

Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests

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Background: Eosinophilic esophagitis (EE) is a recently described disorder identified in patients with symptoms suggestive of gastroesophageal reflux disease (GERD) but unresponsive to conventional reflux therapies. Therapies have included corticosteroids, elemental diet, and diet restriction. We report our experience with skin prick and atopy patch testing and food elimination diets in patients diagnosed as having EE.

Objective: To identify food antigens that cause EE and the characteristics of patients who respond to food elimination vs those who are unresponsive.

Methods: Patients diagnosed as having EE had restricted diets based on skin prick and atopy patch testing results. Additional biopsies were performed after 4 to 8 weeks of restricted diet. Demographics, atopic tendencies, and food antigens were identified retrospectively in our food allergy database.

Results: A total of 146 patients diagnosed as having EE were evaluated with skin prick and atopy patch testing. Thirty-nine patients had unequivocal demonstration of food causing EE, with normalization of biopsy results on elimination and reoccurrence on reintroduction. An additional 73 patients, for a total 112 (77%) of 146 patients, had resolution of their EE as demonstrated by biopsy results. Fifteen (10%) of 146 patients were nonresponders manifested by no significant reduction in esophageal eosinophils despite restricted diet based on skin prick and atopy patch testing. Egg, milk, and soy were identified most frequently with skin prick testing, whereas corn, soy, and wheat were identified most frequently with atopy patch testing.

Conclusion: In more than 75% of patients with EE, both symptoms and esophageal inflammation can be significantly improved with dietary elimination of foods. Skin prick and atopy patch testing can help identify foods in most patients.

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INTRODUCTION

Eosinophilic esophagitis (EE) is characterized by infiltration of the esophagus with eosinophils without infiltration in other parts of the gastrointestinal tract. The symptoms of EE are similar to gastrointestinal reflux disease (GERD) and include vomiting, pain, regurgitation, and dysphagia.¹ Patients with EE are unresponsive to standard GERD treatment and have normal pH probe test results.² The number of eosinophils detected on biopsy of the esophagus is significantly higher in EE than in GERD, and more than 15 eosinophils per high-power field (HPF) is the pathologic criterion that defines EE.³ Limited case series have reported improvement in symptoms and resolution of eosinophilic infiltration in EE with corticosteroid therapy or a strict elemental diet.^{4,5}

Patients with EE often have an allergic background, such as elevated IgE level, peripheral eosinophilia, allergic disease (including asthma, atopic dermatitis, or allergic rhinitis), and

sensitization as demonstrated by a positive skin test result.^{4,6} 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 EE.^{7,8} Unfortunately, dietary restriction based on skin prick testing (SPT) alone may only benefit a select group of patients.¹ Therefore, we previously examined the use of SPT combined with atopy patch testing (APT) to identify foods in 26 patients. We found that this method was highly successful in identifying the causative foods.⁹ We herein report our continued experience with dietary elimination using APT and SPT. We aim to identify food antigens that cause EE and the characteristics of patients who respond to food elimination vs those who are unresponsive.

METHODS

Diagnosis of EE

The diagnosis of EE was made in patients who had at least 1 of the following symptoms: vomiting, regurgitation, abdominal pain, or dysphagia unresponsive to a 2-month therapeutic trial of proton pump inhibitors. Patients were given a constant dose of proton pump inhibitors throughout the study. To confirm the diagnosis, patients underwent esophagogastroduodenoscopy (EGD) with biopsy specimens obtained from the proximal, mid and distal esophagus, stomach, and

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duodenum. The biopsy specimens were evaluated under 40× HPF and reviewed by a board-certified pathologists. EE was diagnosed if patients had more than 15 eosinophils in the most densely involved HPF in the esophagus with normal stomach and duodenal biopsy results. Subsequent biopsy specimens were routinely obtained 6 to 8 weeks after elimination of specific foods. The 26 patients we previously described⁹ are included in this analysis.

Data Collection

Patient test results and histories were collected in our food allergy database in accordance with our protocol, which was approved by the Institutional Review Board of The Children's Hospital of Philadelphia. Data collected as part of routine patient care was then retrospectively analyzed. Patients diagnosed as having EE were referred from the Division of Pediatric Gastroenterology and Nutrition at The Children's Hospital of Philadelphia for evaluation of food allergy during 1999 to 2004. An allergy evaluation was conducted, including a comprehensive food allergy history, to select appropriate foods for SPT and APT. Patients underwent SPT 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, rye, and oat), vegetables (string beans, peas, carrots, squash, potato, and sweet potato), fruits (apples, pears, and peaches), milk, soy, peanut, and egg. If patients were not ingesting the foods in the diet, they were not tested for reactions to those foods. APT was then conducted for the same foods unless large wheal-and-flare reactions (>15-mm wheal) were noted on SPT. This was done to avoid discomfort and irritant reactions. Patients were counseled to avoid all foods that were positive on either test for a minimum of 6 weeks. Patients who had more than 10 positive reactions to foods identified on testing were prescribed elemental diets of Neocate, Neocate 1+ (SHS North America, Gaithersburg, MD), or EleCare (Abbott Laboratories, Abbott Park, IL) given orally or via nasogastric tube. Patients were also prescribed elemental diets if they did not have resolution of biopsy results after eliminating the foods that produced positive reactions by SPT and APT for 2 months.

Foods were introduced at home after serious IgE-mediated reactions were ruled out. After documentation of improvement in biopsy results, 1 food was reintroduced every 7 days and biopsies were performed after reintroduction of 1 to 5 foods to confirm allergic vs nonallergic reactions. Patients were instructed to call if symptoms suggestive of EE returned. Foods that caused symptoms on reintroduction were again eliminated.

Skin Prick Testing

SPT to commercial extract (Greer Laboratories Inc, Lenoir, NC) was performed on the forearm with a bifurcated needle (Allergy Labs of Ohio Inc, 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 in millimeters at 15 minutes. The test

result was considered positive if the wheal was 3 mm greater than the negative control.

Atopy Patch Testing

APT was conducted 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 skim 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 Inc, Petaluma, CA) and adhered to the patient's back based on the methods of Isolauri et al.⁹⁻¹⁴ 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 + for erythema and scattered papules, ++ for erythema and papules, and +++ for erythema and vesicles as per standard patch testing protocols.¹⁵

RESULTS

Demographics

A total of 171 patients (116 boys and 55 girls) with EE were referred for evaluation by SPT and APT for food allergy. Twenty-five patients were excluded: 18 patients had not yet undergone follow-up EGD and no post-food avoidance biopsy specimens were available and 7 patients were lost to follow-up. One hundred forty-six patients were available for evaluation (Fig 1). The mean $\pm$ SD age of this group was 6.50 ± 4.50 years, with a median age of 5.24 years and an age range of 4 months to 20 years. One hundred eighteen (81%) of the 146 patients had an atopic background defined as a physician diagnosis of atopic dermatitis, allergic rhinitis, or asthma.

Most patients with EE have allergic rhinitis or asthma. During this study, patients with these disorders were treated with stable doses of inhaled or nasal corticosteroids. Ninety-one of 146 patients were taking inhaled or intranasal steroids at diagnosis of EE, and no patients were being treated with swallowed inhaled corticosteroids (Table 1).

Clinical Follow-up

After a minimum period of 6 weeks on dietary restriction based on SPT and APT results, patients underwent follow-up EGD with biopsies. One hundred twelve of the patients demonstrated resolution (biopsy revealed <5 eosinophils per HPF) of their EE and were considered responders to dietary restriction. This group had a reduction in the mean $\pm$ SD number of eosinophils from 48.4 ± 24.2 eosinophils per HPF to 1.1 ± 2.1 eosinophils per HPF after dietary restriction (Table 2). Thirty-nine patients had eosinophilia return on food reintroduction, with mean $\pm$ SD eosinophils counts of 35.1 ± 17.6 .

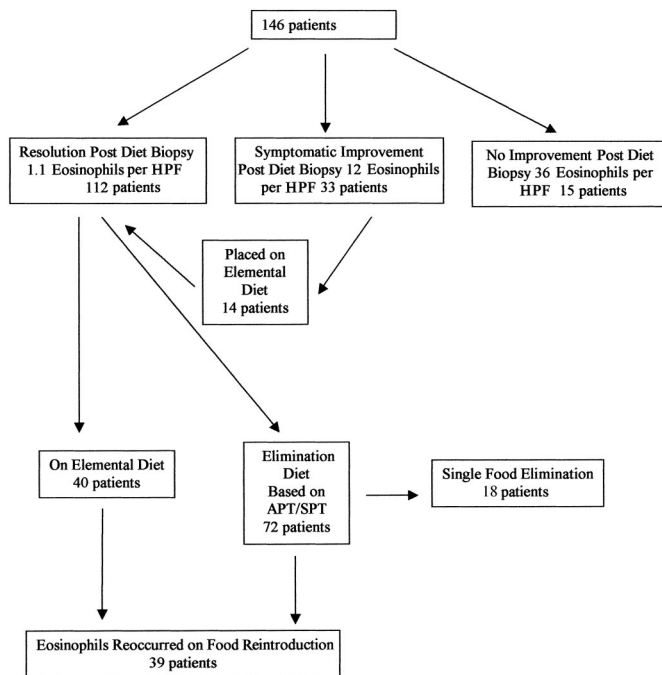


Figure 1. Distribution of patients with breakdown into responders, non-responders, and partial responders. HPF indicates high-power field; APT, atopy patch testing; and SPT, skin prick testing.

Fifteen patients were considered nonresponders to dietary restriction and had no change in eosinophils counts, with a mean $\pm$ SD count of 45.5 ± 19.0 eosinophils per HPF before dietary restriction to 36.3 ± 14.9 eosinophils per HPF after dietary restriction (Table 2). The remaining 19 patients had a partial response, with an improvement in esophageal eosinophilia with a reduction in the mean $\pm$ SD number of eosinophils from 68.8 ± 25.7 to 12.0 ± 3.2 eosinophils per HPF. All 19 partial responders had symptomatic improvement.

A comparison of the characteristics of the group with resolution of EE and the nonresponders is given in Table 1. In all groups, the male-female ratio was approximately 2:1. The age distribution of the participants is shown in Figure 2, with

Table 2. Number of Eosinophils per High-Power Field in the Esophagus Before and After Dietary Restriction

Group	Before dietary restriction, average (SD) [range]	After dietary restriction, average (SD) [range]
Responders (n = 112)	48.4 (24.2) [15–140]	1.1 (2.1) [0–5]
Nonresponders (n = 15)	45.5 (19.0) [20–80]	36.3 (14.9) [15–50]
Improvement (n = 19)	68.8 (25.7) [15–100]	12.0 (3.2) [6–15]

a slightly older age group in the nonresponders. All groups are highly atopic, with a slight difference in environmental sensitization (positive specific IgE results or positive SPT results), since 84% of the responders and 70% of the nonresponders tested positive. There were no apparent differences in the groups if they were taking inhaled, intranasal, or a combination of inhaled and intranasal steroids.

Food Allergy Testing

All 146 patients underwent APT and SPT as directed by the clinical history. Responders had positive SPT results to an average of 3.2 ± 4.3 foods. The most common foods identified by SPT included egg, milk, soy, peanut, chicken, wheat, and beef (Table 3). Responders had positive APT results to an average of 3.1 ± 2.6 foods. The most common foods identified by APT included corn, soy, wheat, milk, rice, chicken, beef, and potato (Table 3). In our total population, foods rarely produced positive results on both SPT and APT, with 57 foods producing positive results on SPT and APT of a total of 810 foods positive on either SPT or APT.

Twenty-six patients were prescribed elemental formulas due to multiple positive foods for nutritional reasons. Twenty-five patients had complete resolution on elemental diet; 1 patient developed eosinophilic gastroenteritis. An additional 14 patients began an elemental diet because of partial but incomplete improvement in their biopsy counts to (14.2 eosinophils per HPF) based on foods identified on SPT and APT. These 14 patients also had complete resolution, with eosinophil counts of 0.5 eosinophil per HPF after starting an elemental diet.

Table 1. Characteristics of the Responders and Nonresponders

Characteristics	Responders (n = 112)	Nonresponders (n = 15)	Improvement (n = 19)
Sex, M/F	73/39	12/3	15/4
Age, average (SD) [range], y	6.3 (4.5) [0.3–20.3]	8.8 (5.4) [2.5–18]	7.9 (4.9) [1.8–17.7]
Patients with allergic disease, No. (%) [*]	90/112 (80)	11/15 (73)	17/19 (90)
Patients with sensitization to environment allergens, No. (%)	61/73 (84)	7/10 (70)	12/15 (80)
No. of positive skin prick test results, average (SD) [range]	3.4 (4.2) [0–23]	2.2 (2.2) [0–7]	1.6 (2.2) [0–9]
No. of positive atopic patch test results, average (SD) [range]	3.0 (2.5) [0–11]	3.2 (3.5) [0–10]	3.7 (2.3) [0–9]
Patients with subjective improvement, No. (%)	109 (97)	0	19 (100)
Patients with no foods identified by skin prick testing, No. (%)	24 (21)	3 (20)	7 (37)
Patients with no foods identified by atopy patch testing, No. (%)	17 (15)	3 (20)	2 (10)
Patients taking inhaled or nasal steroids, No. (%)	71 (63)	8 (53)	12 (63)

^{*}Asthma, allergic rhinitis, or atopic dermatitis.

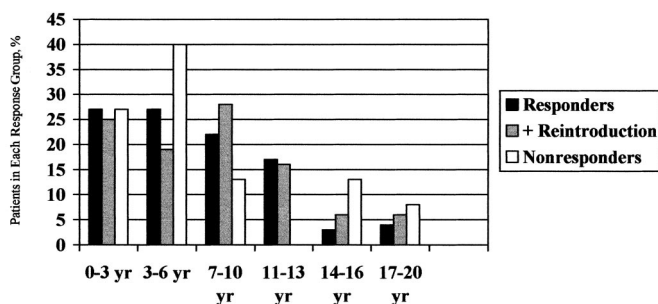


Figure 2. Age distribution of responders (patients with normalization of biopsy results on food elimination), responders with positive biopsy results on reintroduction (eosinophilia on biopsy specimens after food reintroduction and prior normalization after food elimination), and nonresponders (patients had no improvement of biopsy results after food elimination).

Table 3. Number of Positive Skin Prick and Atopy Patch Test Results in Patients Responding to Dietary Restriction

Foods	No. of positive skin prick test results (n = 146)	No. of positive atopy patch test results (n = 146)*
Milk	39	22
Egg	31	18
Soy	31	26
Peanut	26	1
Chicken	19	21
Wheat	19	25
Beef	17	20
Peas	16	9
Corn	13	35
Potato	9	20
Rice	5	21

* Atopy patch testing was not performed on 16 foods in 12 patients because of large wheal-and-flare reactions.

Foods as the Causative Agent in EE

We have identified the causative foods in a subset of patients by elimination of single foods in 18 patients and reintroduction of foods in 21 patients. When patients reintroduced a causative food, esophageal eosinophils increased to the previous levels (35.1 ± 17.6 eosinophils per HPF). Milk, egg, soy, meats, and grains were the most common foods identified as causing symptoms in this population (Table 4). The demographic of this group was nearly identical to the demographics of the general group of responders. The number of positive SPT and APT results was also similar to the larger responder group.

The foods identified in this subset of the responders group were identified by both SPT and APT. The group responded to 4.7 foods (range, 1–11). This group had an equivalent rate of foods that produced positive results on both SPT and APT compared with the other groups. The stronger patch test reactions (grade 2 and 3) were more likely to identify a causative food (Table 4 and data not shown). Two patients were following an elemental diet and had positive biopsy results on reintroduction of milk, despite testing negative on SPT and APT to milk. Most of the 21 patients had multiple food reintroductions with an average of 5 failures noted on biopsy results, which accounts for the multiple food allergies in this group. We did not identify any feature that would separate these patients from the total responder group or nonresponder group. Most of the patients in the responder group have not yet tried food reintroduction and therefore were not included in this subgroup.

Five patients tested negative to all foods tested by both SPT and APT, including 4 in the responder group and 1 in the nonresponder group. In the responder group, 3 of 4 patients with negative SPT and APT results improved after an elemental diet trial. One patient in the nonresponder group with negative SPT and APT results failed to respond to an ele-

Table 4. Causative Foods Confirmed by Biopsy and Reintroduction*

Foods	No. of patients						
	Total	SPT reaction	APT reaction by reaction size			Positive SPT and APT results	Negative SPT and APT results
			1	2	3		
Milk	24	18	0	2	2	0	2
Egg	21	16	1	3	2	1	0
Soy	17	16	2	4	1	6	0
Chicken	15	11	2	5	2	5	0
Wheat	15	9	2	3	2	1	0
Beef	13	8	1	2	3	1	0
Corn	11	6	1	4	5	5	0
Peanuts	10	14†	0	0	0	0	0
Oat	8	3	2	2	1	0	0
Peas	8	9†	1	1	1	4	0
Barley	8	4	1	4	2	3	0

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

*Number of positive SPT and APT results with food confirmed on reintroduction and return of eosinophilia.

†Four patients have false-positive SPT results to peanut and 1 false-positive SPT result to peas.

Table 5. Demographic Characteristics of Population With Confirmed Food Allergies

Characteristics	Finding
Total No. of patients	39
Sex, M/F	26/13
Age, average (SD) [range], y	7.3 (4.7) [0.6–19.3]
Patients with allergic disease, No. (%) [*]	33/39 (85)
Patients with sensitization to environment allergens, No. (%)	23/27 (85)
No. of positive skin prick test results, average (SD) [range]	4.6 (4.5) [0–19]
No. of positive atopy patch test results, average (SD) [range]	3.4 (2.6) [0–11]
Patients with no foods identified by skin prick testing, No. (%)	10 (27)
Patients with no foods identified by atopy patch testing, No. (%)	6 (16)
Patients taking inhaled or nasal steroids, No. (%)	22 (60)

^{*}Asthma, allergic rhinitis, or atopic dermatitis.

mental diet. The final patient demonstrated improvement without dietary restriction but had a relapse of symptoms and esophageal eosinophilia during pollen season.¹⁶

DISCUSSION

EE is a condition with symptoms similar to GERD but unresponsive to conventional stomach acid blockade. There is no consensus on appropriate therapy for EE. Currently, the accepted treatment of EE consists of either the long-term use of corticosteroids or the institution of an elemental diet. Other alternative therapies, including montelukast, have reported improvement in symptoms without resolution of biopsy results.¹⁷

Foods as the Cause of EE

We previously reported our experience treating EE by eliminating food allergens identified by both SPT and APT.⁹ This small group of 26 patients responded to dietary restriction with improvement in symptoms and resolution of the pathologic findings caused by EE. In addition, Markowitz et al¹⁸ reported complete improvement in 51 patients diagnosed as having EE who were treated solely with an elemental diet.

In this study, our 146 patients with postdietary restriction biopsy results available were divided into 3 groups. Responders were patients with symptomatic improvement and normalization of their esophageal biopsy results (<5 eosinophils per HPF) after dietary restriction. The responders were subdivided into patients who had positive biopsy results on food reintroduction, confirming the causative foods. Most of the other responders have not tried food reintroduction at the time. Nonresponders had no change in the number of eosinophils detected in the esophagus after dietary restriction and had continued symptoms. A total of 112 patients (77%) were responders, whereas 15 (10%) were nonresponders. A third group of 19 patients (13%) showed improvement in symp-

toms but only had partial improvement in esophageal eosinophilia (12 eosinophils per HPF) (Fig 1). The high success of dietary avoidance suggests that food plays a major role in the pathogenesis of EE.

However, other investigators have not been successful with dietary elimination as a therapy for EE.¹⁹ A possible reason for failure is that they did not use a combination of SPT and APT and failed to identify all relevant food antigens. Also, when multiple food antigens were identified, the other investigators did not implement an elemental diet. Specific foods were definitely identified as the cause of EE in 39 of our patients. On elimination of the restricted foods, biopsy results normalized and reintroduction of the causative foods resulted in relapse of symptoms and biopsy specimens revealing a return of eosinophilic inflammation in the esophagus. This finding supports a definitive role for food allergy in EE, fulfilling Koch's postulate. These patients, similar to all patients in the study, had no changes in their intranasal or inhaled steroid doses, eliminating this confounder. The most common causative foods were milk, egg, soy, and beef. These patients had similar age, sex, and atopic distribution as the responder group (Tables 2 and 5 and Fig 2), suggesting that in the responder group, foods are playing an essential role in the EE. In contrast to typical IgE-mediated food allergy, where it is rare to have more than 3 food allergies,²⁰ in this population we found an average of 4 food allergies per patient, with a high of 11 food allergies in 1 patient. In addition to the 39 patients in whom specific foods were definitely identified as the cause of EE, an additional 73 patients had resolution of their EE as demonstrated by biopsy results. Overall, 112 patients responded to dietary restriction with resolution of symptoms and normalization of their biopsy results. Seventy-two patients were able to maintain a diet based on foods identified by APT or SPT; however, 26 patients in the responder group required an elemental diet, because they were unable to avoid all of the foods identified by testing. This usually was the result of a severely limited diet due to the high number of food antigens identified. An additional 14 of 112 patients did not follow the initial diet recommendations and required elemental diets for normalization of biopsy results.

Alternative explanations for responses to elemental or restricted diet that are not food related are possible. One possibility is that the patients had increased compliance with their inhaled or intranasal steroids because they were involved in a study. This is unlikely for 2 reasons: the study is a retrospective medical record review; therefore, patients did not realize that they were in a study, making increased compliance not an issue. In addition, almost 40% of the patients were not taking inhaled or intranasal steroids, which could not account for the success in those patients.

Another theoretical possibility is that changes in the environment or in the allergy season led to symptom resolution. Two reports have implied pollen as the antigen that leads to inflammation in the esophagus.^{16,21} However, in our study, patients had positive and negative biopsy results in all sea-

sons. For most patients, we did not detect any seasonality to biopsy results. For example, severe esophagitis had been detected in the middle of winter in homes with dust mite controls and no pets in the home and normal biopsy results in the peak of pollen season in patients. However, in 4 patients (data not shown), we have seen seasonal variations with exacerbations of their EE during pollen seasons or changes in the environment as we reported previously in 1 case.¹⁶

Could the natural history of EE lead to improvement of biopsy results without treatment? This is a theoretical possibility but would not account for the failure of diets to work in our 15 nonresponder patients, failures with other treatments (montelukast),¹⁷ and rebound when stopping oral steroid therapy.⁴

Finally, foods could be causing an irritant effect and the elemental formula could be eliminating this reaction. It is impossible to rule out this possibility, but the success in selective food elimination in our trials and the original work by Kelly et al⁵ suggest that this is unlikely.

These data indicate that foods play a key role in the pathogenesis of EE in most patients. EE may represent oral allergy syndrome in the lower esophagus. The potential mechanisms for foods to cause the immunologic reaction are both IgE and non-IgE in pathogenesis. Since most patients have positive reactions to foods on SPT and APT and have positive reactions to different foods on each test, this indicates a mixed immunologic reaction similar to atopic dermatitis.

The characteristics of the responders and nonresponders were compared to determine if certain features could predict success with dietary elimination. No significant differences occurred between sensitization and allergic disease between the 2 groups with high rates of sensitization as previously reported.²² No definitive features were identified to separate the 2 groups. The nonresponders were slightly older and may have a more diverse diet that led to the failure.

Effectiveness of APT and SPT in Identifying Foods

APT and SPT were able to identify the causative food in at least 72 of 146 patients, for an approximately 50% success rate. Some of the lack of success is due to the fact that 26 patients began elemental diets for nutritional reasons. If these patients are included in the overall success rate, it would increase to 67%. If the patients who had biopsy results that were improved, although not in the normal range, are included, the success rate increases to 82%. The lack of success in the remaining 18% to 33% could be due to 3 factors: (1) not testing for the correct causative foods, (2) patients not compliant with the diet, or (3) inadequate testing techniques. In contrast to SPT, the technique of APT has not been standardized. The size of the Finn chamber and the preparation of allergen often have an effect on results of patch testing,²³ which might account for some of the failures in this study.

For the 15 patients who responded to an elemental diet but not to a diet based on APT and SPT results, the 2 most likely

causes for the failure are not testing all of the relevant foods in the patient's diet or false-negative test results. We have 2 confirmed cases of false-negative test results to milk. Similar reasons can account for the 4 patients with negative SPT and APT results with normal biopsy results after an elemental diet.

The outlier patient who had negative food allergy test results had resolution of EE without dietary restriction. This patient has known pollen sensitization and symptoms occurred during the pollen season.¹⁶ The result suggests that pollen may be an alternative source of antigen, causing eosinophilic inflammation in the esophagus in select individuals.

In EE, we need to perform both SPT and APT, because most patients had different foods that produced positive results on SPT compared with APT, suggesting a mixed immunologic mechanism. We had 810 positive results to foods on testing; interestingly, only 47 foods were positive on both SPT and APT. This number may be artificially low, because we did not perform APT for 16 foods in 12 patients with large wheal-and-flare reactions on SPT.

The Nonresponders

There are several possible explanations for the failure of diet restriction as determined by SPT or APT when treating EE in our nonresponders. The possibilities include noncompliance with the restricted diet, the responsible foods were not included in the testing panel, SPT and APT inadequacies, other antigens such as pollen leading to esophageal inflammation, or other etiologies for the disease process. Dietary restriction, especially when there are multiple foods identified, is difficult to implement. The clinical symptoms of EE are intermittent or are not apparent until weeks after the introduction of the allergic food; thus, parents and older patients have difficulty withholding foods that do not cause immediate adverse symptoms. In our study, we tested against a limited number of foods (approximately 25). This limitation may pose a problem, because older children have expanded diets and it is possible that we are not testing the correct foods. In addition, identifying the causative foods based on history is difficult in patients with EE. Clinical symptoms may not be temporally related to food ingestion, thereby making it difficult to determine problematic foods by history.

Twelve of the 15 nonresponders have not tried or refused an elemental diet. Therefore, we cannot rule out the possibility that foods are causative in these nonresponder patients. We have found only 3 patients in whom elemental diets have failed (data not shown). Two of these patients developed eosinophilic gastroenteritis with eosinophils in the stomach, duodenum, and colon, suggesting an alternative disease.

The 19 partial responders have almost normal biopsy results. These patients were generally asymptomatic, and eosinophils counts were not in the diagnostic range of EE but were not in the normal range either. The potential explana-

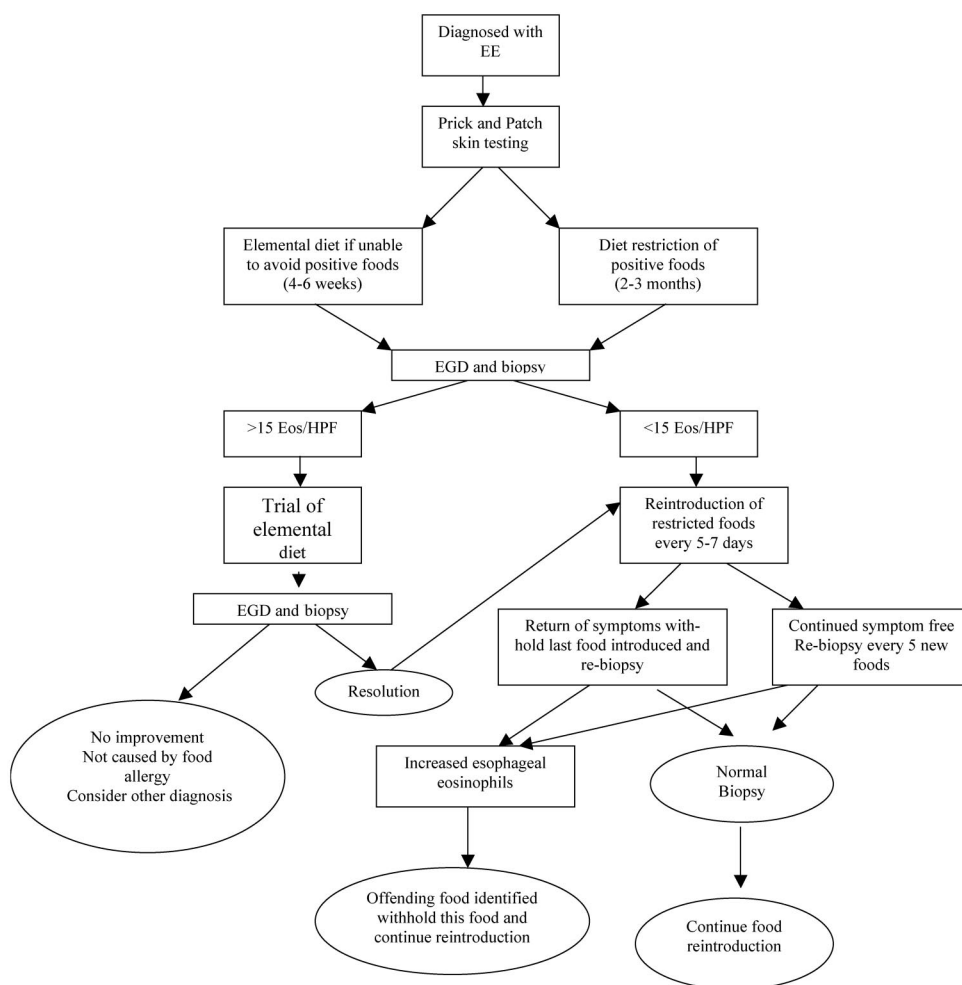


Figure 3. Diagnostic flowchart for treatment and diagnosis of eosinophilic esophagitis (EE). SPT indicates skin prick testing; APT, atopy patch testing; HPF, high-power field; and EGD, esophagogastroduodenoscopy.

tions for this finding are missing foods, noncompliance, or additional effects of environmental allergies, which are similar to the explanations for nonresponders. It is also possible that avoidance of the foods has not occurred for a long enough time for biopsy results to completely normalize. Supporting this theory is the fact that this group had the highest eosinophils counts at baseline. It is possible that if the patient continued the restriction diet for 3 months or longer, we would have been more successful in this group as well.

Additional research is needed to determine individual positive and negative predictive values for SPT and APT in this disorder, which will occur over time as more single removal and reintroduction of foods are performed. Another area that needs research is the long-term course of this disease (ie, whether patients can “outgrow” this food allergy, similar to IgE-mediated reactions). In our preliminary studies, we have seen tolerance to the foods in a 3-year period.

Treatment Guidelines

Since symptoms may not be obvious to patients with EE and definitive diagnosis depends on invasive procedures, we have developed a protocol for the evaluation and treatment of EE based on our previous experience treating these patients (Fig 3). The initial diagnosis is made by a pediatric gastroenterologist and pathologist based on the biopsy results. The patients then receive a complete allergy evaluation, which includes an extensive food allergy history. SPT and APT are directed by the food allergy history, and a standard panel of meats, grains, milk, soy, and egg is conducted. Patients are then counseled to initiate a restricted diet based on the results of both forms of testing. If the patient is unable to comply with the diet or if the diet is too limiting, an elemental formula is recommended. To allow time for reduction in inflammation and with the difficulty of compliance in mind, patients are asked to comply with the restricted diet for 2 to

3 months. In contrast, an elemental diet is followed for 4 to 6 weeks. All patients then undergo additional biopsies. If the biopsy result demonstrates significant improvement (<5 eosinophils per HPF) then patients begin reintroducing new foods every 5 to 7 days. If the biopsy result after the restricted diet shows continued eosinophilia (>10 eosinophils per HPF) and the patient has not yet attempted an elemental formula, they then start a 4- to 6-week trial of an elemental diet. During food reintroduction, if symptoms develop immediately after reintroduction of a specific food, then that food is discontinued. Otherwise, after reintroduction of 4 to 5 foods, a subsequent biopsy is performed 4 weeks after the last food is introduced. If the subsequent biopsy demonstrates significant improvement, then an additional 4 to 5 foods are introduced. Again, a subsequent biopsy is performed to determine if EE has returned. Subsequent biopsies are crucial, because it is often difficult to predict esophageal histologic improvement based solely on clinical symptoms. If EE reoccurs, then those foods are no longer given and new foods are introduced. In general, milk, soy, wheat, and eggs are typically the last food introduced even in the absence of abnormal SPT and APT results. If after 4 to 6 weeks of an elemental diet the patients have no histologic improvement, other diagnoses should be considered.

Our experience with evaluating and treating more than 140 patients with EE indicates that most of these patients are effectively treated with dietary restriction based on SPT and APT. Further evaluation is necessary to determine why some patients fail to improve with dietary restriction and if there are other processes that can lead to EE.

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