

A review of the evidence linking eosinophilic esophagitis and food allergy

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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic inflammation of the esophagus that has been considered an allergic phenomenon based on its similarities to other allergic conditions. More specifically, EoE has been considered a form of food allergy because of patient sensitizations to foods and improvements in symptoms and inflammation after food eliminations. This article presents the currently available evidence regarding the classification of EoE as an allergic condition, the involvement of foods in disease pathogenesis, and the value of different types of allergy testing and elimination diets in management of EoE. Using the search engines PubMed and Ovid, English literature in the past 10 years was reviewed with the use of the following key words: eosinophilic esophagitis, EoE epidemiology, EoE pathophysiology, food allergy, eosinophils, skin-prick testing, atopy patch testing, elemental diet, test directed elimination diet, six food elimination diet. Studies of EoE epidemiology and pathophysiology support the link between EoE and allergy in general, and studies of food allergy testing and elimination diets have supported a link between EoE and food allergy. Although food elimination diets cause resolution of symptoms and pathology in pediatric EoE, the results of testing and diet elimination studies are not as clear in adults, and aeroallergen sensitizations may play a larger role in adult EoE pathophysiology. Although several studies in children and adults support considering EoE a form of food allergy, the usefulness of skin-prick testing and atopy patch testing for food allergies and the optimal elimination diet for disease management are still uncertain.

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Eosinophilic esophagitis (EoE) is a chronic clinico-pathological diagnosis affecting children and adults. Clinically, it is characterized by symptoms of esophageal dysfunction. The most common symptoms in adults are dysphagia, food impaction, chest pain, vomiting, and upper abdominal pain. Children present with a variety of symptoms including vomiting, failure to thrive, heartburn, dysphagia, food refusal, and abdominal pain.^{1,2} Endoscopy in patients with EoE grossly may show esophageal rings, whitish exudates, longitudinal furrows, edema, diffuse esophageal narrowing, or esophageal lacerations during passage of the endoscope.^{3–9} Surface layering of eosinophils, eosinophilic microabscesses, basal cell hyperplasia, dilated intracellular spaces, and fibrosis in the lamina propria are common pathological characteristics.^{10–15} The diagnosis of EoE requires clinical symptoms as well as 15 or more eosinophils per high-power field on esophageal biopsy after 2 months of treatment with a proton pump inhibitor.¹⁶

EoE has been considered an allergic condition because of its similarity in epidemiology to other atopic disorders,^{17–25} its coexistence with other allergic diseases,^{25–30} the presence of antigenic sensitizations in EoE patients,^{29,31–38} and its association with the same T-helper 2 (Th2) cells and mediators involved in the pathogenesis of atopic disorders.^{39–53} In particular, EoE has been considered a form of food allergy because of food sensitizations detected in EoE patients and improvement in symptoms and inflammation after implementation of various elimination diets.^{3,33–37,54–64} A landmark study by Kelly *et al.* in 1995 highlighted this link between food allergy and EoE by showing that children put on a trial of elemental formula all experienced resolution or improvement in symptoms, as well as significant decreases in esophageal eosinophils.⁵⁹ This article reviews current evidence related to the allergic classification of EoE and the role of foods in EoE pathogenesis, testing, and treatment.

EPIDEMIOLOGICAL EVIDENCE

Many parallels exist between the epidemiology of EoE and other atopic disorders. EoE is seen more commonly in male subjects and, like other allergic diseases, it is seen more frequently in Westernized countries and in urban areas of the United States.^{17–21,25} Also, the incidence of EoE has increased significantly, which correlates with the increasing rates of other atopic diseases.^{22–25} Studies have found the incidence of EoE to be approaching or exceeding that of inflammatory

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Table 1 Summary of research on the epidemiology of EoE

Study Title	Author	Patients	Findings
Eosinophilic esophagitis	Noel <i>et al.</i> ²²	315 Pediatric	Increasing incidence, strong familial disease clustering, 71% male predominance
Fourteen years of eosinophilic esophagitis: Clinical features and prognosis	Spergel <i>et al.</i> ²⁶	620 Pediatric	Increasing annual incidence, 3:1 male/female predominance, Caucasian predominance (90%), 2/3 with other allergic diseases
A case-control study of sociodemographic and geographic characteristics of 335 children with eosinophilic esophagitis	Franciosi <i>et al.</i> ¹⁷	335 Pediatric	Predominance of male gender and Caucasian race
Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States	Spergel <i>et al.</i> ²¹	N/A (1836 physicians surveyed)	EoE diagnosed more often in northeastern states and urban areas within the United States
Atopic characteristics of adult patients with eosinophilic esophagitis	Roy-Ghanta <i>et al.</i> ²⁷	23 Adult	High degree of atopy, 78% of patients with other atopic diseases
Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: A prospective study	Veerappan <i>et al.</i> ³⁰	400 Adult	Patients significantly more likely to be male and have a history of asthma
Familial dysphagia and eosinophilia	Zink <i>et al.</i> ⁶⁶	17 Adult and pediatric	Presentation of 17 patients from 7 families with dysphagia and eosinophilia
Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota	Prasad <i>et al.</i> ²⁴	78 Adult and pediatric	Significant increases in the incidence of EoE

EoE = eosinophilic esophagitis.

bowel disease, while the prevalence is assessed to be about that of Crohn's disease, between 40 and 55 per 100,000 individuals.^{24,25,65} Further evidence for the classification of EoE as a form of allergy comes from studies showing that the majority of EoE patients have coexisting atopic conditions.^{25-28,30} More specifically, studies have shown that EoE patients have higher rates of food sensitizations, food allergy, and anaphylaxis.²⁹ There is also an increased rate of family history of atopy in patients with EoE, and the disease tends to occur with familial clustering.^{22,23,66,67} See Table 1 for a summary of available research on EoE epidemiology.

PATHOPHYSIOLOGICAL EVIDENCE

The eosinophilic response to environmental allergens in EoE is thought to be caused by the same sets of

cytokines, chemokines, and immune cells that are involved in the pathogenesis of allergic conditions. Studies have implicated inducers and mediators of the Th2-type immune response such as interleukins (ILs) IL-3, IL-4, IL-5, IL-13, eotaxin, signal transducer and activator of transcription 6 (STAT-6), granulocyte-monocyte colony-stimulating factor, tumor necrosis factor α , and mast cells.³⁹⁻⁵³ Many studies have also shown increased antigen-specific IgE and IgG1 antibodies in EoE; however, at least one study challenges the involvement of antibodies in pathogenesis by showing that esophageal eosinophil accumulation was prevented completely in T-cell-deficient mice, whereas B-cell-deficient mice developed unabated EoE in response to allergen exposure.⁵¹ Although the role of IgE remains unclear, pediatric and adult studies have

shown significant increases in mast cell gene expression in patients with EoE.^{49,53} Interestingly, in these studies the gene expression was significantly reduced by treatment. Others have suggested involvement of IL-15 and fibroblast growth factor 9, and there have been recent studies investigating defects in thymic stromal lymphopoietin as a possible genetic predisposition for EoE.^{68–71}

In particular, the chemokine eotaxin 3 and the classic Th2 cytokines IL-5 and IL-13 have been identified as critical mediators of eosinophilic inflammation in EoE.^{40–48} A review of EoE biomarkers noted eotaxin 3 and IL-13 to be the most promising ones with respect to sensitivity and degree of positive correlation to the disease process, and the potential of IL-5 was highlighted as well.⁷² Eotaxin 3 gene expression was shown to be significantly higher in EoE patients than in healthy individuals, and a single-nucleotide polymorphism in the human eotaxin 3 gene was associated with disease susceptibility.⁴¹ In studies of IL-5, peripheral T cells in EoE patients had increased intracellular IL-5, and IL-5 mRNA was increased in EoE tissue biopsy specimens.^{39,43} Mice genetically deficient in eotaxin, the eotaxin receptor, or IL-5 were all protected from experimental EoE.^{40,41,73} IL-13, an inducer of eotaxin, was identified as the cause of remodeling in EoE, which was independent of eosinophils and suppressed by IL-13R α 2.^{45,46} Intratracheal IL-13 in mice led to development of not only airway but also esophageal eosinophilia *via* an IL-5, eotaxin 1, and STAT6-dependent mechanism, implying a direct contact of allergen with the esophagus is not required for developing EoE.^{41,47} Finally, mice deficient in STAT-6, IL-13, and IL-4, while not completely protected, had lessened esophageal eosinophilia in response to experimental antigen exposure.⁷³ Altogether, these experiments suggest the eosinophilic inflammation seen in EoE is, as in food allergy, a result of external allergens and intrinsic Th2 mediators.

TESTING-BASED EVIDENCE

A growing number of studies regarding food sensitization in EoE patients have suggested that foods play an important role in EoE pathogenesis.^{33–38,29} A series of studies by Spergel *et al.* sought to determine the ability of skin-prick testing (SPT) and atopy patch testing (APT) to identify food triggers of EoE.^{33–37} In the most recent study, all 319 children with EoE tested positive to one or more foods (average of 3.2 foods on SPT and 2.7 foods on APT).³³ A different investigator found that *in vitro* IgE testing detected even more food sensitizations in EoE patients than SPT.³⁸ To determine the significance of identified SPT and APT food sensitizations, testing results were compared with true EoE triggers as identified by histological resolution after

food elimination and histological relapse after food reintroduction.³³ Milk, egg, wheat, and soy were the most commonly identified definitive triggers of EoE.

Comparing test results with true triggers allowed for determination of negative predictive values (NPVs) and positive predictive values (PPVs) of SPT and APT.³³ The NPVs of SPT followed by APT were generally high except for milk, *i.e.*, foods that tested negative were truly unlikely to be EoE triggers (>96% for peanut, beef, corn, chicken, potato, and pork; 93% for egg and soy; 88% for wheat; and 44% for milk). However, the PPVs were generally low except for milk, *i.e.*, foods that tested positive were not necessarily true triggers of EoE (range, 17–42% except for egg at 61% and milk at 82%). SPT and APT to foods appear to be less reliable in adult EoE management.^{29,54,74} Only 13% of causal foods were identified by SPT in one adult study.⁵⁴

Several investigations have suggested that EoE can not be considered solely a form of food allergy, because aeroallergens may play a role in EoE pathogenesis as well.^{31,32,75–77} Support for this comes from studies that showed a seasonal variation in the number of EoE diagnoses, which correlated with pollen counts.^{75–77} One study that analyzed food and aeroallergen sensitizations in children with EoE revealed that younger patients with EoE showed more IgE and patch sensitization to foods, and older children showed greater IgE sensitization to inhalant allergens.²⁹ Another study of 19 children and 25 adults with EoE found that children are more likely to have evidence of food sensitivities than adults, but in that study the occurrence of aeroallergen sensitivity was similar in both groups.⁷⁸

Another group of studies have indicated that adults with EoE are often sensitized to cross-reactive plant allergens, such as profilins and birch pollen.^{79–81} The authors hypothesize the cross-reactivity between these plant antigens and foods may cause the esophageal inflammation of EoE. One small study hypothesized patient sensitizations to wheat and rye may be caused by cross-reactivity with grass pollen; however, eliminating wheat and rye did not decrease disease activity.⁸² Thus, while the testing-based evidence does support the consideration of EoE being caused by aeroallergen/cross-reactive plant antigen sensitizations, especially in older children and adults, further evidence is needed to establish causality between these sensitizations and the inflammation of EoE.

THERAPEUTIC EVIDENCE

The strongest evidence for the role of foods in EoE pathogenesis is the improvement in symptoms and inflammation seen after dietary modifications.^{3,33,37,54–64} Spergel *et al.* showed that an elimination diet based on the results of SPT and APT led to histological resolu-

tion in 77% of patients in an initial study.³⁷ In a subsequent larger study by Spergel *et al.*, testing-directed elimination diet led to histological resolution in only 53% of patients; however, removal of foods identified by SPT and APT plus empiric milk elimination (given the low NPV of milk testing) led to resolution in 77% of patients.³³ The histological resolution rate was also 53% in children treated with a six-food elimination diet (SFED), which involves elimination of milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish. The advantage of the allergy-specific elimination diet was that on average only six foods were removed compared with the eight foods eliminated in the SFED. Kagalwalla *et al.* showed a 74% histological response and 97% symptom response to an SFED in children.⁶³ Henderson *et al.* observed histological remission rates of 65 and 81% for testing-directed elimination diet and SFED, respectively.⁶² Another study showed remission in 65% of children using empiric elimination of cow's milk alone.⁶⁰

It has been proposed that strict use of amino acid-based formula (an elemental diet) is the most effective modality of treatment in EoE, with a general efficacy rate exceeding 90%.^{3,26,58,59,62,63} In terms of pediatric studies, in 1995 Kelly *et al.* showed symptom resolution (80%) or improvement (20%) in 10 children treated with a 6-week trial of elemental formula.⁵⁹ Additionally, the study showed a significant decrease in esophageal eosinophils after the trial. Subsequently, Henderson *et al.* revealed a histological resolution rate of 98% using an elemental diet.⁶² Markowitz *et al.* similarly showed significant symptom improvement and decreased esophageal eosinophils with an elemental diet,⁵⁸ and Kagalwalla *et al.* showed even greater improvements in symptoms and histology using an elemental diet than the already significant improvement their group established with SFED.⁶³

There have been fewer studies of dietary therapy in the management of EoE in adults, and, overall, the results have been less successful. In a study by Molina-Infante *et al.* only one-third of adult patients responded to a SPT- and APT-directed elimination diet.³⁶ This is consistent with a reported loss of response to testing-directed elimination diets in children as they become >14 years of age.^{37,74} Food allergen SPT only detected true EoE triggers in 13% of adults in one study, providing a possible explanation for why adults do not respond as well to testing-directed elimination diets as children.⁵⁴ A study of SFED in adults had better results, with 73% of patients showing improvements in symptoms and eosinophilic infiltration.⁵⁵ In another study of SFED, 50% of adults with EoE achieved histological remission, 70% had posttherapy peak eosinophil counts of ≤ 10 eosinophils per high-power field, and 94% had decreases in symptom scores.⁵⁴ Elemental diet was studied in 18 adult EoE patients and, although

the diet resulted in a 73% histological response rate, there was no improvement in symptoms and adherence was poor.⁵⁷ See Table 2 for a summary of the available adult and pediatric research regarding treatment of EoE with diet modification.

DISCUSSION

The findings from epidemiological and pathophysiological studies are strong to consider EoE an allergic condition. Epidemiologically, many studies have shown similarities between atopic disorders and EoE, including a rising incidence in Westernized countries, higher prevalence in urban areas of the United States, coexistence with other allergic conditions, and familial clustering of disease.^{17–28,30,66,67} Pathophysiologically, studies have indicated that EoE is associated with the same Th2 immune mediators involved in allergic conditions.^{39–52,68,72,73} The presence of antigen-specific antibodies has also been shown; however, there is insufficient evidence regarding the role of these antibodies in EoE pathogenesis. At least one study has shown that as opposed to T cells, such antibodies are not necessary for development of disease.⁵¹ Additional pathophysiological studies are needed to clarify the usefulness of IgE testing in EoE management.

In the pediatric population, the strongest evidence for considering EoE a form of food allergy has come from many dietary trials using amino acid-based formulas. Elemental diets consistently led to improvement, generally resolving the inflammation and symptoms of EoE in >90% of children.^{3,26,58,59,62,63} Several pediatric studies of an SFED showed lesser but still significant histological improvement (53, 74, and 81% of patients), and milk elimination alone led to a 65% resolution rate.^{33,60,62,63} There is insufficient data regarding the use of an elemental diet in adult patients. To our knowledge, there has only been one such study ($n = 18$), which led to a 73% histological resolution in the context of poor overall compliance.⁵⁷ Two larger studies of an SFED provided stronger evidence for the role of foods in adult EoE, because the diet resulted in histological resolution in 70 and 73% of adults.^{54,55}

Although the aforementioned studies and, particularly, the ones in children, support that EoE is a form of food allergy, the role of allergy testing in guiding dietary therapy remains a major unresolved issue. Studies have consistently shown that pediatric patients have food sensitizations identified by SPT and APT; however, Spergel *et al.* showed that the PPVs of such testing are generally low, with milk testing being the exception.³³ The generally high NPVs of SPT and APT support a more important role of testing in ruling out dietary causes of disease. The three pediatric studies of testing-directed elimination diets discussed in this article led to histological resolution in 53, 65, and 74% of

Table 2 Summary of research on dietary treatments of EoE

Study Title	Author	Patients	Findings
Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula	Kelly <i>et al.</i> ⁵⁹	10 Pediatric	Elemental diet resolved symptoms in 80%, with improvement in 100%
Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents	Markowitz <i>et al.</i> ⁵⁸	51 Pediatric	Elemental diet improved both symptoms and histology; average time to clinical improvement 8.5 days
Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests	Spergel <i>et al.</i> ³⁷	146 Pediatric	SPT + APT-directed elimination diet improved symptoms and inflammation in 77%
Eosinophilic esophagitis: A 10-year experience in 381 children	Liacouras <i>et al.</i> ³	132 and 172 Pediatric	SPT + APT-directed elimination or elemental diet improved symptoms/histology in 57 and 97%, respectively
Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis	Kagalwalla <i>et al.</i> ⁶³	35 and 25 Pediatric	SFED or elemental diet improved inflammation in 74 and 88%, respectively
Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis	Henderson <i>et al.</i> ⁶²	49, 26, and 23 Pediatric	Remission occurred in 96, 81, and 65% on elemental diet, SFED, and SPT-directed diet, respectively
Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet	Spergel <i>et al.</i> ³³	319 Pediatric	SFED and SPT + APT-directed diet led to resolution in 53%; testing-directed elimination plus empiric milk elimination led to resolution in 77%
Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: A historical cohort	Lieberman <i>et al.</i> ⁶¹	17 Pediatric	Elemental diet or SFED + testing-directed diet reversed fibrosis in 18% of patients
Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis	Kagalwalla <i>et al.</i> ⁶⁰	17 Pediatric	Empiric cow's milk elimination alone induced remission in 65%
Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors	Gonsalves <i>et al.</i> ⁵⁴	50 Adult	SFED led to histological resolution in 70%, and decreased symptom scores in 94% of patients
Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis	Molina-Infante <i>et al.</i> ⁷⁴	15 Adult	Only 26% of patients achieved remission using a SPT + APT-directed elimination diet
Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: A prospective study on the food cause of the disease	Lucendo <i>et al.</i> ⁵⁵	77 Adult	SFED improved histology in 73%, IgE levels and SPT had no concordance with disease on food reintroductions
Elemental diet induces histologic response in adult eosinophilic esophagitis	Peterson <i>et al.</i> ⁵⁷	18 Adult	Elemental diet resolved histology in 72%, but provided no symptomatic relief

EoE = eosinophilic esophagitis; SPT = skin prick testing; APT = atopy patch testing; SFED = six-food elimination diet.

children, with the resolution rate in the largest study increasing from 53 to 77% after adding empiric milk elimination.^{33,37,62} Testing-directed elimination diets were on average less restrictive than the SFED, while leading to similar histological results. Of course, the benefit of less restriction must be weighed against the cost and burden of testing.

There is less evidence to support food allergy testing and testing-directed elimination diets in adults with EoE. Older patients generally had the same or more aeroallergen sensitizations and had less food sensitizations than younger patients.^{29,78} As opposed to the work of Spergel *et al.* showing high NPVs of SPT and APT in children, in one study the majority of adults with negative SPT went on to have definitive food triggers identified by endoscopy. Notably, the study did not include APT of the adult patients.⁵⁴ To our knowledge, there has only been one adult study ($n = 15$) that eliminated foods based on the results of both SPT and APT, and only one-third of those patients showed histological improvement.⁷⁴ Taken altogether, these studies imply that either different factors aside from foods (*e.g.*, aeroallergen/cross-reactive plant allergen sensitizations) may be playing a role in the pathogenesis of this disease in older children and adults, or our current diagnostic tests are not adequate for identifying food sensitivities in this population.

CONCLUSION

Overall, this article presents compelling epidemiological, pathophysiological, testing-based, and therapeutic data that EoE is an allergic condition and a form of food allergy; however, many questions and issues remain. Investigations in the pediatric population are needed to confirm the PPVs and NPVs of food allergy testing, as are further studies of testing-directed elimination diets in combination with empiric milk elimination. Initial investigations of these topics are needed in adult EoE patients to help establish testing and treatment recommendations. In particular, given the disputed role of antibodies in EoE pathogenesis, additional studies designed to highlight any differences in the effectiveness of SPT versus APT in detecting EoE triggers are needed to guide future EoE management. Finally, this article provides preliminary evidence to suggest that food allergens are not the sole cause of EoE. Given aeroallergen and cross-reactive plant allergen sensitizations in EoE patients, seasonal variations in EoE diagnoses, and incomplete resolution of EoE even when treated with elemental formula,^{75–77} the role of nonfood allergen sensitizations in EoE pathogenesis is another area where further investigation is needed.

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