, the optimal method for identifying foods is unclear. Unfortunately, dietary restriction based on skin prick tests (SPTs) alone might only benefit a very select group of patients. Recently, Erwin et al¹⁰ described the rates of serum specific IgE to identify foods in children with EoE. We previously explored the use of SPTs combined with APTs to identify causative foods, with an approximately 70% success rate.¹¹ Similar success rates have been reported by using an empiric elimination diet (6-food elimination diet [SFED]) that excludes milk, egg, wheat, soy, peanut/tree nuts, and seafood (fish/shellfish).⁸ An inherent difficulty to dietary management of EoE is that despite the effectiveness of both methods, there is currently no standard approach to food antigen restriction in this disease. To date, there have been no studies that have directly compared the effectiveness of various diets in improving esophageal eosinophilia in patients with EoE.

In the current study we performed a retrospective review of foods triggering EoE and present negative predictive values (NPVs) and positive predictive values (PPVs) of SPTs and APTs, identifying definitive foods in our cohort of patients. We also compare the effectiveness of targeted food antigen restriction

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Abbreviations used

APT: Atopy patch test
 EoE: Eosinophilic esophagitis
 hpf: High-power field
 NLR: Negative likelihood ratio
 NPV: Negative predictive value
 PLR: Positive likelihood ratio
 PPV: Positive predictive value
 SFED: Six-food elimination diet
 SPT: Skin prick test
 TSLP: Thymic stromal lymphopoietin

based on SPTs/APTs to several other dietary approaches used at our institution, including the SFED.

METHODS**Center for Pediatric Eosinophilic Disorders database**

The study was approved by the Children's Hospital of Philadelphia's Institutional Review Board. All patients seen in the Center for Pediatric Eosinophilic Disorders and any patient seen with eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis were entered into the database. Data were entered in a prospective manner, and the data analysis was performed retrospectively.

Definition of EoE

Patients were given a diagnosis of EoE per the most recent 2011 consensus document.¹ The maximal eosinophil count in the most severely affected esophageal biopsy specimen was used to determine response to therapy. Patients were receiving a stable dose of inhaled steroids for their asthma and intranasal steroids for their allergic rhinitis as needed (see the **Methods** section in this article's Online Repository at www.jacionline.org for additional details).

Definition of IgE-mediated food allergies

The diagnosis of food allergy was confirmed based on the criteria of Thompson and Hanifin.¹² IgE-definitive foods (>20 points; see the **Methods** section in this article's Online Repository) were also confirmed based on positive skin test results or specific IgE levels meeting 95% PPVs, as previously published by Sampson and Ho.¹³

Allergy testing

SPTs and atopy patch tests (APTs) were performed as previously described (see the **Methods** section in this article's Online Repository for more detail).¹¹ Briefly, all patients underwent SPTs to foods based on their clinical history in addition to a standard panel of meats (beef, chicken, turkey, and pork), grains (rice, wheat, barley, corn, and oat), vegetables (string beans, peas, carrots, and potato), fruits (apples and peaches), milk, soy, peanut, and egg. If patients were not ingesting the foods in the diet, they were not tested to those foods. APTs were then conducted for the same foods unless the patient had a positive wheal-and-flare reaction (>3-mm wheal) on an SPT.

Identification of foods causing EoE

Definitive foods causing EoE were determined based on the addition of 1 food causing an esophageal biopsy specimen to change from normal (0 eosinophils/hpf) to greater than 15 eosinophils/hpf or removal of 1 food leading to normalization of the esophageal biopsy specimen. Symptomatic foods were defined based on parental identification of foods causing significant symptoms that did not allow the subject to continue to ingest the food as part of his or her diet. Examples include the following.

First, if a patient removed milk, egg, and wheat from their diet and results of a repeat endoscopy and biopsy were normal, food reintroduction was started. After milk was reintroduced, if symptoms returned and biopsy specimens were abnormal (>15 eosinophils/hpf), then milk was identified as a causative food. Second, if egg was added without symptoms and a normal endoscopy and biopsy occurred, then egg was considered a tolerated food. Third, if wheat was added and significant symptoms developed (vomiting), leading to removal of that food before an endoscopy/biopsy could be performed, then wheat was considered a symptomatic food. IgE-mediated symptoms (urticaria and anaphylaxis) were classified as IgE-mediated foods as above.

Diet analysis

All patients were started on a restricted diet based on allergy testing directing the diet. After esophageal biopsy specimens normalized, attempts to add back foods were analyzed. Definitive foods were identified based on the results of the esophageal biopsies. After completion of food reintroduction, except for foods causing EoE or IgE-mediated food allergies, we designated this population as the "EoE definitive food population." These definitive foods were compared with various diet options in a retrospective fashion. The options (based on analysis of the most common foods causing EoE) were as follows: (1) no milk; (2) no milk, egg, and wheat; (3) SFED⁸; (4) removal of foods based on positive APT/SPT results; (5) removal of foods eliciting positive SPT/APT results and milk removal; (6) no milk, egg, soy, wheat, or meats (chicken, turkey, beef, or pork); or (7) a vegan diet (no milk, egg, chicken, beef, turkey, or pork). The patients were not started on these diets directly, but their final diet was compared with these 7 options.

Predictive values

NPVs and PPVs along with specificity, sensitivity, positive likelihood ratios (PLRs), and negative likelihood ratios (NLRs) were calculated in the EoE definitive food population.

RESULTS**Demographics**

One thousand one hundred eighty-seven patients were included in the Center for Pediatric Eosinophilic Disorders database at the Children's Hospital of Philadelphia. All patients with eosinophilic gastrointestinal disease were included, as were patients referred for second opinions with esophageal eosinophilia. Forty-eight patients with eosinophilic gastroenteritis, 7 patients with eosinophilic colitis, and 191 patients with proton pump inhibitor-responsive EoE were excluded (Fig 1). Among the 941 patients with confirmed EoE, the male/female ratio was 2.8:1 (n = 695/247), which is similar to that seen in previous studies.^{2,4,9} The population was also 80% self-reported white, which is similar to our previous results.¹⁴ The average age was 6.4 years at the time of testing, with a range of 1 to 18 years. The patients with EoE had high rates of concurrent atopic diatheses: 64% had allergic rhinitis, 50% had asthma, and 24% had atopic dermatitis. Eighteen percent of the patients had no atopic disorders. The distribution of the endoscopies showed results of 48% were positive and results of 52% were negative based on an eosinophil count of greater than 15 eosinophils/hpf.

Regarding the identification of foods, we excluded patients who were being treated with either swallowed corticosteroids (130 subjects) or anti-IL-5 (18 patients). Of the 793 remaining patients, we were able to identify causative foods in 319 patients based on changes in the biopsy findings and classified them as the "definitive EoE food population." The remaining 60% had histologic resolution of eosinophilia when multiple or all foods were eliminated. Individual foods were not added back into the

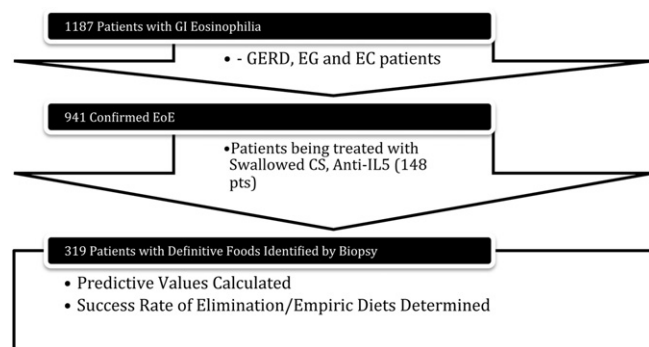


FIG 1. Patients with EoE identified in the study. Patients with gastroesophageal reflux disease (*GERD*), eosinophilic gastroenteritis (*EG*), or eosinophilic colitis (*EC*) or being treated with swallowed corticosteroids (*CS*) or anti-IL-5 were excluded. The patients with foods identified based on addition or removal of a single food were defined as the definitive food cohort.

diet to allow for identification of the individual causative foods. For example, if a patient eliminated 2 foods and was asymptomatic and content with his or her diet, we were unable to determine which food or foods led to disease, and therefore these patients could not be included in the definitive EoE food population.

Foods causing EoE based on symptoms and biopsy results

A strict elemental diet was used in less than 5% of patients, with improvement in biopsy results in upward of 98%. One hundred sixty-five (17.5%) patients from the original 941 cohorts received at least 50% of their calories from elemental formulas (along with limited foods) for the diet treatment. The population was younger (2.8 years) than the general EoE population (6.4 years), possibly because of compliance issues with the elemental diet in older patients. Many of these patients (13% of the entire EoE cohort) reacted to some fruits and vegetables, and dietary advancement was difficult.

Milk was the most common food identified in the entire EoE cohort, followed by wheat, soy, and eggs (Table I). These data are very similar to those of Kagalwalla et al⁷ found in their food re-introduction from an SFED diet.¹⁵ In examining the final foods, the most common were milk, egg, and wheat, followed by beef, soy, and chicken (Table I). The foods that caused EoE symptoms (primarily vomiting and abdominal pain) were milk, egg, soy, and wheat. In those patients who had a poor response to food reintroduction, the average eosinophil count was 49 ± 2.6 eosinophils/hpf.

IgE-mediated food allergies

IgE-mediated food allergies have been reported more commonly in EoE cohorts (up to 20% compared with 6% in the general population).^{3,16} We found that 14.8% of the population had confirmed IgE-mediated food allergies. Allergies to peanut, egg, and milk were the most commonly identified (Table I). All patients with IgE-mediated food allergy had an apparent history of reaction. The age at presentation of IgE-mediated food allergy was 2.4 ± 1.3 years, which was younger than the age at presentation of EoE.

Food combinations in patients with EoE

Of the 319 patients, 38% reacted to 1 food, 19% reacted to 2 foods, 14% reacted to 3 foods, and 28% reacted to 4 or more foods (Fig 2). There was no significant difference based on sex. The patients reacting to 1 or 2 foods were significantly older (6.8 ± 0.45 years) at the age of diagnosis compared with the patients with 3 or more food allergies (4.6 ± 0.45 , $P < .0005$). The 2 most common food combinations were as follows: (1) milk and 1 or more meats or (2) milk, soy, egg, and wheat (Table II). The combination of milk plus another food was seen in more than two thirds of the patients.

Predictive values for allergy testing

In the EoE definitive food population, we calculated NPVs, PPVs, PLRs, NLRs, sensitivities, and specificities for SPTs (see Table E1 in this article's Online Repository at www.jacionline.org), APTs (see Table E2 in this article's Online Repository at www.jacionline.org), and the combination of the 2 testing methods (Table III and see Table E3 in this article's Online Repository at www.jacionline.org). It is important to note that our testing was done in sequence: SPTs followed by APTs. If a patient had a positive SPT response to a food, APTs were not performed to that food. Sufficient data were lacking to calculate predictive values for serum food-specific IgE. For SPTs, the NPVs were greater than 90% for all foods except milk (30%), egg (90%), wheat (79%), and soy (86%). The PPVs ranged from 26% to 96%, with an average of 47% (see Table E1). The use of APTs after SPTs had a similar NPV, which ranged from 31% for milk to 99% for peanut (with an average of 90%). The PPVs of APTs ranged from 12% to 86%, with an average of 44% (see Table E2). For the combination of SPTs and APTs, the NPVs in general were greater than 96% for all foods except milk (44%), egg (93%), and wheat (88%, Table III). For the combination of SPTs and APTs, the PPVs were poor, ranging from 17% for pork to 82% for milk. Overall, the NPVs averaged 92% and the PPVs averaged 44%, results that were similar to those of SPTs for IgE-mediated reactions for the majority of foods except milk (for which we found a very high false-negative rate). The sensitivity and specificity improved with the combination of APTs and SPTs compared with those for only 1 test (see Tables E1 and E2 and Table III). We also calculated likelihood ratios (PLRs and NLRs). The SPT/APT combination is very good, with PLRs of greater than 4 and NLRs of less than 0.4 for many individual foods.

Dietary treatment options

In our initial 26-patient cohort, we reported a 74% response rate to food removal based on SPT and APT results.¹¹ Kagalwalla et al⁷ reported a similar response to empiric removal of milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish (the top 8 foods), which is called the SFED. We compared various diet options in our definitive EoE food population. After the definitive foods were identified, we compared success rates for various treatment options based on these final foods (Fig 3). First, we compared the removal of foods based on positive SPT and APT results with the SFED. The response rate was identical at 53% for both methods; however, the number of foods removed were different in both groups. The patients in the allergy testing group had less than 6 foods removed, an average of 3.2 ± 0.13 foods identified on

TABLE I. EoE and IgE-mediated foods identified in patients with EoE

	EoE foods by biopsy (n = 602)	EoE foods by symptoms (n = 726)	IgE-mediated foods (n = 269)	Combined (n = 1597)
Milk	211 (35%)	139 (19%)	27 (10%)	377 (24%)
Egg	78 (13%)	81 (11%)	47 (17%)	206 (13%)
Wheat	72 (12%)	65 (9%)	2 (<1%)	139 (9%)
Soy	52 (9%)	75 (10%)	10 (4%)	137 (9%)
Peanut	16 (3%)	37 (5%)	58 (22%)	111 (7%)
Beef	33 (5%)	59 (8%)	1 (<1%)	93 (6%)
Corn	39 (6%)	51 (7%)	0 (<1%)	90 (6%)
Chicken	32 (5%)	52 (7%)	2 (<1%)	86 (5%)
Potato	21 (3%)	34 (5%)	0 (<1%)	55 (4%)
Pork	19 (3%)	29 (4%)	0 (<1%)	48 (3%)
Rice	14 (2%)	29 (4%)	0 (<1%)	43 (3%)
Other	15 (2%)	75 (10%)	122 (45%)	212 (13%)

Foods were identified based on symptoms, changes in esophageal biopsy specimens, or IgE-mediated reactions. EoE biopsy foods were identified based on changes from normal (0 eosinophils/hpf) to abnormal (>15 eosinophils/hpf) values or vice versa. The average eosinophil count on reintroduction was 49 eosinophils/hpf. EoE food symptoms were based on foods causing symptoms per parental report that did not continue in the diet. IgE-mediated foods were foods that caused urticaria or anaphylaxis on food exposure. Percentages represent the percentage of each food per total number of foods per column.

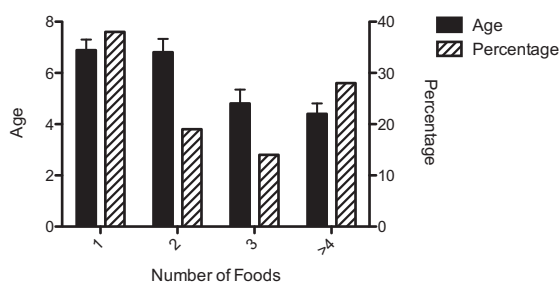


FIG 2. Percentage of patients with EoE with 1, 2, 3, or 4 or more food allergies in the definitive food cohort. Food or foods were identified based on changes in esophageal biopsy specimens from normal to abnormal (>15 eosinophils/hpf) after addition of a single food or normalization of esophageal biopsies (0 eosinophils/hpf) after removal of a single food. Age of diagnosis was expressed as mean ± SEM values.

SPTs and 2.7 ± 0.10 foods identified on APTs, compared with the 8 food groups in the SFED. We examined only removing those with a 30% response rate. We also examined the removal of the 3 most common foods (milk, egg, and wheat), which led to a 47% response rate. We also examined milk elimination plus removal of foods found on allergy testing (SPTs/APTs), which revealed a response rate of 77%. We examined the removal of the most common food groups (milk, egg, soy, wheat, and meats [chicken, turkey, beef, and pork]), for a total of 8 foods that had a similar response rate to allergy testing plus milk removal at 77%. Finally, we examined a diet devised to be more adherent in our adolescent population (the vegan diet: no milk, egg, fish, shellfish, or meats; 5 food groups), which had a similar response rate to removal of milk, egg, and wheat at 48%.

DISCUSSION

We were able to identify definitive foods in 319 patients from the entire 793-patient cohort. The remaining population was divided into 2 groups: 151 patients on elemental diets because of their age or having symptoms/biopsy changes when introducing simple fruits and vegetables. In these patients an elemental diet led to resolution in greater than 95% of the patients (similar to previous published studies).¹⁵ For the second group of 245 patients, dietary restrictions were successful, with resolution of

TABLE II. Most common food combinations in patients with EoE

Food	No. of subjects
Milk	78
Milk, meats*	24
Milk, egg, wheat, soy	20
Milk, soy	15
Grains*	13
Milk, egg, wheat, meats	11
Egg, wheat	10
Milk, egg	8
Milk, egg, wheat	8
Egg	8
Soy	7
Wheat	5

Food combinations were identified based on biopsy results. Each food is identified by a change in esophageal biopsy results from normal (0 eosinophils/hpf) to greater than 15 eosinophils/hpf when 1 food was added. Milk was seen in 7, egg in 13, wheat in 11, and soy in 10 other food combinations, respectively.

*Grains, Rice, oat, or wheat; meats, beef, chicken, turkey, or pork.

symptoms and normalization of histology. However, we were unable to identify the causative foods because either the families were uninterested in adding back foods or more than 1 food was added back at the same time. The difference in these populations suggests at least 2 types of patients with EoE, with 1 group allergic to select major allergens and a second smaller group (approximately 20%) allergic to a more diverse group of foods. Interestingly, in the patients with more diverse food sensitivity, many patients had symptoms to fresh fruits and vegetables, suggesting an oral allergy variety of EoE.

Within the definitive EoE population, approximately 70% of patients were allergic to only 1 to 3 foods (Fig 2). The patients with fewer food allergies presented at significantly older age compared with a subset with a more severe phenotype who presented at a younger age and with more food allergies. These findings suggested multiple phenotypes of EoE because patients with a more severe phenotype present at a younger age. The number of food allergies was similar to observation by Kagalwalla et al⁷ in their cohort of patients responding the SFED, with 72% of their population only responding to one food. Similar to Kagalwalla et al, milk, egg, wheat, and soy were the most common foods identified by means of endoscopy and based on symptoms (Table I). The

TABLE III. Predictive values of APTs and SPTs in patients with EoE

Food	No.	Combination of SPTs and APTs					
		NPV	PPV	Sensitivity	Specificity	NLR	PLR
Milk	211	44.4%	81.5%	50.2%	77.8%	0.64	2.26
Egg	78	93.0%	60.6%	80.8%	83.0%	0.23	4.75
Wheat	72	87.9%	42.0%	65.3%	73.7%	0.47	2.48
Soy	52	92.8%	33.3%	71.2%	72.3%	0.40	2.57
Peanut	16	99.6%	22.4%	93.8%	82.8%	0.08	5.46
Beef	33	96.3%	31.2%	72.7%	81.5%	0.33	3.92
Corn	39	99.1%	42.0%	94.9%	81.8%	0.06	5.21
Chicken	32	98.3%	32.9%	87.5%	80.1%	0.16	4.41
Potato	21	98.5%	36.2%	81.0%	89.9%	0.21	8.04
Pork	19	96.9%	17.2%	57.9%	82.3%	0.51	3.28

Predictive values of allergy testing when used in combination of SPTs and APTs are shown.

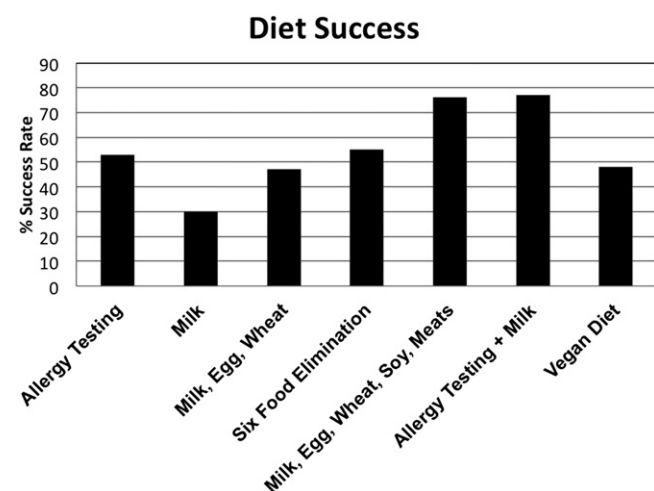


FIG 3. Success rate of various diet therapies in patients with EoE. Retrospective examination of various diets in the EoE definitive food cohort patients (319 patients). Diet successes were defined as identification of all of the causative foods in patients with EoE that led to normalization of esophageal biopsy specimens.

other major foods fell into 2 general classes: grains and meats. Individual patients can be allergic to any or all meats, but most patients were allergic to a single type (beef or chicken). We have found that patients react to all or some of the grains. However, wheat was found most commonly (similar to recent results of Gonsalves et al¹⁷) and oat less so. For those avoiding wheat, many removed all gluten.

Milk was the most common food in isolation or with combination with other foods, which is similar to the findings of Kagalwalla et al⁷ and Gonsalves et al¹⁷ (Table II). Milk and soy were another common combination also observed in infants with food protein–induced enterocolitis.¹⁸ This suggested, particularly in the younger EoE population, that foods that are commonly ingested are triggers for EoE. Conversely, in this study we found that tree nuts, peanuts, and seafood were uncommon EoE triggers, despite the prevalence of these foods in the American diet.

However, peanut IgE–mediated allergy was very common in our cohort (9% compared with 1.4% in the general population).¹⁹ IgE–mediated food allergies affected almost 15% of our EoE cohort compared with 2% to 6% observed in the general population.¹⁸ In addition, the majority of our patients (75%) were atopic.

Nearly two thirds of the patients had allergic rhinitis, and 50% had asthma. The fact that the EoE population was highly atopic suggested a general upregulation of genes controlling atopy. Recent work from our institution identified polymorphism in thymic stromal lymphopoietin (TSLP)²⁰ and upregulation of TSLP-dependent basophils in patients with EoE.²¹ Therefore it is possible to speculate that variation in TSLP leads to upregulation of T_H2 cytokines and atopy, causing not only EoE in these patients but also a general increase in their atopic status.

We next examined the predictive nature of allergy testing for foods in patients with EoE. We examined the standard SPTs performed with a bifurcated needle and APTs that we have been using for the last 8 years. NPVs and PPVs were determined based on foods that caused definite changes in esophageal biopsy specimens. The definitive foods were single items that led to an increase in eosinophil numbers from normal baseline to greater than 15 eosinophils/hpf or normalization of esophageal biopsy specimens (0 eosinophils/hpf) with removal of a single food. Skin testing in general had a good NPV for the uncommon foods but was found to be less useful for the more common foods, such as milk, egg, soy, and wheat. There was a particularly high false-negative rate (34%) with milk (see Table E1). The PPVs in general were low (20% to 40%), except for milk (86%) and egg (62%), which were substantially higher. In general, SPT predictive values were worse in patients with EoE than in those with IgE–mediated food allergies.²² APTs were used in conjunction with SPTs in a sequential manner, and therefore if a patient had a positive result to a food on a SPT, patch tests to those foods were not performed. APTs were similar to SPTs, with a high NPV (>95%) for all foods except for milk, egg, wheat, and soy. The PPVs were low only for peanut, potato, and pork at 0% to 30%, with higher values for corn, beef, chicken, soy, wheat, egg, and milk, ranging from 30% to 90% (see Table E2). This finding indicated that additional testing with APTs had some value. We also calculated likelihood ratios. In general, a ratio of greater than 1 was associated with disease, and a ratio of less than 1 was not associated with disease. The ideal test has a PLR of greater than 5 and an NLR of less than 0.2. In patients with EoE, the combination of these APTs and SPTs reached that value for individual foods, and overall, the PLR was 4.78 and the NLR was 0.25. These predictive values were based solely on the EoE population because they would differ in the general population, with the values needing to be corrected for the prevalence of EoE in the general population at 1:1500 (see Table E4 in this article's Online Repository at www.jacionline.org).

In our clinical practice we performed a combination of SPTs and APTs; therefore we examined the predictive values when both tests were used. PPVs were based on a positive result of either an SPT or APT, and NPVs were based on negative results on both tests. The PPVs remained low for all foods (20% to 40%), with the exception of milk and egg. NPVs continued to improve with greater than 96% for all foods except milk, egg, wheat, and soy. The combination of testing brought the NPV to greater than 88% for wheat, egg, and soy. However, milk NPVs remained low at 44%.

Because of the poor predictive values and labor-intensive nature of allergy testing and previous results indicating a high success rate with empiric diet plans in treating EoE, we examined various dietary options (Fig 3). We first compared an SFED diet with removal of foods based on SPTs/APTs to the food. Previous literature suggested both had a response rate of 74%.^{8,11} In the current cohort the success rate was still identical but at a lower rate. We found a success rate of 53%, which was closer to the rate seen by Gonsalves et al.¹⁷ The difference was probably due to the 15% of patients who needed elemental formula and were not included in the previous analysis or in the study by Kagalwalla et al.⁷ The allergy testing–directed diet removed approximately 6 foods, whereas the SFED diet removed more foods because it removed milk, egg, soy, wheat, peanut, all tree nuts, all fish, and all shellfish.

Because milk, egg, and wheat were the most common foods identified in our and other studies,^{2,7,17} we examined elimination of milk only, leading to a 30% response rate. Removal of milk, egg, and wheat increased the success rate to 47%, nearing the 53% rate observed with allergy testing and the SFED. Because milk was the most common food allergy in patients with EoE and because of its high false NPV, we combined an empiric and allergy testing method by removing milk and positive foods on SPTs and APTs. This combination method increased the success rate to 77%. We also compared this with empiric elimination of the top 8 allergens (milk, soy, egg, wheat, and meats [chicken, turkey, pork, and beef]). Removal of these top 8 allergens has an identical success rate of 77%, but it removed more foods than allergy testing plus milk (7 foods) compared with the 8 foods with the empiric elimination diet.

Because of the high incidence of milk, egg, and meats as a common foods causing EoE, we examined the use of a vegan diet in treating patients with EoE. We proposed that this diet might be easier and more socially acceptable. We found a similar success rate of 48% for removal of milk, egg, and wheat in patients with EoE.

Of the original 793 patients, 319 were included for evaluation. It remains possible that the larger cohort would have yielded different results. However, a separate and smaller cohort from Cincinnati that was published concurrently showed similar findings.²³ On the basis of demographics and allergy testing, there was no significant difference between the patients who finished adding all foods into their diet and those patients who were content with having foods remain out of the diet without additional diagnostic testing.

Our results indicated that food allergies could be identified in patients with EoE. Patients had a higher incidence of IgE-mediated food allergies because many common foods (milk, soy, egg, and wheat) triggered their EoE. There was also a subpopulation of about 15% who had multiple food allergies that required an elemental formula. For the identification of food, an empiric diet or allergy testing–based methods have had equal success in pediatric patients with EoE. The one potential

advantage for allergy testing was that fewer foods were removed. This must be weighed against the time and effort for testing and preparation. The predictive values indicate the need for better testing, especially for milk-induced EoE.

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Clinical implications: An empiric elimination diet is equivalent to the use of allergy testing–directed diets for the treatment of EoE.

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METHODS

Diagnosis of EoE

All patients with confirmed EoE had isolated eosinophils (≥ 15 eosinophils/hpf) in the esophagus after other diseases were ruled out. All patients with confirmed EoE were treated with at least 8 weeks of a high-dose proton pump inhibitor before the defining upper endoscopy and biopsies were performed. All patients had a minimum of 4 biopsies in the esophagus and separate biopsies in the stomach and duodenum. The numbers of eosinophils per hpf were abstracted from the surgical pathology reports by Michele Shuker and reviewed and confirmed by Jonathan M. Spergel. As per the current consensus document, we recorded the maximal number of eosinophils per hpf. For means and distribution of eosinophils per hpf, we count greater than 100 eosinophils/hpf as 100 eosinophils/hpf.

Diagnosis of IgE-mediated food allergies

The clinical symptoms were assigned to a points system, and the sum of these was used to assign definite (>20 points), probable (15–20 points), or possible (5–15 points) food allergy. Major criteria (15 points each) were the presence of lip or face swelling, urticaria, nausea, vomiting, wheezing, or respiratory distress after food ingestion. Minor criteria (5 points each) were repeated reaction on exposure to the same food and a reaction happening within 30 minutes of ingesting the food.

Allergy testing

Briefly, SPTs done with commercial extracts (Greer Laboratories, Lenoir, NC) were performed on the forearm with a bifurcated needle (Allergy Labs of Ohio, Columbus, Ohio) by pricking through a drop of the extract, which was then absorbed. Reactions were recorded by measuring the largest diameter of the wheal-and-flare response in millimeters at 15 minutes. The test result was considered positive if the wheal was 3 mm larger than that elicited by the negative control.

APT were conducted by using 2 g of dry foods in 2 mL of isotonic saline solution for soy infant formula, dried egg white, wheat, oat, barley, rye, rice flour, corn meal, and dehydrated potatoes. Three grams of powdered milk was

mixed with 1 mL of isotonic saline solution for the milk patch testing. The mixtures were placed in aluminum cups (6- or 12-mm Finn chambers on Scanpore; Allerderm Laboratories, Petaluma, Calif) and adhered to the patient's back based on the methods of Isolauri et al.^{E1-E6} The size of the Finn chambers was determined in an age- and size-dependent manner. Single-ingredient, commercially prepared baby food, including fruits, vegetables, and meats, was placed in Finn chambers undiluted. The patches were removed at 48 hours, and results were read at 72 hours. Reactions considered positive were classified as 1+ for erythema and scattered papules, 2+ for erythema and papules, and 3+ for erythema and vesicles, as per standard patch test protocols.

Avoidance of foods and treatment regimens

All patients with IgE-mediated food allergies were required to avoid all foods that caused IgE-mediated reactions, and autoinjectable epinephrine was prescribed. For EoE reactions, patients avoid food or foods in all sources for a minimum of 2 months before the repeat diagnostic endoscopy and biopsy.

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TABLE E1. Predictive values for SPTs in patients with EoE

Food	Skin test				NLR	PLR
	NPV	PPV	Sensitivity	Specificity		
Milk	29.3%	86.3%	26.6%	87.8%	0.84	2.18
Egg	89.5%	62.2%	70.0%	85.8%	0.35	4.92
Wheat	78.5%	29.5%	18.1%	87.4%	0.94	1.44
Soy	86.3%	32.9%	40.4%	82.1%	0.73	2.25
Peanut	99.3%	30.0%	88.2%	88.4%	0.13	7.61
Beef	93.2%	42.1%	45.7%	92.3%	0.59	5.90
Corn	91.2%	31.4%	30.6%	91.5%	0.76	3.60
Chicken	94.4%	38.8%	55.9%	89.5%	0.49	5.31
Potato	96.4%	47.1%	42.1%	97.0%	0.60	14.04
Pork	96.0%	26.3%	29.4%	95.4%	0.74	6.34

PPVs and NPVs along with PLRs and NLRs with specificity and sensitivity were determined in a patient population, with definitive foods determined based on esophageal biopsy changes only.

TABLE E2. Predictive values for APTs in patients with EoE

Food	APT					
	NPV	PPV	Sensitivity	Specificity	NLR	PLR
Milk	31.4%	86.2%	29.9%	87.0%	0.81	2.30
Egg	90.6%	51.3%	48.8%	91.4%	0.56	5.70
Wheat	86.5%	48.2%	57.1%	81.8%	0.52	3.14
Soy	92.1%	38.2%	52.5%	86.7%	0.55	3.95
Peanut	99.3%	12.0%	60.0%	92.6%	0.43	8.15
Beef	95.3%	33.3%	55.6%	89.1%	0.50	5.11
Corn	98.7%	49.3%	92.1%	86.7%	0.09	6.91
Chicken	96.8%	34.0%	68.0%	88.0%	0.36	5.67
Potato	98.6%	25.7%	69.2%	91.3%	0.34	7.93
Pork	96.7%	20.5%	47.1%	89.6%	0.59	4.51

PPVs and NPVs along with PLRs and NLRs with specificities and sensitivities were determined in patient populations with definitive foods determined by using esophageal biopsy changes only.

TABLE E3. Number of patients undergoing the combination of SPTs and APTs among patients with EoE

Food	No. confirmed by biopsy	SPTs/APTs			
		True positive	True negative	False positive	False negative
Milk	211	106	84	24	105
Egg	78	63	200	41	15
Wheat	72	47	182	65	25
Soy	52	37	193	74	15
Peanut	16	15	251	52	1
Beef	33	24	233	53	9
Corn	39	37	229	51	2
Chicken	32	28	230	57	4
Potato	21	17	268	30	4
Pork	19	11	247	53	8

The number of patients with true-positive, false-positive, true-negative, and false-negative allergy test results for definitive foods confirmed based on esophageal biopsy changes are shown.

TABLE E4. Predictive values for the combination of SPTs and APTs in a healthy population

Food	Combined allergy testing	
	PPV	NPV
Milk	0.15%	99.93%
Egg	0.32%	100%
Wheat	0.17%	100%
Soy	0.17%	100%
Peanut	0.36%	100%
Beef	0.26%	100%
Corn	0.35%	100%
Chicken	0.29%	100%
Potato	0.53%	100%
Pork	0.22%	100%

Predictive values are calculated based on the estimated prevalence of EoE in the general population at 1:1500.