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Allergies and Eosinophilic Esophagitis—Current Updates for the Pediatric Gastroenterologist

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Abstract

Purpose of Review The purpose of this article is to review recent developments demonstrating the role of allergies, the utility of allergy testing, and the role of the allergist in eosinophilic esophagitis (EoE) management.

Recent Findings The majority of patients with EoE have concurrent atopic disorders including food anaphylaxis, asthma, allergic rhinitis, and eczema. An atopic population likely is at greater risk for EoE. Delayed type hypersensitivity to food antigens is the most common pathogenic mechanism. Aeroallergens and pollen-food cross-reactivity also can trigger EoE. Th2 cell–mediated adaptive and innate immunity in response to epithelial damage occurs via IL-13- and IL-4-producing T cells and innate lymphoid cells. While IgE testing for foods is insufficient to build an elimination diet, IgE-mediated allergy may play a role in EoE severity and clinical course.

Summary There is strong evidence that Th2 immunity drives EoE. Optimal EoE management should include elucidating and managing EoE triggers and concurrent atopic diatheses.

Keywords Eosinophilic esophagitis · Food · Allergy testing · Atopy · Elimination diet · Allergist referral

Introduction

Eosinophilic esophagitis (EoE) is a chronic antigen-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant, Th2 inflammation when other secondary systemic and local causes of esophageal eosinophilia are excluded [1]. EoE has been the focus of ongoing research since the early 1990s when it emerged as its own disease entity.

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Pediatric EoE incidence and prevalence are increasing. A systematic review determined that the overall incidence rates of pediatric EoE varied by geographic region, specifically up to 10 per 100,000 children in the USA (annual percentage increase of 12 to 17%). In the USA, prevalence of EoE was up to 42 per 100,000 children (annual percentage increase of 56% due to the chronic nature of the disease) [2]. Overall, rates of EoE are estimated at 0.5 to 1 case/1000 persons with an incidence of 10/10,000. The prevalence rates of EoE in the USA are similar to those in Australia, Switzerland, Spain, and Canada (range of 0.34 to 1/1000 persons), and incidence in these countries ranges from 6.4 to 12.8/100,000. Reported EoE rates in Denmark and the Netherlands are lower (prevalence of 0.02 and 0.04/1000 persons respectively) [3]. EoE is more prevalent in Caucasian males who have other concurrent atopic diatheses.

The pathogenesis of EoE is multifactorial, involving environmental, immune, and genetic factors. The most common EoE triggers are food antigens which incite a delayed hypersensitivity Th2 response. IL-13 is a master regulator of EoE and is expressed by adaptive CD4+, prostaglandin D synthase (HGPDS)+ effector memory Th2 cells [4, 5•]. IL-13 is also likely produced by infiltrating type 2 innate lymphoid cells [6, 7]. Recently, single-cell RNA sequencing identified two T cell populations termed “T7” and “T8” as the key CD4+ T cell

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populations increased in active EoE patients [5•]. These two cell populations resembled likely dysregulated T regulatory and memory effector Th2 cells respectively. Together, these cells appeared to be ineffective in appropriately suppressing the adaptive response and also stimulated Th2 cytokine production [5]. In line with this, therapies that target receptor blockade of the Th2 interleukins IL-4 and IL-13 have been preliminarily successful in adult EoE [8, 9].

Activated epithelial cells produce eotaxin-3 (CCL26), driving tissue eosinophil accumulation [10, 11]. Inflammatory cell–derived IL-5 activates eosinophils, and IL-9 can drive mast cell accumulation [12]. Structural cells such as epithelial cells and fibroblasts along with inflammatory cells such as mast cells and eosinophils produce pro-fibrotic factors such as TGFβ1 and TNFα, leading to changes in disease severity and complications such as food impactions and strictures [13, 14].

The purpose of this review is to describe the most recent studies associating the role of allergies and allergy testing with EoE.

Allergies and EoE

Environmental Allergies

The majority of patients with EoE have associated atopic disorders such as allergic rhinitis, asthma, and atopic dermatitis [15••, 16, 17••]. In a retrospective cross-sectional review including 456,128 patients, 59.8% of patients with EoE had asthma vs. 21.4% of those without EoE; 17.8% of EoE patients vs. 6.6% non-EoE patients had atopic dermatitis. In addition, the majority of EoE patients had concurrent sensitization to aeroallergens with 60% having allergic rhinoconjunctivitis [16]. Aeroallergens can be the sole driver of esophageal eosinophilia in some patients and can exacerbate existing disease in others [18, 19]. Seasonal variation in EoE diagnoses has been reported with more newly diagnosed EoE cases in the spring or summer months [20–22]. A recent study demonstrated that 70% of EoE patients ($n = 13$) experienced increased symptoms, endoscopic severity, and peak eosinophil counts (increasing from 6.8 to 86.8 eosinophil per high-power field ($p < .001$)) in fall and summer months [23]. A single-center pediatric study showed that children with EoE had seasonal esophageal eosinophil exacerbations that corresponded to their aeroallergen sensitization [19]. Murine models using Aspergillus fumigatus, cockroach, or dust mite antigen provide further proof of concept that aeroallergens drive esophageal eosinophil accumulation [24–26]. Indeed, recent data also demonstrate local deposition of dust mite antigen directly into the mucosal surface of EoE subjects [27, 28•]. This aligns with reports that demonstrate that aeroallergen sublingual immunotherapy can incite EoE [29–31]. The role of subcutaneous immunotherapy to aeroallergens as an isolated or adjuvant treatment for EoE has been successful in case reports, but randomized controlled trials of this intervention can be challenging, especially in children [32]. However, given the immunologic mechanism of desensitization using immunotherapy, the conceptual framework is likely sound [33•].

Interestingly, there may be an interplay between acid and aeroallergens, whereby acid-induced esophageal epithelial damage could allow antigen penetration. Twenty-six percent of pollen-allergic patients without gastroesophageal reflux who were symptomatic during the pollen season had significantly increased esophageal eosinophilia when compared with control, non-allergic patients (0%). Patients without atopy but who had confirmed gastroesophageal reflux also had esophageal eosinophilia present (21%) [34]. Allergic rhinitis is reported to predispose to loss of PPI response in those initially identified to be PPI responsive [35]. Together, these data signify the role of aeroallergens functioning as EoE triggers.

Food Allergies

An abundance of literature supports the role of a delayed hypersensitivity reaction to common food antigens as a main driving event in EoE. In 1995, Kelly et al. demonstrated EoE resolution in children with gastroesophageal reflux and persistent symptoms despite various anti-reflux therapies after treatment with an exclusive elemental diet [36]. Since then, multiple studies have confirmed these findings [37–39]. A recent systematic review and meta-analysis included 33 references analyzing a total of 1317 patients with EoE receiving different dietary treatments. Of these, 13 studies of 429 EoE patients showed an overall efficacy of elemental diet in achieving histologic remission of EoE in 90.8% of patients. An overlapping group of 14 studies with 626 patients who had allergy testing–directed food elimination diets showed an overall efficacy of 45.5%. A further seven studies of 197 patients demonstrated that empiric six-food elimination diet (SFED; diet excluding milk, eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish) induced EoE remission in 72.1% of subjects [37]. More recently, a prospective trial in children demonstrated that 4-food elimination of milk, wheat, egg, and soy was as effective as the reported rates of 6-food elimination [40]. Thus, it appears that elemental diet establishes remission in nearly all patients; empiric four- and six-food elimination diets provide remission rates of close to 70% while allowing a more normal and less-expensive diet; and allergy testing–directed elimination may not increase the remission rate but may detect food antigens that are not detected by empiric avoidance.

Eighty-eight percent of patients undergoing reintroduction of foods following successful six-food elimination diet develop recurrence of disease [41]. Molina-Infante and colleagues reported a step-up elimination diet in which EoE patients

initially started a two-food group elimination diet (TFGED; cow's milk and wheat) and proceeded to four (FFGED; TFGED plus eggs and legumes) and then six-food group elimination diet (SFGED; FFGED plus peanuts, tree nuts, fish, and shellfish) in a stepwise approach based on clinico-histologic response. The efficacy of each diet was 43%, 60%, and 79% for the two-, four-, and six-food group elimination diets respectively. On reintroduction of foods, 70% of responders to TFGED had one identified trigger, 70% of FFGED responders had one or two triggers, and 100% of SFGED responders had three or more triggers [42]. In line with the delayed type hypersensitivity to foods, new-onset EoE disease prevalence of 2.7% has been reported to occur in patients undergoing peanut, milk, or egg oral immunotherapy as treatment for IgE-mediated food allergy, with EoE often resolving after OIT was discontinued [43]. Together, these data support the hypothesis that food allergens are a main trigger for EoE disease pathogenesis.

Immediate hypersensitivity reactions to foods are immunoglobulin E (IgE)–mediated, while EoE instigation is IgE independent. However, the prevalence of EoE in pediatric patients with IgE-mediated food allergy is higher than that in the general population (4.7% vs. 0.04%) [17]. In a cohort of 198 children with EoE analyzed retrospectively, the prevalence of IgE-associated food allergy at time of EoE diagnosis was 29%. Patients with immediate hypersensitivity to foods presented clinically at younger ages than those without food allergies (6.05 vs. 8.09 years; $p = 0.013$) and were more likely to have comorbid allergic disease. In addition, children with immediate food hypersensitivity presented with significantly more symptoms of dysphagia, gagging, cough, and poor appetite when compared with those without food allergies. Of note, younger age, allergic rhinitis, male gender, and presence of dysphagia were all independently associated with having EoE plus immediate food hypersensitivity [44]. In adults with EoE, gliadin antigen can be found to be deposited on the surface of the esophagus, suggesting a local mechanism for food reactions [45].

While IgE is not required for EoE instigation and isolated anti-IgE therapy is not effective in treating EoE, IgE food sensitization and, possibly IgG4, may exacerbate EoE [46, 47]. Children with genotype TT at the TGFβ1 promoter and IgE sensitization to EoE triggering foods have more severe histologic EoE, and children with an EoE risk allele in the thymic stromal lymphopoietin (TSLP) gene have greater numbers of foods that trigger their EoE [48, 49].

Allergy Testing in EoE

The three primary methods for testing for food sensitization in EoE are serum IgE testing, skin prick testing (SPT), and atopy patch testing (APT) (Table 1). IgE-mediated reactions can be identified with serum IgE levels or SPT in the context of immediate and repeated clinical reaction to the food. APT is used to assess cell-mediated (delayed) reactions and has been standardized and validated for contact dermatitis and dust mite allergies. There are mixed data regarding whether food allergy testing is indeed useful in guiding dietary elimination therapy in EoE. The most commonly identified positive testing to food antigens in EoE patients includes milk, egg, wheat, and soy [39, 50]. However, diets exclusively based on isolated IgE serum or skin prick testing are not successful in eliminating the appropriate food triggers in EoE. In children, there is literature suggesting that the combined use of food patch and prick testing–based targeted food elimination can be successful in as many as 74% of patients ($n = 24$) [50]. However, overall, the rates for testing-based elimination diets are not superior to empiric elimination of common foods (milk, egg, soy, wheat), and testing-based diets tend to be unsuccessful in adults [38, 39, 51].

SPT alone has insufficient negative predictive values (NPV) for remission of 40–67% for various food groups, with the lowest NPV being to milk [38]. Individual or combined SPT and APT give low positive predictive values (44% on average) but better negative predictive values for most foods [39]. This is the general rule in food testing even for IgE—the predictive value of a negative test outweighs the positive predictive value of a positive test. In adult EoE patients, SPT, APT, serum IgE, basophil activation tests, and serum food–specific IgG were unable to accurately predict EoE triggers [52, 53]. Component-resolved diagnosis (CRD)–based diet therapy has also been attempted. However, due to failure of treatment in over 90% of patients, the study was not completed [54]. This indicates that currently available allergy testing is not adequate alone to design elimination diet therapy for EoE management.

In some cases, testing for food triggers can be important. For example, in children, a subgroup of patients may have improvement in their disease following allergy testing–based diets and such diets may remove fewer foods [38]. Since the prevalence of food allergies and anaphylaxis is higher in patients with EoE, skin prick testing or serum IgE testing for immediate hypersensitivity for foods is warranted for IgE-mediated allergy-eliciting foods and for education on which food avoidances could cause anaphylaxis as opposed to simply causing EoE [55]. Thus, food allergy testing may be useful to reduce unnecessary avoidance of non-trigger foods.

Esophageal prick testing (EPT) has been piloted in a group of 8 EoE and 3 control patients. Although no systemic anaphylaxis reactions occurred in any patients, at least half of EoE patients had chest pain and/or acute transient complete luminal obstruction and blanching of mucosa at injection site. There was poor concordance with EPT and SPT or serum testing [56]. Because of the undesirable reactions reported with EPT and the potential of anaphylaxis when antigen is

Table 1 Role of testing in eosinophilic esophagitis

Test	Serum IgE	Skin prick test	Atopy patch test	Utility
Food	NA	X	X	Antigen-based elimination diet
	X	X	NA	Food antigen avoidance needed for history of immediate food hypersensitivity; Food antigen that may require office challenge by allergist for loss of tolerance
Aeroallergen	X	X	NA	Identify triggering antigens to control allergic rhinitis, asthma, eczema, and EoE exacerbations; Identifying season of increased esophageal eosinophilia

injected into the mucosal surface, the risks likely outweigh the benefits of the procedure.

Esophageal tissue from EoE patients has demonstrated significantly increased IgG4 compared with controls. EoE patients also had increased serum levels of IgG4 for milk, wheat, egg, and nuts [46, 57]. Elevated total IgG4 and food-specific IgG4 have also been reported in the serum and esophageal tissue of EoE patients by several other authors [58–60]. However, the role of IgG4 in EoE still remains unclear. Patients with IgE-mediated food allergy have increases in specific IgG4 during successful desensitization processes. As such, elevated IgG4 in EoE may simply reflect the disease mechanism of cellular, rather than IgE, mediated disease. It is possible the serum food–specific IgG4 could function as a biomarker for EoE, but this remains to be systematically evaluated.

Testing for aeroallergens in patients with EoE is of utility. Asthma literature has long supported the avoidance of triggering environmental antigens for asthma control. Given the similar Th2 pathogenesis between EoE and asthma, the fact that intranasally deposited antigens can drive experimental EoE, that seasonal aeroallergens can clearly exacerbate EoE, and that asthmatic patients with EoE tend to have higher esophageal eosinophil counts, avoidance of those environmental antigens that test positive is a reasonable and important consideration in EoE patients [18–25, 26•, 27, 28•, 61].

Referral to an Allergist

The allergist is important in EoE management. This is especially true for elucidating EoE environmental triggers, for understanding the potential for IgE-mediated food anaphylaxis following avoidance of a food for which an individual had positive IgE testing, and for treating and considering the side effects of treatment for concurrent diatheses [33]. Loss of tolerance to specific foods in IgE food–sensitized children after an elimination diet creates the potential for onset of anaphylaxis on food reintroduction, and the decision to prescribe injectable epinephrine therapy can be made by the patient's allergist [62]. In addition, an office-supervised food challenge may be a safer way to introduce a food that has been avoided but which carries a theoretically high risk of IgE-mediated allergy.

Allergic co-morbidities are higher in EoE patients than the general population. In other disorders such as allergic rhinitis and asthma, often considered "one airway," chronic allergies and sinusitis can predispose to poor asthma control [63, 64]. Indeed, children with asthma and indoor allergen sensitizations are less likely to outgrow their asthma [63]. In addition, oral steroid–dependent asthmatics had asthma control upon house dust mite avoidance, an elegant and classic allergy study [65]. As such, concurrent atopic disorders in EoE patients should be evaluated and optimally treated. Knowing that EoE can worsen with aeroallergen exposure and that aeroallergens and foods can deposit directly into the esophagus, a strategy for escalating and de-escalating therapy during exacerbations can also be built and the timing of endoscopies can be tempered to seasonality if needed [27, 45]. Children with EoE who are mold- or cockroach-sensitized are more likely to fail combination diet and swallowed corticosteroid treatment ($p = 0.02$ and $p = 0.002$) [66]. This suggests that sensitization to perennial allergens may lead to nonresponsive EoE in some patients, and thus is important clinical information to obtain when treating EoE. Educating patients about allergen avoidance may therefore alter their response to therapy. In addition, the rates of oral allergy syndrome are high in EoE subjects (up to 50%) and the avoidance of triggering foods and cross-reacting pollens may be helpful in controlling disease [67–69].

Novel therapies, such as epicutaneous immunotherapy for milk, may be of utility in EoE [70]. The practicing allergist would be most knowledgeable for deciding which patients may benefit from such an intervention, the timing and follow-up required, and the potential need for further research-based testing such as that for activated milk-specific T cells [71].

As aeroallergen immunotherapy can be used to desensitize allergic patients, the allergist can help determine if immunotherapy is indicated in a patient who also has EoE. In contrast, there have been several reports of EoE occurrence with oral,

sublingual, and subcutaneous immunotherapy for foods and aeroallergens [29, 43, 71]. However, in cases where aeroallergens may be driving the disease, immunotherapy may be useful for the IgE-mediated processes [32, 72, 73]. This decision must consider the severity of allergic symptoms requiring immunotherapy and the patient's EoE disease phenotype and maintenance of EoE remission. It is also important to note that primary immunodeficiency disorders can present with secondary gastrointestinal eosinophilia [74–76]. In such cases, it is essential not to miss a primary immune disorder, since these carry a risk of complications such as autoimmunity and malignancy. The intrinsic complexity and constantly growing body of literature in allergy/immunology should be considered closely when managing EoE.

Conclusions

There is clear evidence that food and aeroallergens induce inflammation that leads to esophageal eosinophilia and associated symptoms and complications of EoE. Although both play a role in disease pathogenesis, foods are the predominant allergen trigger in EoE. Ongoing studies aim to delineate the pathways through which this inflammation is occurring. These pathways may be different depending on the antigen stimulus, the location and duration of exposure, patient age and genetic make-up, and EoE phenotype/endotype [77••]. Overall, recent studies demonstrate that EoE is a cell-mediated immune process and that the presence of IgE sensitization and concurrent atopic diseases can alter the course of EoE [33, 44, 48, 49, 77••, 78•].

In EoE, the goals of diagnosis, induction of remission, control of potential complications, and remission maintenance are best achieved through a multidisciplinary team of gastroenterologists, allergists, and dieticians whenever possible. The allergist's role in elucidating, treating, and educating patients on allergic triggers and inflammation in EoE is important for comprehensive EoE patient care.

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Compliance with Ethical Standards

Conflict of Interest Prerana Williamson declares no conflict of interest. Seema Aceves is a co-inventor of oral budesonide suspension, patented by UCSD and licensed by Shire-Takeda, is a consultant for AImmune, and has research funding from the NIH.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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