

Allergic components of eosinophilic esophagitis



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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List of Design Committee Members: Jonathan Spergel, MD, PhD, and Seema S. Aceves, MD, PhD (authors); Zuhair K. Ballas, MD (editor)

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: The authors have declared that they have no relevant conflicts of interest. Z. K. Ballas (editor) disclosed no relevant financial relationships.

Activity Objectives:

1. To understand the pathogenesis of eosinophilic esophagitis (EoE).
2. To know the common triggers of EoE.
3. To become familiar with testing methods and their limitations for identifying triggers in patients with EoE.

Recognition of Commercial Support: This CME activity has not received external commercial support.

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Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: The exam authors disclosed no relevant financial relationships.

Eosinophilic esophagitis (EoE) is a disorder of increasing prevalence worldwide, causing clinical symptoms of vomiting, failure to thrive, and dysphagia and complications of esophageal remodeling with strictures and food impactions. Molecular profiling demonstrates EoE to be an eosinophil-predominant disorder with a T_H2 cytokine profile reminiscent of other allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis. Environmental antigens in the form of foods and aeroallergens induce eosinophil, basophil, mast cell, and T-cell infiltration. Pathogenesis depends on local epithelial immune activation with production of thymic stromal lymphopoietin and eotaxin-3. Complications mirror asthmatic airway pathogenesis, with increases in subepithelial collagen deposition, angiogenesis, and smooth muscle hypertrophy. The removal of instigating antigens, especially foods, causes disease resolution in more than

50% of adults and children. The prevalence of concurrent atopic disorders in patients with EoE and the need to control antigen-specific T_H2 inflammation underscore the importance of testing for allergens and treating the entire atopic subject to control the potential interplay between organ-specific allergic responses. (J Allergy Clin Immunol 2018;142:1-8.)

Key words: Esophagitis, food allergy, allergic rhinitis, antigens, allergy testing

Eosinophilic esophagitis (EoE) was first demonstrated to exist as a disease entity in atopic male subjects in the late 1970s.^{1,2} Since then, prevalence rates in adults and children have increased significantly to as much as 1 in 1000.³ The concept of EoE as a food antigen-triggered disorder was based initially on the

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J.S. has received funds from the Stuart Starr Endowed Chair and the Children's Hospital Food Allergy Fund. Support was also provided from National Institutes of Health/ National Institute of Allergy and Infectious Diseases (NIAID) grants AI 092135 (to S.S.A.) and K24AI135034 (to S.S.A.). Both J.S. and S.S.A. have received funding from the Consortium for Gastrointestinal Eosinophilic Researchers (CEGIR). CEGIR (U54 AI117804) is part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), and is funded through collaboration

between NIAID, National Institute of Diabetes and Digestive and Kidney Diseases, and NCATS.

Received for publication January 23, 2018; revised May 11, 2018; accepted for publication May 11, 2018.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2018.05.001>

Abbreviations used

EoE: Eosinophilic esophagitis
 ISAC: Immuno Solid Phase Allergen Chip
 PPI: Proton-pump inhibitor
 PR-10: Pathogenesis-related class 10 protein
 SLIT: Sublingual immunotherapy
 TSLP: Thymic stromal lymphopoietin

observation of eosinophils characteristic of allergic diseases in combination with the presence of concurrent asthma in the first case reports. Further substantiation of the hypothesis came from the finding that in children, elemental formula, but not acid blockade with H₂ blockers, caused histologic EoE disease remission.⁴ Since that time, specific antigen elimination diets have demonstrated utility in US and European EoE populations.^{5,6} In addition, EoE onset during oral immunotherapy for foods and the sustained antigen sensitization to EoE-triggering foods, such as egg and milk, have underscored the importance of T cell-mediated hypersensitivity.^{7,8} Additional data have demonstrated that the presence of IgE sensitization to pollens and indoor aeroallergens can trigger EoE, affect therapeutic effectiveness, or both (Fig 1).^{9,10}

The pathogenesis of EoE aligns with other atopic disorders, such as asthma and eczema. Esophageal epithelial damage induced by acid and antigens invokes a T_H2 immune response with production of thymic stromal lymphopoietin (TSLP) and eotaxin-3, with subsequent influx of eosinophils, mucosal tryptase-positive mast cells and basophils, innate lymphoid cells, and adaptive B and T lymphocytes (see other reviews in this issue).^{11–14} Chronic, unbridled T_H2 inflammation causes epithelial and subepithelial remodeling, with loss of barrier function, fibrosis, angiogenesis, and smooth muscle hypertrophy.^{15,16} Together, these molecular events cause complications of esophageal rigidity and dysmotility, with clinical symptoms of vomiting, dysphagia, food impactions, and strictures. Whether antigen avoidance of food allergens or aeroallergens can control the natural history to strictures is not currently clear, but other interventions, such as topical corticosteroids, can decrease the rate of complications.^{17–20}

Here we review the current understanding of the role of allergens in provoking a T_H2-mediated immune response in the esophagus. We further discuss the current state of allergy testing for patients with EoE, the importance of treating the whole atopic subject as opposed to utilizing an isolated EoE therapy in a patient with concurrent allergic diseases, and the future directions for elucidating the role of allergens in patients with EoE.

FOOD ANTIGENS

Food antigens have long been indicated as a trigger in patients with EoE. The first descriptions of food elimination to treat EoE by Kelly et al⁴ showed that complete removal of dietary antigens with an elemental formula led to resolution of symptoms and normalization of esophageal eosinophilia. Resolution of symptoms and eosinophils occur in both adults²¹ and children²² within 4 weeks of treatment with an elemental diet. The current data demonstrate that the rate of disease resolution with an elemental diet is greater than 90%, and the rate with empiric or

allergy testing can both reach nearly 80%, indicating that most EoE is due to food allergens.^{22,23}

The removal and subsequent addition of foods leading to EoE resolution and recurrence fulfills Koch's postulate that food antigens cause EoE.^{24–26} The penetration of antigens into the esophageal mucosa has been demonstrated recently for gliadin, supporting the potential for local antigen uptake, processing, and presentation in the esophagus.²⁷

Multiple studies have examined and tried to identify the most common foods that cause EoE. There appear to be some geographic and age differences. In US children milk, egg, and wheat are the most common, whereas in adults milk and wheat are the most common (Table 1).^{5,6,23,26,28–36} Soy and other legumes are allergens that are more common in Spain than in the United States.^{6,30,32} Interestingly, fish, tree nuts, and shellfish infrequently cause EoE, yet they are among the top 8 foods in most studies examining IgE food allergies.³⁷ Overall, in the various studies throughout the world, milk is the most common allergen causing disease in about two thirds of patients, followed by egg and wheat in another one fourth of patients. Although milk is the most common antigenic trigger for EoE, EoE is also triggered in many patients by other foods. About 30% to 50% have 1 food causing disease, followed by 30% having 2 and the remaining 30% having 3 or more foods causing EoE.^{5,6,23,31}

Testing modalities for EoE-triggering foods

Several investigators have examined testing methods for identifying food allergies in patients with EoE using either percutaneous skin testing^{23,31,38–41} or serum specific IgE measurement.^{42–45} Alternative methods for measuring food-specific IgE levels, including the basophil activation test and the Immuno Solid Phase Allergen Chip (ISAC) test, have been studied. Potential methods for testing non-IgE methods include IgG₄ or atopy patch testing. Retrospective studies of empiric food elimination that subsequently examined specific IgE have shown a varying range of success, ranging from 8% to 53%.

In general, specific IgE testing is better in children compared with adults. A few retrospective studies have compared an allergy testing–based diet with an empiric elimination diet.^{23,31} In adults specific IgE–based elimination diets showed resolution in 73% of patients compared with 53% for a 6-food elimination diet, a difference that was not statically significant.³³ A recent study documented the use of intraesophageal injection of food antigen that caused both an immediate and delayed reactions in 5 of 8 patients with EoE tested. However, none of the “positive” antigens were used in dietary management nor was the presence of IgE to these antigens verified.⁴⁶ The clear documentation of systemic reactions when food antigens are administered subcutaneously, the potential for anaphylaxis, even to aeroallergens on ingestion, and the local esophageal response of “complete luminal obstruction” underscore the importance of using caution when techniques, such as intraesophageal testing, are considered.

Studies have also examined the use of component testing with ISAC tests for serum IgE to specific allergen components.^{44,47,48} Erwin et al⁴⁴ found more positive components to milk (Bos d 4 or Bos d 5) compared with specific IgE or skin prick tests in their population, suggesting increased sensitivity of milk component testing. However, these proteins are minor allergen components of milk protein, were found at low serum levels, and did not

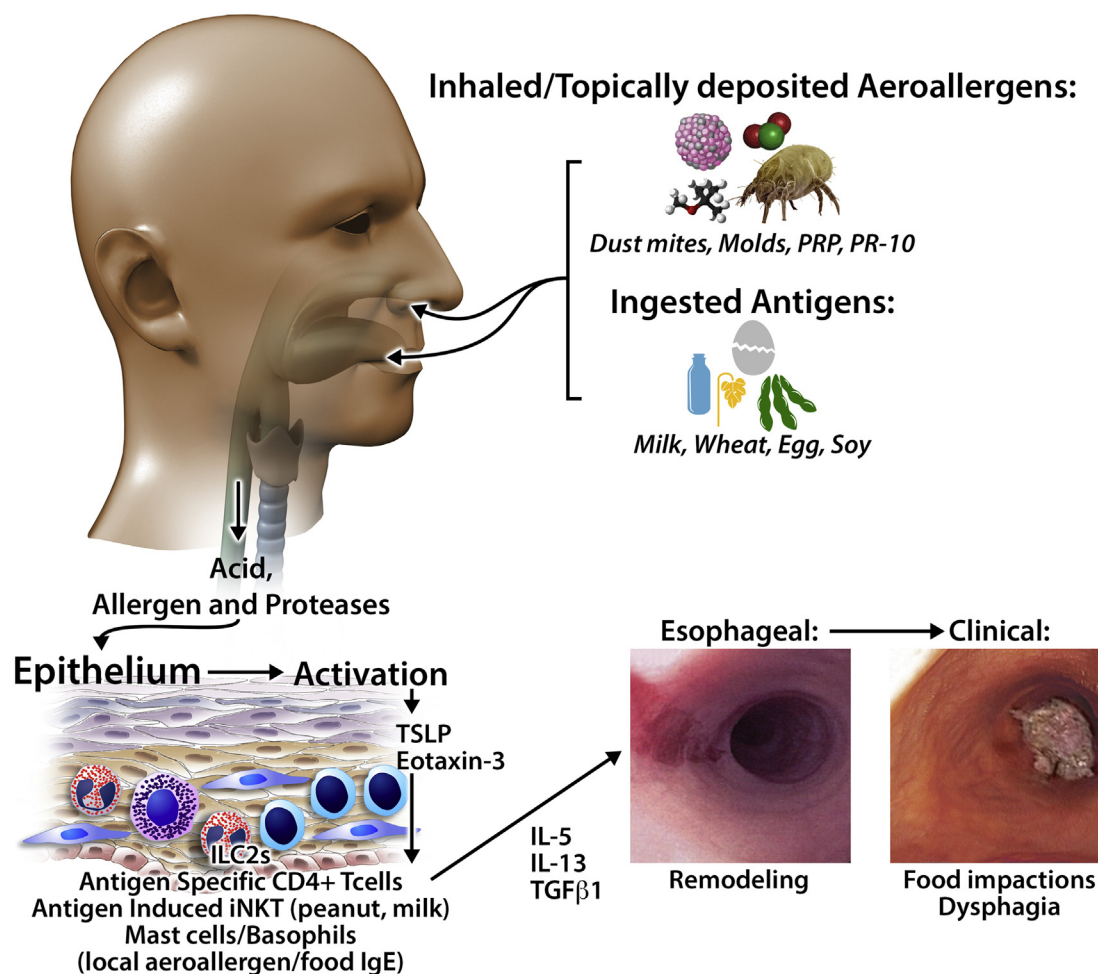


FIG 1. Food and aeroallergen antigens in patients with EoE. Ingested and inhaled antigens, in conjunction with acid and proteases, activate the epithelium to produce chemotactic and activating factors for innate (mast cells, basophils, invariant natural killer T [*iNKT*] cells, and innate lymphoid cells) and adaptive (T cells) immune cells. Infiltrating cells can produce T_H2 cytokines, such as IL-13 and IL-4, as well as profibrotic factors. Chronic inflammation initiates tissue remodeling, with resulting dysphagia, food impactions, and strictures.

correlate with symptoms or biopsy results.⁴⁹ A separate study demonstrated that food elimination based on ISAC testing did not show any improvement in esophageal eosinophilia.⁴⁷ Currently, the general conclusions from the literature demonstrate that although ISAC or component testing of foods show increased sensitization, the clinical significance and utility are unclear.^{44,45,49}

In general, isolated testing for IgE-mediated allergy has been largely inadequate for determining EoE-triggering antigens. Philpott et al⁵⁰ examined the use of 5 different testing modalities for identifying foods that contribute to EoE in their cohort from Australia. They found that neither basophil activation test results, skin test results, specific IgE levels, or allergen-specific IgG₄ levels correlated with improvement in esophageal biopsy specimens in patients responding to a 6-food elimination diet. The overall success rate for IgE testing for identifying the right food was 36%.

Empiric elimination diets usually avoid the 6 most common allergenic food groups based on the top 8 foods causing IgE-mediated food allergy (milk, egg, soy, wheat, fish/shellfish, and

peanut/tree nuts). Kagalwalla et al²⁹ found about 60% improvement in esophageal biopsy specimens in the original 6-food elimination study in a pediatric population. Similar efficacy was found in adult studies.^{26,28} Recent studies have looked at various 2-, 4-, and 6-food elimination diets in a prospective manner.^{5,6,32} It is important to remember when looking at these diet studies to carefully examine what is being eliminated. For example, sometimes “wheat free” can be all gluten or gluten-like foods, including oat, as opposed just wheat.⁵¹ Similarly, “soy” can be all legumes, or in other studies, it is strictly just soy. In Kagalwalla et al’s multicenter study of 78 pediatric patients, they had a 60% response rate with a simple 4-food elimination of removing milk, wheat, soy, and egg.⁵

Similarly, a study by Molina-Infante et al⁶ found 53% of subjects responded to a 2-food-group elimination (milk and gluten). The 47% who did not respond to this 2-food-group diet were switched to a 4-food-group elimination diet (milk, gluten, egg, and legumes with soy) with a 60% response rate, and the nonresponders were switched to a 6-food group elimination diet (milk, gluten, egg, legume-soy, fish, shellfish, peanut, and tree

TABLE I. Most common foods in patients with EoE

Food study	No.	Pediatric/adult	Milk	Egg	Wheat	Peanut/tree nuts	Soy/legumes	Fish/shellfish
Gonsalves et al ²⁸	20	Adult	50%	5%	60%	10%	10%	
Kagalwalla et al ²⁹	36	Pediatric	74%	17%	26%	6%	10%	
Lucendo et al ³⁰	42	Adult	62%	26%	28.6%*	16.7%	23.8%	19%
Henderson et al ³¹	26	Pediatric	65%	40%	37%			
Spergel et al ²³	319	Pediatric	66%	24.5%	22.6%	5%		0%
Molina-Infante et al ³²	28	Adult	50%	36%	31%*		18%	
Rodriguez-Sanchez et al ³³	46	Adult	64%	21%	28%		7%	
Wolf et al ³⁴	11	Adult	44%	44%	22%	11%	11%	11%
Molina-Infante et al ⁶	64	Adult	81%	15%	43%*	1%	9%	6%
Kagalwalla et al ⁵	78	Pediatric	85%	35%	33%		19%	
Kruszewski et al ³⁵	20	Pediatric	64%					
Total of 702 patients		Average	66%	24%	27%	4%	12%	2%

*All gluten-containing foods.

nuts) with a 79% response rate. Together, studies (Table I) have shown that milk is the most common food that causes EoE. In fact, in milk elimination–only studies, the rate of success has been around 65%.^{35,52}

Alternative approaches for identifying the causative food have included both IgG₄ measurement and atopy patch testing. Clayton et al⁵³ first identified increased IgG₄ levels in esophageal biopsy specimens, which has been confirmed by others.^{41,54} Wright et al⁵⁵ found that IgG₄ levels were increased in the esophagi of patients with active EoE compared with those with controlled EoE. In addition, recent work by Wilson et al⁵⁴ found that IgG₄ levels were increased in sera about 100 times greater in patients with EoE than in control subjects. However, they did not examine whether there was any correlation with symptoms or resolutions of esophageal eosinophilia,⁵⁴ and using IgG₄ as a marker of causative foods has not been revealing to date.⁵⁰ Currently, it is clear that IgG₄ levels are increased in patients with EoE, but its role as a pathogenic marker versus an epiphenomenon is unclear. It is interesting to note that IgG₄ can cause fibrotic disease, but it remains unclear whether IgG₄ plays a causative role in patients with EoE complications.

Despite IgE not having a major role in detecting foods causing EoE,⁵⁶ pediatric patients with IgE-mediated allergy to foods are 100 times more likely to have EoE compared with the general public.³⁵ This high correlation indicates that these patients are atopic and that their allergic diseases share common mechanistic pathways that involve cytokines, such as IL-13, a master regulator of EoE.⁵⁷ Genetics studies have indicated that T_H2 genes, including *TSLP*, eotaxin, and signal transducer and activator of transcription 6 (*STAT6*), are genetic risks for disease.^{13,58} Furthermore, T_H2 cytokines predominate when examined in esophageal biopsy specimens.^{31,59–62} Work by Wen et al⁶⁰ has identified a unique molecular signature to active EoE in esophageal biopsy specimens that encompasses many T_H2 genes. In murine models IL-13 expression can mimic the molecular phenotype of the disease.⁶³ Recently, Cianferoni et al⁶⁴ have identified activated T_H2 cells with the CD154⁺IL-5⁺ phenotype in the peripheral blood of patients with active EoE but not in control atopic subjects or patients with inactive EoE. Furthermore, these peripheral T cells can be stimulated by milk antigens in patients with milk-induced EoE but not in control subjects.⁶⁴ These studies indicate that EoE is a T_H2 antigen–driven

disease with activation of T_H2 cytokines in both peripheral blood and local tissue.

Because EoE is a T_H2 disease, examination of foods by using patch testing would make logical sense. Atopy patch testing was originally used to detect foods in patients with atopic dermatitis and was found to be particularly useful for patients with delayed gastrointestinal symptoms.⁶⁵ In EoE studies using atopy patch testing, triggering foods were confirmed as pathogenic when biopsy results normalized after removal of the food and/or if appearance of esophageal eosinophilia occurred after addition of the identified food.^{23,66} Retrospective studies found that atopy patch tests were able to detect the correct food trigger approximately 50% of the time and had a high negative predictive value of nearly 90%, except for milk.^{24,66}

Comparison of the success rates of allergy testing–based (atopy patch test and skin test) versus empiric elimination diets in retrospective analyses done by 2 independent centers found similar rates between these 2 interventions.^{23,31} A large study of patients with EoE performed at the Children's Hospital of Philadelphia found a 52% response rate using empiric elimination of milk, egg, wheat, and soy, which was identical to the success rate of combined atopy patch and skin tests.²³ When milk was empirically eliminated in addition to positive foods found on skin and atopy patch tests, the success rate approached 75%. One potential advantage of using an allergy test–based diet in children is the elimination of 1 fewer food on average compared with an empiric elimination diet. However, disadvantages of the allergy test–based diet include the time and costs required for additional testing.

Aeroallergens as antigens in patients with EoE

Animal models were the first to document a close immunologic link between the airway and esophagus. Intranasal instillation of aeroallergen antigens, including dust mite, *Aspergillus fumigatus*, and cockroach, causes onset of experimental EoE.⁶⁷ In addition, epicutaneous sensitization can drive EoE in animal models.⁶⁸ Intranasal instillation of food antigens, such as peanut, also induces esophageal eosinophilia, a process that appears dependent on the proximity of the shared lymph node chain between the trachea and esophagus and on the presence of invariant natural killer T cells.⁶⁹

An initial case report documented aeroallergens as a trigger for EoE in an elemental formula–resistant patient with EoE with

spontaneous disease remission and recurrence during the pollen season.^{22,70} A single case series of adults demonstrated new-onset EoE after a high load of exposure to environmental aeroallergens, including dust mites, pollen, and mold. However, allergic sensitization to the triggering antigen was only demonstrated in 1 patient (the other 2 were not tested).⁷¹

A number of studies have demonstrated that EoE diagnoses can have seasonality, with increased esophageal eosinophilia occurring during the spring and summer compared with the winter months.⁷²⁻⁷⁶ Indeed, EoE exacerbations with recurrent food bolus impactions can also be linked to the pollen season.⁷⁷ However, only 1 study to date has demonstrated the presence of increased esophageal eosinophilia during a pollen season with proved relevance to the patient; that is, the patients' EoE exacerbation timing matched their pattern of aeroallergen sensitization. Of 1180 children with EoE at a single institution, 20% of those suspected to have a pollen trigger showed biopsy-proved esophageal eosinophilic exacerbations that occurred during a pollen season for which they had specific pollen sensitization. Of these patients, 84% had allergic rhinitis, and 75% had asthma.⁹

Further support for the role of aeroallergens in patients with EoE is the finding that sublingual immunotherapy (SLIT) for aeroallergens can drive esophageal eosinophilia. The first case report documented initiation of EoE after 4 weeks of SLIT with hazelnut, birch, and alder and EoE resolution after 4 weeks of SLIT discontinuation.⁷⁸ A similar case was reported recently in a child who was proton-pump inhibitor (PPI) resistant but responsive to discontinuation of SLIT.⁷⁹ Because serial rounds of *in vitro* differentiation in the presence of antigen drive CD4⁺/IL-5⁺ cells *in vitro*, it is possible that aeroallergen-specific T cells develop during EoE pathogenesis because of chronic local aeroallergen and antigen exposure.⁸⁰

Oral allergy syndrome in patients with EoE

Clinically symptomatic pollen-food cross-reactivity occurs in patients with allergic rhinitis at a rate of approximately 7% to 8%. By contrast, 50% of patients with EoE studied concurrently at 2 referral centers had symptomatic oral allergy syndrome, as determined by using a standardized questionnaire. Interestingly, although greater than 90% had aeroallergen sensitization, only half had symptoms of allergic rhinitis, suggesting that aeroallergens might be equivalently likely to cause nasal or oral allergy symptoms in patients with EoE.⁸¹ Adult studies have documented the presence of cross-reacting food-pollen antigens, specifically pathogenesis-related class 10 protein (PR-10) and profilins with oral allergy syndrome in 30%, but the clinical implication of these sensitizations for EoE management remains unclear.^{48,82} It is possible that sensitization to food-pollen cross-reacting antigens associates with dysphagia to specific foods, such as bread (profilins and PR-10) and apple (PR-10).⁸² Although 39% of subjects in 1 study were sensitized to PR-10 proteins in multiple foods (hazelnut, apple, peach, peanut, soy, kiwi, and celery), 40% of adults were sensitized to profilins in another smaller study.^{78,82}

A new study demonstrated that 88% of patients with EoE in Spanish population had sensitizations detected on component-resolved diagnostics. The majority of the allergens were grasses and/or lipid transfer proteins from mugwort, peach, hazel, and walnut. The investigators used the component-resolved

diagnostics panel to build elimination diets, allergen immunotherapy, or both with high success rates (78%). Follow-up occurred for 3 years, and in this period more than 75% of subjects were disease free.⁸³ As such, antigen resolution using finer techniques, such as component testing for food-pollen cross-reactivity, might be useful when creating antigen avoidance regimens.

POTENTIAL PROGNOSTIC FEATURES OF ALLERGIC SENSITIZATION

Data from 1 study suggest that food sensitization can associate with more severe histologic disease in the context of a promoter single nucleotide polymorphism at -509 of the TGF- β 1 promoter. Children with the TT genotype had increased numbers of esophageal TGF- β 1⁺ cells compared with children who had the CC or CT genotype at the TGF- β 1 single nucleotide polymorphism -509.^{18,84} Although there were increased numbers of mast cells in children with EoE of the TT genotype, there were not increased numbers of eosinophils. The difference in numbers of tryptase-positive and TGF- β 1⁺ cells was more pronounced in children who had the TT genotype and concurrent food sensitization to milk, wheat, egg, and/or soy. Among those with the TT genotype, children with food sensitization had higher fibrosis scores.⁸⁴ These data suggest a gene-environment pathway involving food-specific IgE-expressing mast cells.

Recent work by Fahey et al⁸⁵ on genotype-phenotype interactions has shown that homozygosity or heterozygosity at the risk allele for TSLP variants is associated with the presence of 3 or more EoE food triggers.⁸⁵ These data suggest that the risk allele at TSLP might predispose to more EoE-relevant food antigens and perhaps suggest a more severe disease course.

Genetic changes in the TGF- β 1-signaling pathway that cause connective tissue disorders, such as Loeys-Dietz and Marfan syndromes, can also associate with EoE.^{86,87} Subjects with Loeys-Dietz syndrome have increased rates of IgE-mediated food allergy, and animal models can demonstrate spontaneous EoE, underscoring the potential importance of both IgE and TGF- β 1 in EoE. It will be interesting to understand whether subjects with connective tissue diseases have altered response rates to usual EoE-directed therapies.

Together, these genetic studies lend preliminary insight into a potential link between food allergy and EoE severity.

IgE sensitization to *Candida* species has been shown to occur in 16% to 43% of adults with EoE studied in Europe.^{82,88} Active EoE was associated with decreased barrier protein expression and decreased cathelicidin levels, even with topical corticosteroid treatment, leading the authors to postulate that topical corticosteroid therapy can lead to decreased innate immunity, potential *Candida* species colonization, and subsequent increased IgE sensitization to *Candida* species.⁸⁸ However, compared with the high rates of IgE sensitization, the rates of *Candida* species-related esophagitis are lower, and yeast/hyphae are not detected regularly on biopsy specimens, suggesting that the presence of serum *Candida* species IgE might be nonspecific to EoE. It is also possible that the presence of IgE sensitization to *Candida* species decreases the rate of steroid responsiveness.

Aeroallergen sensitization can decrease the success of EoE-directed therapy. In subjects who initially respond to high-dose PPIs, long-term response is more likely to be lost if there is concurrent allergic rhinitis.⁸⁹ In children with

sensitization to aeroallergens, such as cockroach and molds, there was a tendency for nonresponse to EoE-directed therapy.¹⁰ These findings implicate the importance of environmental antigen avoidance for successful EoE therapy. In addition, it is possible that in patients with EoE, as in those with asthma, sensitization to aeroallergens can predict lack of EoE resolution.

Modulation of the immune system toward aeroallergen tolerance might relieve EoE. Although such studies are clinically challenging to complete in a prospective controlled fashion, there has been 1 case of EoE responding to subcutaneous immunotherapy. A young child with EoE not responsive to PPIs or high-dose fluticasone was found to be dust mite sensitive. He was started on a 2-year course of subcutaneous immunotherapy to dust mite. After the 2-year course, the repeat biopsy was normal off PPIs and swallowed steroids.⁹⁰ Further studies to understand whether nonoral methods of aeroallergen immunotherapy could be successful as isolated or add-on therapy for EoE remain to be completed.

DISCUSSION

In summary, there are multiple lines of evidence demonstrating that EoE is an allergic disorder. These data include the presence of antigen-specific cells, such as milk-specific lymphoid cells, and recent data demonstrating detection of antigens, such as gliadin and pollen tube callose, in the esophagus.^{27,64,91} The ability to treat EoE with antigen elimination for foods and/or pollens and/or cross-reacting food-pollens underscores the importance of specific antigens. Triggering damage could include currently unappreciated adjuvants, as occurs with diesel exhaust in patients with allergic rhinitis and/or an interplay between acid and antigens.⁸⁹ Indeed, acid can alter epitopes, potentially predispose to food allergy, and disrupt epithelial barriers, thereby allowing transit of food and aeroallergen particles locally into the esophagus. Systemic and other local cues, such as those derived from cells immigrating and emigrating from shared lymph node chains (tracheal and gastric), likely also plays a role in triggering an antigen-specific response in the esophagus.

Like other allergic disorders, it is likely that EoE is influenced by concurrent atopy. In addition, it is possible that there are common triggers for EoE and concurrent allergic diatheses; for example, viral illnesses could trigger both asthma and EoE. Some of the clearest examples of this are EoE exacerbations during the pollen season or instigation by an aeroallergen that also exacerbates clinical allergic rhinitis.⁹ Data supporting altered therapeutic response to topical corticosteroids or PPIs because of aeroallergen sensitization also support the importance of allergy testing and avoidance of potentially relevant antigens.¹⁰ Indeed, it has been noted that most subjects treated with topical corticosteroids have eventual loss of control of complete histologic normality and recurrence of lower levels of eosinophilia despite continued therapy.⁹² Whether this reflects a shift in the balance between therapy-induced disease control and allergic sensitization remains to be understood. Similar to asthma, in which dust mite avoidance can induce complete control of airways hyperreactivity, it is possible that complete EoE resolution requires avoidance of all relevant antigens. This might include foods and even food-pollen antigens in some subjects.

EoE is a chronic disease in the majority of subjects, and long-term avoidance of food antigens is likely required. In a large

single-center study, only 9 (0.5%) of 1812 pediatric patients tolerated an unrestricted diet after food elimination.⁹³ Factors that predispose to disease retention versus resolution remain unclear but might well include the presence of antigen sensitization. Although it did not alter response rates, children with concurrent asthma and EoE had higher esophageal eosinophil counts than those without asthma.¹⁷ In addition, the ability of immunomodulation early in the disease course to modify the natural history toward chronic EoE is not clear but would be of interest to study. Blockade of T_H2 cytokines, such as IL-13, might be of utility in this regard.⁹⁴

In conclusion, EoE is an antigen-driven T_H2 disease in which allergen avoidance can function as a single or adjuvant therapy for disease control. Identification of specific subsets of antigen-specific innate and adaptive lymphocytes and novel ways to identify allergic triggers will be essential for optimal EoE management. When using allergen-based testing, it is imperative to consider the safety of the testing, as well as its accuracy. Novel applications of tools, such as component-resolved diagnostics, hold promise for finding EoE-triggering foods/pollens, and further tests for reactive lymphocytes that are pathogenic *in situ* might yield novel therapeutic targets. Although much has been understood over the past 20 years, much work remains for researchers working on allergens and their role in EoE.

What do we know?

- EoE is an antigen-driven disease.
- The most common EoE triggers are foods, especially milk, egg, soy, and wheat.
- Antigen-specific IgE seems expendable for disease instigation but might play a role in prognosis or severity.
- A T_H2 cytokine profile predominates in EoE disease pathogenesis.
- Combined skin prick and patch tests might be of utility in children with EoE but do not routinely demonstrate triggering food antigens in adults.
- Oral immunotherapy to foods and pollens can trigger EoE.

What is still unknown?

- What is the best approach to test for triggering antigens in patients with EoE?
- Are there antigen-specific T cells in the esophagus that could be therapeutic targets in patients with EoE?
- Are there allergen immunotherapy regimens that could treat EoE?
- What are the mechanisms of atopic disease interplay in patients with EoE?
- Does pollen or food sensitization have prognostic or severity implications for the natural history of EoE?

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