

The Role of Allergy Testing in Eosinophilic Esophagitis

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Abstract: Eosinophilic esophagitis (EoE) is defined as a chronic, immune/antigen-mediated esophageal disease that can lead to symptoms of esophageal dysfunction. This disease is seen in both children and adults. Approximately 70% of patients with EoE have food antigen sensitization or other atopic conditions, suggesting an allergic etiology in the pathogenesis of the disease. The role of allergy testing to identify foods that lead to EoE is unclear. Three types of allergy tests currently exist: skin prick testing, atopy patch testing, and immunoassays for serum food-specific immunoglobulin E. It is important for gastroenterologists to work in conjunction with allergist colleagues in the care of patients with EoE, particularly in the management of comorbid atopic conditions.

Eosinophilic esophagitis (EoE) is a chronic, inflammatory disorder of the esophagus with increasing prevalence. The disease is characterized by an eosinophilic infiltrate in the esophageal epithelium with associated esophageal symptoms. Both genetic and environmental factors are thought to play a role in the disease's pathogenesis.¹

EoE is seen in both children and adults. The mean age at diagnosis in children is 6 to 7 years, and in the second to fourth decades of life in adults.²⁻⁵ Previous studies have found a male predominance of 3:1, with a higher frequency of disease in non-Hispanic whites.^{2,5} EoE is commonly seen in patients with other atopic diseases, such as allergic rhinitis and asthma.^{2,3,6} Symptoms tend to vary by age, with infants and young children often presenting with feeding difficulties and failure to thrive, school-age children with vomiting or abdominal pain, and adolescents and adults with dysphagia or food impaction.^{2,7,8}

On endoscopy, the findings of esophageal strictures, concentric rings, and narrowing are more commonly seen in adults, whereas children may have plaques or furrows.^{7,9} However, endoscopy may show a completely normal esophagus in both children and adults as well; therefore, esophageal biopsies are required to diagnose EoE regardless of endoscopic appearance.⁷⁻⁹

Keywords

Eosinophilic esophagitis, food allergy, allergy testing

The Role of Allergies in the Pathogenesis of Eosinophilic Esophagitis

Approximately 70% of patients with EoE have food antigen sensitization or other atopic conditions, which suggests a role for allergies in the pathogenesis of the disease.¹⁰ The most common food antigens implicated in EoE are milk, wheat, egg, and soy. Nearly 70% of children and 50% to 60% of adults with EoE will have positive skin prick testing (SPT) and serum testing to food antigens.⁹ Several studies have shown symptomatic, endoscopic, and histologic improvement in disease with elimination diets, which further supports an allergic component to the pathogenesis of this disease.^{11,12}

The pathogenesis of EoE is similar to that of other atopic disorders, such as asthma, atopic dermatitis, and allergic rhinitis.¹³ It is now known that food antigens function as triggers for esophageal eosinophilia and inflammation in EoE. In experimental animal models, food antigen exposure can lead to local eosinophilia in the esophagus, and induce features of EoE such as basal cell proliferation, esophageal eosinophilia and mastocytosis, lamina propria remodeling, and fibrosis.¹⁴

Moreover, it has been hypothesized that both immunoglobulin (Ig) E-mediated and cell-mediated mechanisms may play a role in the pathogenesis of EoE.⁷ Research has found increased production of Th-2-associated cytokines (interleukin [IL]-5 and IL-13) in sensitized individuals in response to exposure to food antigens.¹⁵ Research in asthma, allergic rhinitis, and atopic dermatitis has also shown evidence of IL-13 dysregulation.¹³ The IL-13 cytokine upregulates IgE and participates in adhesion, eosinophil recruitment, and survival.¹⁶ However, the role of IgE in the pathogenesis of EoE remains unclear. Animal models have shown that EoE can be induced in B-cell-deficient mice, but not in mice that are T-cell-deficient. Recently, there has been increasing evidence that B cells do not have a prominent role and, instead, that T cells have an important role.¹⁷⁻²⁰

Studies suggest that aeroallergens have a role in the pathogenesis of EoE. In murine models, sensitized mice that are exposed to intranasal *Aspergillus fumigatus*, dust, and cockroach mites develop resultant esophageal eosinophilia.^{21,22} Similarly, a subset of patients with EoE report a seasonal variation of their symptoms in accordance with their other atopic diseases.^{2,23} Fogg and colleagues found seasonal variation of EoE, with worsening of symptoms and increased eosinophilic infiltration on esophageal biopsies during the pollen season, with subsequent improvement during the winter months.²³ It has been suggested that adult patients may present with greater aeroallergen sensitivity, whereas pediatric patients tend to have more food allergies.⁷

Table. Types of Allergy Tests Available for Food Testing

Test	Mechanism
Atopy patch testing	Delayed hypersensitivity
Skin prick testing	Presence and function of specific IgE
Serum food-specific IgE	Presence and level of specific IgE

Ig, immunoglobulin.

Both food antigens and aeroallergens can cause esophageal eosinophilia and symptoms of EoE. Therefore, it is imperative to consider both atopic diseases in addition to food antigens when managing flares of EoE, as flares of atopic diseases and EoE can often occur simultaneously.

Types of Allergy Tests Available

Food allergies are known to play a role in the pathogenesis of EoE; therefore, allergy testing is sometimes used to identify potential food triggers in individual patients. There are 3 types of allergy tests currently available: SPT, atopy patch testing (APT), and serum food-specific IgE (sIgE) testing (Table).

Food allergy testing is based on immediate and delayed hypersensitivity reactions. Immediate food hypersensitivity reactions are IgE-mediated reactions that occur within minutes to hours following ingestion of a culprit food. Patients are reported to have a food allergy when they have a repeated clinical reaction when exposed to a food in which they have an associated IgE.⁷

SPT and serum allergy testing utilize the immediate hypersensitivity reaction. In SPT, commercial food extracts, fresh food, or aeroallergen extracts are pricked through the surface of the skin of the forearm.^{3,7,9} In a susceptible patient, this will cause mast cells in the skin, which are bound to IgE, to degranulate in response to the particular antigen, and subsequently cause a wheal or hives at the site.⁹ A positive test is a wheal greater than 3 mm at the site within 15 minutes.²⁴

Serum allergy testing is used to determine the presence and level of IgE in the blood. The serum test is an enzyme-linked immunosorbent assay-based test.^{7,9} Serum tests measure the quantity of antibodies present to specific antigens or foods.⁷ A positive test produces a color reaction for a patient who has a particular IgE that binds to an antigen on a solid phase.⁹ Younger children tend to have reactions at lower IgE serum levels than older children.⁷

APT is based on a non-IgE, cell-mediated, delayed hypersensitivity reaction.⁷ Patch testing is performed by placing fresh or dried single-ingredient foods into separate metal chambers and taping the chambers to a patient's

back for 48 hours. Results are then interpreted at 72 hours.^{3,7,9,25} A positive test is defined as skin induration and the presence of papules at the site.²⁵

Currently, the benefit of allergy testing in the diagnosis and management of EoE remains under investigation. Generally, SPT or serum testing alone does not provide useful information for management of this disease.⁷ SPT has a poor positive predictive value (PPV), but the negative predictive value (NPV) for all foods on SPT, with the exception of egg, wheat, soy, and milk, is greater than 90%. However, milk and wheat are the culprit food allergens in the vast majority of patients, particularly in the adult population. The combination of SPT with patch testing has been reported at 1 center to increase the NPV to 92% for all foods excluding milk and wheat.^{3,26}

Food Allergy Testing in Patients With Eosinophilic Esophagitis

Over the years, 3 major dietary therapies have evolved for EoE: (1) total elimination of all food allergens with an elemental or amino acid–based formula (elemental diet [ELED]); (2) targeted elimination diet guided by allergy testing (typically SPT or APT); and (3) empiric 6-food elimination diet (SFED) removing 6 of the most common food groups known to be triggers of EoE (milk, wheat, egg, soy, nuts, and seafood). Previous uncontrolled studies have demonstrated symptomatic and histologic improvement/resolution in pediatric patients with all 3 therapies, and the current recommendation is treatment for 4 to 8 weeks with dietary therapy, followed by endoscopic evaluation for remission and reintroduction of foods.⁸ However, given the social and economic factors involved, the choice of dietary therapy is still mostly individualized and based on patient and family preferences.

Most studies assessing dietary therapies have been performed in the pediatric population, and elemental formula has shown great efficacy in terms of resolution of symptoms and histology.^{27–30} Likewise, SFED has been shown to be an effective treatment modality^{11,12}; however, limitations to both SFED and ELED include cost, need for extensive patient and family participation, and social factors. The efficacy of allergy testing to identify food triggers is still controversial and under investigation. Of the 3 major forms of testing currently available (SPT, APT, and immunoassays for sIgE), no single modality has been adopted as a test of choice, and even though these tests may reveal specific food triggers in EoE, false-positive results may occur due to cross-reactivity with environmental allergens. Most trials assessing allergy testing in EoE have been in the pediatric population, which corresponds to the development and course of hypersensitivity reactions, as young children are more likely to have food

sensitization and allergic responses than older children and adults. Summarized below are the current data regarding food allergy testing and targeted elimination diets.

Data in Pediatric Patients

Spergel and colleagues performed the first prospective study investigating food allergy testing–guided diets in children in 2002.³ Twenty-six children with biopsy-confirmed EoE underwent SPT and APT, and then were placed on a testing-directed diet for at least 6 weeks. Milk and egg were identified as the most common positive food allergies via SPT, whereas wheat was the most common via APT. Of the 24 children able to be followed, 18 had resolution of symptoms and 6 had partial improvement via endoscopic and biopsy confirmation, and all had greater than 50% decrease in eosinophils per high-power field (eos/hpf). This was followed by a larger prospective study (n=146) in 2005 in which 77% of patients had resolution of EoE via biopsy after undergoing dietary elimination of foods identified by SPT and APT.³¹ The same authors later carried out a retrospective study of all children with EoE seen at Children's Hospital of Philadelphia between 2000 and 2011 (n=793).²⁶ Milk, egg, wheat, and soy were found to be the most common food allergens in 319 patients, and approximately 70% of children had at least 1 positive SPT result to foods. SFED or testing-directed diets (via APT or SPT) both yielded 53% success rates. In addition, removal of dietary triggers via allergy testing plus empiric elimination of milk led to resolution in 77% of patients. The study also found that patients with fewer food allergies presented at a significantly older age compared with a subset of patients with a more severe phenotype who presented at a younger age and with a greater number of food allergies, consistent with the previously described natural history of food allergy.

Although these results were encouraging, other groups have demonstrated variable success with allergy testing–directed diets in children.^{30,32,33} In 2011, Rizo Pascual and colleagues performed a prospective pilot study that included 17 individuals age 0 to 14 years with EoE.³² Fifteen of 17 patients were found to be sensitized to 1 or more foods, and 9 patients achieved remission with either swallowed corticosteroids (1/4, 25%), ELED (3/3, 100%), or avoidance diet (5/12, 42%). The study did find, in agreement with prior studies, milk and egg to be the foods most commonly implicated.³² These findings were supported by later studies conducted by Henderson and colleagues and Al-Hussaini and colleagues demonstrating remission and partial remission rates of allergy testing–guided diets to be 65% and 40%, respectively.^{30,33} Plausible reasons for the variability in results include lack of standardization in subject selection, number and type

of antigens examined, and technical differences in allergy testing techniques and results.

Data in Adult Patients

There are limited studies examining food allergy testing in the adult population. One study conducted by Penfield and colleagues from 2006 to 2008 at the Cleveland Clinic demonstrated a high prevalence of food allergen involvement in the adult population (81%).³⁴ This was supported by data showing food sensitization detection in approximately 95% (18/19) of adult individuals tested via SPT/APT, with peanut, egg, and soy as the most common culprit foods.³⁵ Although food allergy testing seems to demonstrate a high prevalence of food allergen involvement in the adult population with EoE, data on allergy testing-directed diets have not been convincing. Simon and colleagues showed only 1 of 6 individuals having improvement in clinical symptoms after treatment with an allergy testing-directed diet for 6 weeks.³⁶ Likewise, in studies by Molina-Infante and colleagues and Wolf and colleagues, only 29% and 32% of patients, respectively, were found to achieve histologic remission (≤ 15 eos/hpf) after undergoing allergy testing-directed diets for 6 weeks.^{37,38} In addition, a recent comprehensive systematic review and meta-analysis that included 33 studies and 1317 patients with EoE showed similar findings in which only 45.5% of allergy testing-directed diets were shown to have an effective outcome.³⁹

Fewer studies have been performed examining the efficacy of detecting food sensitization and sIgE-directed diet in treating patients with EoE. There is some evidence demonstrating higher sensitivity in detecting food sensitization via sIgE than SPT^{40,41} and effectiveness of sIgE-directed diets in achieving disease remission in adults with EoE.^{42,43} A recent study by Rodríguez-Sánchez and colleagues showed that in 26 patients who underwent sIgE-directed diets, 73.1% achieved histologic remission.⁴⁴ Although there were no statistical differences in histologic response between sIgE-directed diet and SFED ($P=.17$), the mean number of eliminated foods per patient was significantly lower in the sIgE-directed group. These data suggest that sIgE-directed dietary therapy may be a viable treatment option, although further studies need to be performed.

Although dietary restriction via SPT/APT seems to have conflicting data regarding efficacy in treating pediatric and adult populations with EoE, most studies were able to demonstrate high NPVs for food allergy testing. In the previously described study by Spergel and colleagues, PPVs and NPVs were calculated and separated into SPT alone, APT alone, and combined SPT and APT in patients with EoE.³ Notably, for SPT alone, the PPVs had an average of 47%, whereas the NPVs were consistently

greater than 90% for the majority of foods tested, with the exception of egg, wheat, and soy (70%-90%). Milk had the lowest NPV, with 30%. NPVs for APT alone had a similar trend, averaging 90%, with the exception of milk (31%), and PPVs averaged 44%. Combining SPT and APT increased the NPVs to at least 93% for all foods except for wheat (88%) and milk (44%). These results are important in providing useful clinical information because if allergy testing results are negative, then there is a greater than 90% chance that the patient will not have an IgE-mediated reaction. As noted above, pediatric patients with EoE have higher rates of immediate food hypersensitivity reactions (urticaria, anaphylaxis) than the general population (15%-24% vs 3.9%, respectively), with peanut, egg, and milk being the most common triggers of anaphylaxis.^{3,45-47} Hence, the presence of food-related IgE and high NPV may help prevent and predict potential for serious allergic reactions (eg, anaphylaxis) if the given food is not being consumed regularly.

Empiric Diets Vs Allergy Testing-Guided Diets and Remission

As previously described, ELED and empiric elimination diet therapy (ie, SFED) have shown positive results in EoE remission both with regard to symptoms and histology. In particular, when Kelly and colleagues first introduced ELED in 1995 to a group of 10 children with EoE, all of the subjects were found to have symptomatic improvement, and up to 90% exhibited histologic improvement (≤ 15 eos/hpf).²⁸ This high rate of success was supported by later pediatric studies showing similar efficacy.^{27,29,30} Studies examining the role of ELED in treating adults with EoE are limited. Peterson and colleagues demonstrated that in 18 adults with EoE who underwent treatment with ELED (2-4 weeks), 17 (94%) showed histologic improvement; however, there was not a significant decrease in symptoms.⁴⁸ A lack of adherence to the ELED (33% dropout rate), compared to prior pediatric data, was noted to contribute to the discrepancy in symptomatic response rate.

Six-Food and Four-Food Elimination Diets

Due to the significant cumbersome nature of ELED, SFED was later introduced in 2006 by Kagalwalla and colleagues, which aimed to eliminate only the 6 most common foods (ie, milk, soy, egg, wheat, nuts, and seafood) associated with IgE-mediated food allergy and EoE.¹² It was found that 26 of 35 (74%) children with EoE who underwent SFED treatment for at least 6 weeks achieved histologic and clinical remission (≤ 10 eos/hpf) compared to 22 of 25 (88%) subjects who were given an amino acid-based ELED. Given the promising results

in the pediatric population, follow-up studies were performed examining the effectiveness of SFED in adults. Gonsalves and colleagues demonstrated 70% histologic remission (≤ 10 eos/hpf) and 94% symptomatic improvement among 50 adults with EoE after 6 weeks of treatment with SFED.¹¹ This study found that SPT accurately predicted merely 13% of causative agents in EoE, whereas 67% of patients with EoE who had a food trigger identified by means of the food reintroduction process had a negative SPT to all foods. A prospective trial by Lucendo and colleagues showed that 73% of patients ($n=64$) had symptomatic and histologic (≤ 15 eos/hpf) improvement after treatment with SFED (plus empiric elimination of legumes) for 6 weeks.⁴⁹ According to these 2 studies, milk (50.0%-61.9%), wheat (28.6%-60.0%), egg (26.2%), and legumes (23.8%) were the most common food triggers of EoE. Based on these results, Molina-Infante and colleagues examined the efficacy of a newly proposed 4-food elimination diet (FFED) in adults with EoE.⁵⁰ It was found that 28 of 52 (54%) patients achieved histologic remission (≤ 15 eos/hpf) after treatment with FFED, which eliminated wheat, dairy, egg, and legumes, for 6 weeks. The nonresponders were then offered SFED, and, of the 19 patients who underwent rescue SFED, 6 (32%) achieved histologic remission. Notably, the study found that all patients had 1 or 2 food triggers, with cow's milk as the only trigger in 27% of patients. Interestingly, studies have also examined empiric elimination of cow's milk in children with EoE and have found a moderate rate of histologic response (64%-65%) in the tested subjects.^{51,52} However, in 1 of these studies, subjects were also undergoing treatment with proton pump inhibitors, and no trials have yet been conducted on empiric milk elimination diets in adults.⁵¹ Thus, the role of empiric milk elimination diet in treating EoE warrants further evaluation.

Comparing Elimination Diets and Allergy Testing-Directed Diets

Comparison studies evaluating empiric elimination diets and food allergy testing-directed diets are scarce. Two studies have been performed comparing SFED and either sIgE-directed or SPT-directed food elimination diets in adults with EoE. The aforementioned study by Rodríguez-Sánchez and colleagues compared the efficacy of sIgE-targeted elimination diet (sIgE-ED) and SFED.⁴⁴ Subjects underwent sIgE, SPT, and APT, and those subjects with at least 1 positive IgE test were given a 6-week sIgE-ED, whereas non-IgE-sensitized patients underwent a 6-week SFED. The authors found no statistical difference in histologic response between sIgE-ED and SFED.⁴⁴ The aforementioned study by Wolf and colleagues involved a retrospective assessment comparing adults (age ≥ 18 years) with EoE who either underwent allergy testing-directed

elimination diet (22/31) or SFED (9/31).³⁸ The results showed 68% symptomatic and 53% endoscopic response in subjects treated with allergy testing-directed diet compared to 78% symptomatic and 56% endoscopic response with SFED. It is worth noting that in both of these studies, SFED success rates were found to be lower (52%-56%) than previously described, which could be explained by differences in study design, possibly giving rise to potential selection biases and variability in dietary compliance.

Although ELED has been shown to be the most effective treatment in children with EoE (and of moderate efficacy in adults with EoE), the long-term use of this treatment is limited by patient and family participation, lifestyle impact, and socioeconomic factors. In addition, ELED does not seem to be a long-term nutritional treatment for EoE, which is a chronic disease. Thus, the role of ELED may be limited to achieving disease remission in children who are not yet eating solid foods or children who can follow this diet for a period of time to achieve disease remission prior to food reintroduction, and when other treatment options have failed.⁵³ As for food allergy testing-directed diets, multiple studies have consistently reported low efficacies in achieving histologic remission in patients with EoE, particularly in the adult population.³⁶⁻³⁹ This can be explained by the fact that EoE pathogenesis is likely unrelated to an IgE-mediated allergy as previously described. Thus, the efficacy of using IgE-directed testing modalities to detect food allergens and develop diet therapies in the treatment of EoE is questionable. Lastly, although prior studies have demonstrated higher rates of attaining histologic remission with empiric elimination diets than with allergy testing-directed diets, recent studies have not been able to replicate the same efficacy, although this may be due to uncontrolled secondary variables.^{38,44}

New Technologies for Food Allergy Testing in Eosinophilic Esophagitis

Given the inadequate understanding of the pathogenesis of EoE and evidence against IgE playing a central role in EoE, current allergy testing methods (including APT, SPT, and sIgE testing), although proven in identifying hypersensitivity reactions, do not accurately reflect food triggers in EoE. Therefore, the lack of reliable and specific diagnostic tools to identify food allergens in patients with EoE calls for the need to explore novel diagnostic tools.

To date, several diagnostic tools have been proposed, but the majority are still focused on immediate hypersensitivity reactions. For example, the concept of component-resolved diagnosis (CRD) has been proposed as an alternative diagnostic method and to help guide targeted dietary elimination. CRD involves using

microarrays in the measurement of sIgE epitopes against food allergen molecules. A few studies have identified aeroallergen cross-reactivity as a culprit in food sensitization in adults with EoE, and the idea of using CRD-guided diets was subsequently proposed as an alternative treatment modality.^{43,54}

However, studies assessing CRD-guided diets thus far have not been promising. In a prospective study, only 7% of the study population (n=15) achieved histologic remission during interim analysis, and the trial was prematurely terminated due to the low response rate and ethical concerns.⁵⁵ A follow-up CRD study has also found low correlation between CRD and sIgE in identifying food allergens in patients with EoE.⁴¹ These studies all used a single specific CRD method; thus, it is unclear if employing other CRD methodologies would yield similar results.

Another interesting future area of research relates to IgG4. There is strong evidence that IgG4, instead of IgE, plays an important role in the pathogenesis of EoE, and it has been proposed to use IgG4 assays to identify food triggers and develop guided dietary therapy.⁵⁶⁻⁵⁸

A recent study conducted by Warners and colleagues proposed the idea of performing esophageal prick testing (EPT) as a new modality to identify esophageal sensitization.⁵⁹ EPT was performed in this study by injecting 6 allergens in the esophageal mucosa of study subjects, including both patients with EoE and controls. In subjects with EoE, EPT was performed after 4 weeks of empiric (SFED) or ELED treatment due to concerns that severe esophagitis would interfere with esophageal responses to culprit allergens. The 6 allergens injected included wheat, milk, soy, and 3 other allergens based on the individual patient's history. The esophageal mucosa was monitored for 20 minutes postinjection, and biopsy specimens were obtained to evaluate for histologic disease activity. A repeat endoscopy was also performed after 24 hours to evaluate for any delayed response. For comparison, the authors also performed SPT and sIgE testing with the same allergens used for EPT. Overall, 5 of 8 patients with EoE had evidence of an acute response, whereas 2 other patients had a delayed reaction. In 6 of 8 patients, SPT results were positive for at least 1 food allergen, and in 5 of 8 patients, increased sIgE antibodies were detected against at least 1 food allergen. All tests were negative in controls. However, significant differences in the type and number of food allergens were detected between EPT and SPT/sIgE. This suggests that response to dietary triggers in EoE may be restricted to the esophagus, which may explain why skin tests and sIgE tests perform poorly as tools to guide elimination diets. This pilot study also introduced EPT as a promising alternative to conventional skin allergy testing and sIgE to help guide future

elimination dietary therapy, but further trials are needed for validation.

Summary

The role of allergy testing to identify foods that lead to EoE is controversial. Some centers have adopted the use of allergy testing-guided dietary therapy in pediatric patients. However, data showing that SPT may only be 13% predictive in identifying the dietary trigger of adults with EoE suggest that the benefits of such testing in adults may be limited. It is important for gastroenterologists to work closely with allergist colleagues in the care of patients with EoE, particularly in the management of comorbid atopic conditions. Novel techniques are under development, including EPT, a technique that shows promise in the identification of food allergens that lead to EoE.

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