

PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Food Allergy Testing in Eosinophilic Esophagitis: What the Gastroenterologist Needs to Know

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This article has an accompanying continuing medical education activity on page e72. Learning Objectives—Upon completion of this exam, successful learners will be able to explain the role of food antigens in EoE and identify the role of food allergy testing in EoE management.

Eosinophilic esophagitis (EoE) is a clinicopathologic disease of increasing prevalence in children and adults. The triggering antigen in EoE is often a food that initiates a cascade of Th2-associated interleukins such as interleukin-5 and interleukin-13 and chemokines such as eotaxin-3 as well as esophageal eosinophilia and mastocytosis. Amino acid-based formulas have high efficacy rates in EoE and constitute the first evidence for food-triggered esophageal eosinophilia. Animal models have demonstrated the sufficiency of food antigens in triggering both the inflammatory and remodeling complications of EoE. Food elimination diets that are followed by single food introduction with repeat biopsy have proven the efficacy of empiric and allergy testing based elimination diets in children and adults. Although the ideal allergy test for identifying food antigens in EoE remains to be elucidated, the utility of food skin prick combined with atopy patch testing has been shown in large pediatric cohorts. By comparison, smaller, non-U.S. adult cohorts have not had similar results. Currently, a positive test on food allergy evaluation suggests a food trigger for EoE but does not substitute for biopsy-based tissue evaluation after food removal and reintroduction. The higher rates of food anaphylaxis in children with EoE, potential loss of tolerance to immunoglobulin E-positive foods that can occur with food avoidance, and the high rates of other atopic diatheses in EoE subjects all support the evaluation of EoE subject by an allergist, consideration for allergy testing, and an integrated approach by allergists, gastroenterologists, and pathologists in EoE management.

Keywords: Eosinophilic Esophagitis; Elimination Diet; Allergy Test; Remodeling; Eosinophil.

See similar article on page 1272 in this issue of *Clinical Gastroenterology and Hepatology*.

Eosinophilic esophagitis (EoE) is a clinicopathologic entity of increasing worldwide prevalence that affects both children and adults.^{1,2} EoE is a chronic, immune, antigen-mediated disorder with a pathogenesis akin to other allergic diseases such as asthma and eczema in which an antigen induces a cascade of Th2

interleukins (ILs) and chemokines in addition to inflammatory cell infiltration.^{1,3,4} The diagnosis of EoE relies on the presence of robust esophageal eosinophilia of ≥ 15 eosinophils per high-power field that persists after a proton pump inhibitor trial.¹ The process is frequently pan-esophageal and accompanied by histologic remodeling inclusive of submucosal fibrosis and angiogenesis, which translates clinically into esophageal rigidity and dysmotility and symptoms of dysphagia.^{5–10} Important molecular factors for eosinophilia and remodeling include IL-5, IL-13, eotaxin-3, and transforming growth factor β -1.^{3–5,11–14}

Food antigens clearly function as antigenic triggers for EoE induction and exacerbation in pediatric and adult populations.^{15–19} In 1995, Kelley et al¹⁷ postulated that acid-resistant esophageal eosinophilia could be due to food antigen exposure in children. On the basis of this hypothesis, these investigators treated children with gastrointestinal symptoms and esophageal eosinophilia with amino acid formula. After a minimum of 6 weeks of treatment, all of the children experienced resolution or improvement of symptoms, with significant reductions in esophageal eosinophilia. Since then, these data have been validated at multiple centers. Indeed, amino acid formulas are one of the most effective EoE therapies, with resolution rates often higher than 96% in children.^{16,18,20,21} The removal of all food antigens from the adult diet is also effective in resolving EoE, with improvements in endoscopic and histologic features in 72% of subjects after 4 weeks of treatment.²²

A second line of evidence in support of food antigens in the pathogenesis of EoE is the clinicopathologic response to specific food elimination in the form of empiric elimination diets.^{15,16,23,24} Empiric elimination of

Abbreviations used in this paper: APT, atopy patch testing; EoE, eosinophilic esophagitis; Ig, immunoglobulin; IL, interleukin; SPT, skin prick testing.

specific food groups (milk, egg, soy, wheat, peanuts/tree nuts, fish/shellfish) is highly effective in controlling EoE-associated symptoms, endoscopic abnormalities, and eosinophilia. In children and adults, the empiric elimination diet resolves EoE in more than 60% of subjects.^{15,16,18,25} Food antigen elimination can also resolve fibrosis, at least in children.²⁶ As such, this food elimination diet not only provides a therapeutic remedy in EoE but also provides proof of concept that food antigens are EoE instigators. Further evidence for the sufficiency of food antigens in initiating EoE comes from experimental models in which both peanut and egg exposure can cause the accumulation of eosinophils in the murine esophagus.^{6,27} In these animal model systems, food antigen exposure induces many features of EoE inclusive of basal cell proliferation, esophageal eosinophilia and mastocytosis, and lamina propria remodeling with fibrosis.^{6,27}

Allergy Testing

Allergy testing is generally aimed at elucidating 2 distinct mechanisms of hypersensitivity. Immediate reactions are gauged by the presence of immunoglobulin E (IgE) in the context of clinical history and the presence of food-specific IgE. Clinically meaningful, immediate food hypersensitivity reactions are defined as the presence of food-specific IgE and a reproducible clinical reaction occurring within minutes to a few hours (up to about 4 hours) after ingestion of the instigating food. Food allergy in general, however, is defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”²⁸ Food-specific IgE can be detected either by skin prick testing (SPT) or by serum IgE testing. SPT assesses both the presence and the function of mast cell-bound IgE, whereas serum IgE documents the presence and quantity of food-specific IgE. SPT can be done by using commercially available food extracts or fresh foods. The more common testing reagents in food allergy are commercially prepared food extracts. IgE food allergy testing is standardized and validated in the context of immediate reactions such as hives, eczema flares, angioedema, and symptoms of anaphylaxis. However, food-specific IgE is detectable in some individuals even in the absence of clinical reactions to the particular food. The clinical state of having IgE to a food is referred to as sensitization.²⁸ When this is coupled with a predictable and repeatable clinical reaction on food ingestion, it is termed an allergy. Subjects who eat a food and have no detectable clinical reaction are tolerant. It can be difficult to accurately predict if a sensitized person who has never consumed the food to which he/she is sensitized will have a reaction on consumption of that food. However, predicting the likelihood of a response is usually based on the level of serum-specific IgE and/or on the size of the wheal on SPT. In addition, the loss of food tolerance can occur when a food-sensitized subject begins to avoid the food to which they carry IgE. This loss of tolerance can occur

relatively rapidly, in weeks to months, and is manifested by the onset of clinical immediate hypersensitivity reactions such as hives, angioedema, and/or respiratory distress on ingestion of the previously tolerated food. Current data suggest that continued consumption of a food once desensitization has occurred is likely an essential component for the maintenance of tolerance.²⁹

Serum IgE is done by a number of laboratories. However, the literature for predictive tests for serum IgE testing in pediatric subjects with immediate food hypersensitivity is based on the Phadia ImmunoCAP system (ImmunoDiagnostics, Uppsala, Sweden). A study assessing this system in comparison with other serum IgE food tests (Turbo-MP and Immulite) found that values were significantly different for milk, egg, and peanut.³⁰ As such, the results obtained from different tests are not comparable. Testing, which was previously done by radioactivity and known as RAST (radioimmunoassay), has been entirely replaced by non-radioactive enzyme-linked immunosorbent assay testing. Unlike IgG testing, which is entirely unwarranted in food allergy with the exception of IgG4 for research purposes, IgE testing requires the detection of nanogram quantities of antibody. This is due to the fact that the majority of IgE is bound to tissue cells such as mast cells and basophils. The pre-bound nature of IgE to its receptor is pivotal for the rapid time course of immediate hypersensitivity because the cell is essentially “primed” for its allergic response. In addition, the predictive values for reactions based on serum food IgE are specific to the food and the age of the subject such that younger children can have immediate reactions at lower food-specific serum IgE levels than older children. Because of the complexity of food allergy testing and evaluation, referral to an allergist is warranted when there are concerns for immediate hypersensitivity.

The second type of food allergy testing is atopy patch testing (APT), which is used to assess the presence of non-IgE, cell-mediated food reactions. The histologic recrudescence of EoE after food reintroduction is relatively rapid, within 3–7 days.^{15,22} This time course supports a delayed-type hypersensitivity/cell-mediated mechanism. In contrast, there is no clinical evidence for reactions that are as rapid as those seen in subjects with food-induced anaphylaxis, that is, within minutes of food consumption, or that food impactions are due to sudden esophageal spasm caused by allergen exposure. APT is the most studied delayed allergy testing. The most rigorously investigated APT has been in the context of chemical and environmental contact dermatitis. In this context, both the specific chemical components and the best vehicle for solubilizing the chemical have been standardized. Results of food APT have been most closely evaluated in eczema.^{31–34} APT is done by placing fresh or rehydrated foods in metal Finn chambers, applying the chambers to the back for 48 hours, and reading the results at 72 hours by using European guidelines for the analysis of food patch testing.³⁵ For food APT in EoE, there have been no studies that have incorporated skin

biopsies to verify the presence of an immunologic infiltrate at the cutaneous site of a positive patch test.

Food Allergy Testing in Eosinophilic Esophagitis

Both cell-mediated and IgE-mediated mechanisms may be at work in the EoE esophagus. Immunologic class switch machinery is present at elevated levels in the EoE esophagus as are B cells, IgE/IgE receptor-positive cells, and ILs such as IL-13 that promote class switch to IgE.^{3,36,37} As such, there is a precedent for in situ esophageal-specific IgE production. Animal models of allergen-induced experimental EoE show a dependence on T cells, recombination, and basophils but not on B cells or mast cells for disease induction.^{38,39} In addition, animal models deficient in IgE have EoE induction, suggesting that IgE plays a role in sustaining or exacerbating but not in inciting EoE.^{38,39} Interestingly, there have been reports of EoE onset during oral desensitization trials for egg and milk.^{40,41} This clearly suggests that the mechanism of food allergy in EoE is not through IgE but, instead, through a cellular process.

The current data for allergy testing to elucidate food triggers in EoE support a number of conclusions. First, allergy testing for foods may be more useful in the pediatric than the adult population. In this context, it is important to keep the natural history of the atopic march in mind. Young children tend to have food sensitization and allergic responses, whereas older children and adults have aeroallergen allergies. Second, the negative predictive values for foods generally tend to be superior to the positive predictive values. If SPT is negative for a food allergen, there is a greater than 90% chance that the patient will not have an IgE-mediated reaction. An exception to the negative predictive value of food testing in EoE is milk.²¹ Third, the presence of food-specific IgE can be due to cross-reactivity with environmental allergens. For example, a patient may have wheat-specific IgE that is due to a grass allergy. Fourth, the current data do not support a role for serum IgE-based dietary elimination and also do not support the use of serum food allergy panels. Last, although positive SPT and/or APT to foods may reveal a food EoE trigger, the testing does not provide an alternative to endoscopic and biopsy evaluation after food elimination and reintroduction (Figure 1).

Generally, EoE subjects are highly atopic and tend to have polysensitization to both food and aeroallergens, with children having more food sensitization and adults having more aeroallergen sensitization, consistent with the natural history of allergy. Both SPT and APT in EoE have been more rigorously studied in the pediatric population. Currently, IgE food testing has been most rigorously studied via SPT. The exact extent that sensitization reflects clinically relevant EoE food triggers continues to be investigated; the current data are summarized in this review. However, on the basis of the

current observations and our understanding of EoE disease mechanisms, isolated IgE testing via SPT or serum is very unlikely to provide meaningful data for generating a foundation for elimination diets.

Overall, 77% of children have at least 1 positive SPT to foods, and up to 50% of adults have positive testing to foods.^{21,42} In adult patients with EoE, peanut, egg, and soy are most commonly positive on IgE testing.⁴³ A recent study of adult EoE patients in Spain showed that 45% (total N = 22) have no positive foods by SPT by using food extracts, whereas 27% had no food positives by fresh food SPT, suggesting that fresh foods may be more sensitive for detecting mast cell-bound food-specific IgE.⁴⁴ Overall, legumes were the most common positive foods identified by either commercial or fresh food extract.⁴⁴ It is common that serum-specific IgE to food is detected in EoE patients, but there is a paucity of data on the utility of serum IgE for guiding the design of elimination diets.¹ One pediatric study demonstrated that serum IgE was more sensitive than SPT for finding food-specific IgE but did not use serum data for dietary intervention.⁴⁵ It is important to note that among pediatric EoE subjects, there are higher rates of immediate food hypersensitivity reactions (urticaria, anaphylaxis) than in the general population (15%–24% in EoE as compared with rates of 3.9% in the general population), with peanuts, eggs, and milk being the most common triggers of anaphylaxis.^{1,21,30,46} As such, the presence/level of food IgE may predict a potential for anaphylaxis if the food is not being consumed regularly.

Current data, largely from the Children's Hospital of Philadelphia, have built predictive values for SPT, APT, and combined SPT and APT in EoE.²¹ Similar to what is seen in IgE-mediated food allergy, the negative predictive value of food allergy SPT exceeds the positive predictive value. Whereas positive predictive values varied from 26%–96% depending on the food (average of 47%), the negative predictive value was >90% for all food, with the exception of egg, wheat, and soy (which ranged from 79%–90%) and milk (30%).²¹ APT predictive values followed a similar trend, with negative predictive values averaging 90% except for milk (31%) and positive predictive values averaging 44%. Combining SPT and APT for building an elimination diet increased the negative predictive value so that all foods had negative predictive values equal to or in excess of 93% except for milk (44%) and wheat (88%). However, the positive predictive values were not greatly increased (average of 44%).²¹ In a study from a second center, the negative predictive values for milk, egg, and wheat were each slightly lower (milk 40%, egg 56%, and wheat 67%).¹⁸ Sensitivity and specificity were also increased by using the combination of prick and patch tests, with sensitivity rates of 65%–95% (with the exception of milk and pork, which were in the 50% range) and specificity rates of 78%–90% (inclusive for all foods) (Table 1).²¹

Because of these data, the issue remains whether food allergy testing provides a useful tool in EoE. The

pediatric data from 2 separate centers show that this may be the case. One study demonstrated that either empiric food elimination of milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish or an APT + SPT directed elimination diet had equivalent response rates of 53%.²¹ Because of the poor predictive values of milk testing, the empiric elimination of milk along with a targeted, testing-based diet resulted in a 77% histologic response rate in children with EoE, a rate higher than that seen with empiric or targeted elimination alone.²¹ Children who used a targeted diet based on testing had to avoid fewer foods (average of 3 based on SPT and 2.7 on APT) than those on empiric elimination (8 food groups with multiple foods in the tree nut, shellfish, and fish groups).²¹ In a second study, testing-based diets resulted in a 65% response rate in children (Table 1).¹⁸

Both of the pediatric studies included large cohorts of 319 and 98 subjects who were systematically tested for foods with repeat endoscopy and biopsy to assess histologic response after single food reintroduction. This type of large cohort data does not currently exist for the adult population, but smaller studies have not demonstrated success rates that mirror the pediatric data. In a group of 15 adult subjects treated prospectively with SPT-based and APT-based elimination diets, 4 (26%) and 1 (6.7%), respectively, achieved complete and partial histologic resolution.⁴⁴ In a study of 30 adult subjects treated with the empiric 6-food elimination diet, SPT alone would have predicted only 13% of the triggering food allergens.¹⁵ APT was not performed in this study. In addition, a recent retrospective case review showed that in 61 Canadian children, only 14% had positive APT.⁴⁷ The reason for the differences between the results at these centers is not clear but could include differences in age, genetics, and geography, all of which could affect EoE phenotype.

Future Diagnostic Tests for Food Allergies

Currently, the best approach to testing for food allergens that underlie the clinicopathologic features of EoE is not certain. Although IgE testing is standardized and validated in immediate hypersensitivity reactions, the role of IgE in largely cell-mediated disorders like EoE is questionable. It is certainly possible that local IgE production is not reflected in the peripheral serum or in the cutaneous mast cell population. In such a scenario, SPT and serum IgE would not accurately reflect EoE food triggers.

There are a number of future diagnostic tools for food allergies that have been primarily developed to assess for immediate hypersensitivity. To date, none have been systematically studied to identify food allergens in EoE. Peptide microarrays gauge the repertoire of IgE in patient serum and are limited to linear as opposed to conformational epitopes. Component-resolved diagnostic

testing assesses which particular epitopes within a food antigen are recognized by patient serum. These can be used in the context of food-pollen syndrome in which a local immune mucosal response occurs to a food because of its botanical cross-reactivity with pollen and can help to predict the severity of an IgE-mediated response to food.^{48,49} Last, basophil release assays and analysis of activated basophils in the periphery by using basophil activation markers such as CD63 and CD203c may be of use.^{50,51} One study to date has found an increased number of IL-33 receptor-positive basophils in the periphery of pediatric EoE subjects.⁵² Last, the numbers of peripheral eosinophils can correlate with the numbers of tissue eosinophils.⁵³ As such, serum eosinophil markers such as eosinophil peroxidase may function as markers of cellular allergy in EoE.⁵⁴

One of the most intriguing findings in eosinophilic gastroenteritis patients is that food-specific, CD4-positive, IL-5-producing T cells can be found in the peripheral blood. By contrast, IL-4-producing food-specific CD4+ T cells are found in subjects with immediate hypersensitivity.⁵⁵ IL-5-producing T cells require longer culture times to develop in vitro, and the production of IL-5 is dependent on chromatin remodeling.⁵⁶ Currently, it is not clear whether these IL-5-positive, CD4+ T cells exist in the esophagus as well as the periphery, but it will be intriguing to learn whether assays for peripheral food-specific T cells can function as markers for EoE food triggers.

Clinical Recommendations and Conclusions

In conclusion, the role of food allergy testing in EoE subjects continues to require more investigation. Current data in children show that it is reasonable to use an SPT-based and APT-based strategy to build an elimination diet (Figure 1, Table 1). However, there is a paucity of data to support the use of such a strategy in adult subjects. Generally, targeted testing-based diets will have almost equivalent success rates as empiric food elimination (6-food elimination diet) but may require elimination of fewer foods. It is possible that the foods eliminated by using testing-based diets will leave food in the diet that the child prefers, an issue that plays in to adequate weight gain in pediatric patients. There is a paucity of data to support the use of serum food-specific IgE for building elimination diets in children or adults. Serum IgE food-specific IgE panels should not be used for EoE. In addition, other Ig testing to foods, such as IgG, is not indicated because the presence of IgG to a food only reflects that this food has been ingested in the person's lifetime and has been recognized by the immune system and not that the food functions as an antigenic trigger. Indeed, certain types of IgG, specifically IgG4, are associated with tolerance rather than allergy. Importantly, positive food SPT or APT in EoE suggests

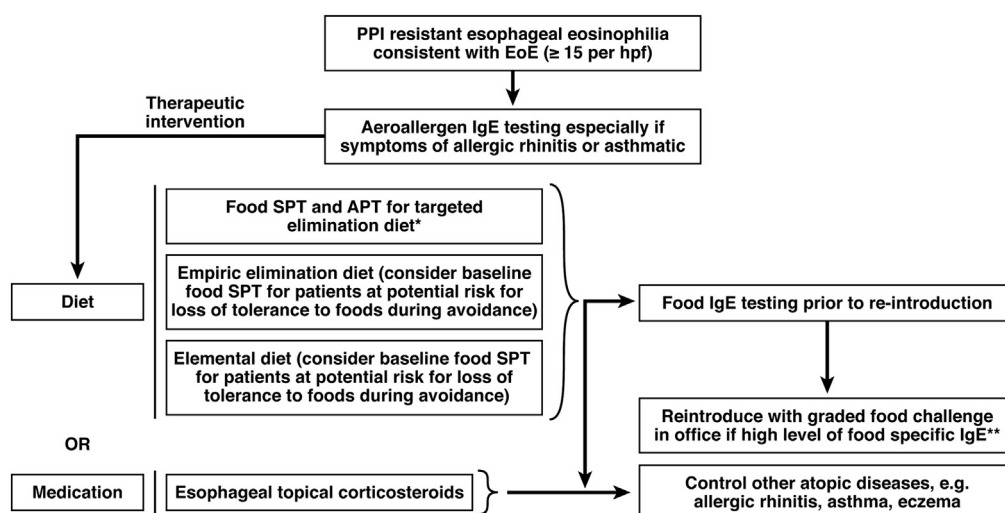


Figure 1. Testing algorithm. *Data supportive in pediatrics. **Must have appropriate staff, medications, and equipment in place to deal with anaphylactic reaction; allergist's office is recommended. hpf, high-power field.

the specific food trigger but does not substitute for biopsy evaluation after food elimination and reintroduction to verify the inciting food.

Food testing should be geared toward those foods that trigger EoE more commonly and those foods that are consumed regularly in the diet. Testing to foods, especially IgE testing, leads to recognition of food sensitizations that may not be clinically relevant and that, on elimination, could result in the loss of tolerance to the foods. Although not published for EoE subjects, personal experience and expert opinion support the possibility for loss of tolerance after a period of food avoidance in a sensitized subject. Loss of tolerance to peanuts during avoidance has been clearly documented in the context of immediate food hypersensitivity.²⁹ As such, food elimination must be applied judiciously and with clear explanation of potential risks and benefits to the patient. If a food with a large SPT or high serum level is removed from the diet, an allergist will often consider prescribing injectable epinephrine in case of accidental ingestion in the context of loss of tolerance. If foods are eliminated either empirically or by using a testing-based strategy,

repeat food testing for immediate hypersensitivity reactions via SPT or serum IgE is warranted before food reintroduction. This will facilitate decisions of whether the food should be reintroduced in a controlled setting such as with a food challenge in the allergist's office. In the case of a large SPT reaction (eg, a wheal larger than 8 mm that can be >95% predictive of a clinical immediate hypersensitivity reaction) or a high level of serum-specific IgE (the predictive level will depend on the food and the age of the subject), it would be clinically justified to reintroduce the food in an allergist's office. An allergist's office is recommended because anaphylactic reactions are expected during standard clinical care because of the use of interventions such as allergen immunotherapy (Figure 1). As such, the staff is appropriately trained to recognize and treat anaphylaxis. In addition, the necessary medications (epinephrine, antihistamines, prednisone, oxygen, intravenous and intubation equipment) are readily available. Reintroduction can be done as an open food challenge where escalating doses of the food antigen are introduced in a controlled setting by using defined oral challenge guidelines.⁵⁷

Table 1. Current Literature for Food Testing in EoE

Type of test	Mechanism	Utility in EoE	References
SPT	Presence and function of specific IgE	Can be helpful to assess triggering foods in pediatric EoE when used in combination with APT Of importance when assessing potential for immediate hypersensitivity after food elimination Not of use as an isolated test for food triggers in EoE May not be of significant utility in adult EoE	Spergel et al, ²¹ 2012 Henderson et al, ¹⁸ 2012 Boyce et al, ²⁸ 2010 Liacouras et al, ¹ 2011 Spergel et al, ²¹ 2012 Gonsalves et al, ¹⁵ 2012
Food-specific serum IgE	Presence and level of specific IgE	Often detectable but not currently recommended for identifying food triggers in pediatric or adult EoE Of importance when assessing potential for immediate hypersensitivity after food elimination	Multiple showing detectable levels, summarized in Liacouras et al, ¹ 2011 Liacouras et al, ¹ 2011
APT	Delayed hypersensitivity ^a	Can be helpful to assess triggering foods in pediatric EoE when used in combination with SPT Unclear utility in adult EoE	Spergel et al, ²¹ 2012 Henderson et al, ¹⁸ 2012 Molina-Infante et al, ⁴⁴ 2012

^aNo current data showing that there is a cutaneous immunologic infiltrate at the site of the patch test in EoE subjects.

As a new disease, the natural history of EoE is unclear. Current data suggest that the disease is chronic, and that >90% of pediatric subjects have disease recrudescence with food reintroduction.⁵⁸ In addition, only 8% of children will become tolerant to all foods that cause their EoE.⁵⁸ This is in stark contrast to the natural history of pediatric immediate hypersensitivity to most foods, in which case, 80% of children will eventually outgrow an allergy to milk, egg, wheat, and/or soy.²⁸ It seems that EoE is a food-driven immunologic process that remains intact for many years in most people. Whether the food or aeroallergen sensitization patterns associate with EoE natural history is unclear. However, studies in other allergic diseases such as asthma suggest that this is a possibility. For example, subjects with indoor allergen sensitization tend to have persistent or recurrent asthma.⁵⁹

It is likely that there is interplay between the various atopic diatheses in a single individual. As such, as a part of EoE management, it is important to assess and manage the multiple allergic disorders in a single individual (Figure 1). A classic asthma study demonstrated that when subjects with both house dust mite allergy and steroid-dependent asthma were placed in a hospital setting with strict dust mite avoidance, there was decreased medication use and increased asthma control, thereby illustrating the powerful impact of antigen avoidance on asthma control.⁶⁰ It is also common that atopic diatheses flare simultaneously. For example, a viral infection can lead to simultaneous asthma and eczema exacerbations. Whether this occurs in EoE remains to be assessed. There is ample evidence from animal models that aeroallergens (dust mite, cockroach, *Aspergillus* species) can induce EoE. Pollens can cause both esophageal eosinophil accumulation and EoE.^{61–63} More recent evidence supports that aeroallergen immunotherapy may be a management strategy in EoE.⁶⁴ Because both the human and animal models evidence that aeroallergens can trigger EoE, the season of an EoE exacerbation should be taken into consideration.^{62,65} Because of these scenarios, it is important to assess and manage all atopic diatheses in addition to food allergies in a subject with EoE.

In conclusion, there is clearly a role for an immunologic food reaction in EoE adults and children. Although the perfect test to determine food antigen triggers in EoE is still pending, because of its allergic nature, the increased rates of immediate hypersensitivity, potential complications such as loss of tolerance during food avoidance, and the multiple concurrent allergic diatheses that occur in EoE subjects, this is a disease best served by an integrated clinical approach that involves gastroenterologists, allergists, and pathologists.

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Conflicts of interest

The author discloses no conflicts.

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