



Food and aeroallergens in eosinophilic esophagitis: role of the allergist in patient management

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Purpose of review

Eosinophilic esophagitis is a clinicopathologic disease of increasing worldwide prevalence that is triggered by food antigens. The concurrent management of all of the atopic diseases affecting a single individual is likely to be important for successful long-term eosinophilic esophagitis management. This review covers the role of the allergist in eosinophilic esophagitis with a focus on the literature from the past 2 years.

Recent findings

Studies in the past 2 years document that testing for immediate and delayed allergic hypersensitivity to foods can be of utility in building elimination diets in children, but that this may not be the case in adults. In addition, it has been shown that a number of cells and interleukins involved in Th2 inflammation such as invariant natural killer T cells, basophils, and interleukin-9 are important in eosinophilic esophagitis pathogenesis. Finally, the role of foods in generating esophageal remodeling has been shown using murine models.

Summary

Recent studies support the role of the allergist in eosinophilic esophagitis management, especially for food allergen testing, interpretation, and the management of food allergies concurrent atopic diatheses. In addition, allergists have made significant research contributions in our understanding of eosinophilic esophagitis.

Keywords

eosinophil, fibrosis, food allergy, food sensitization, remodeling

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, antigen-mediated disease of increasing prevalence in both adults and children [1[•]]. The immunopathogenesis of EoE involves a Th2-associated cytokine response, often to food antigens, with elevated levels of chemokines and interleukins such as eotaxin-3 and interleukin (IL)-5 that both attract and activate eosinophils [2,3]. In addition, a number of mast-cell promoting interleukins such as IL-9 are increased, as are proremodeling factors involved in fibrosis and angiogenesis, for example, TGFβ1, VEGF-1, CCL-18, and its receptor, CXCR-8 [4,5[•],6[•],7–9]. The molecular pathogenesis of EoE appears to align significantly with other atopic disorders such as asthma, allergic rhinitis, and eczema. Consistent with the concept that EoE is part of the allergic sequence known as the ‘allergic march’, it often appears that a patient shifts his or her allergic status to include the esophagus.

A number of studies published over the last 1–2 years support the role of food and aeroallergens as EoE triggers and underscore the importance of

allergists in EoE management. Indeed, a number of insights in both disease mechanisms and management have come from collaborative efforts between allergy, immunology, pathology, and gastroenterology physicians and researchers. This article describes the seminal findings as they relate to allergy in EoE.

THE ROLE OF AEROALLERGENS IN EOSINOPHILIC ESOPHAGITIS

Initial reports supporting the role of aeroallergens in EoE came from animal models that demonstrated the onset of esophageal eosinophilia in response to the instillation of intranasal aeroallergens such as

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Curr Opin Gastroenterol 2014, 30:391–395

DOI:10.1097/MOG.0000000000000088

KEY POINTS

- EoE is an allergic disease of Th2, eosinophilic inflammation akin to other atopic diatheses.
- The role of allergy testing and interpretation is important in the management of food and aeroallergen triggers for EoE.
- The allergist should play an integral role in EoE management.

Aspergillus, house dust mite, and cockroach [10,11]. In addition, case reports documented the spontaneous recurrence and remission of EoE during the pollen season [12]. Whether there is seasonality to EoE may depend on the geographic location of the population [13,14]. However, what is clear is that EoE individuals have higher rates of aeroallergen sensitization than the general population [1¹¹].

A recent case report of a child with house dust mite sensitization and difficult to manage EoE demonstrated that specific immunotherapy using dust mite antigen was useful in controlling EoE symptoms and histology [15]. Whether this is generally true in patients with aeroallergen sensitization or whether aeroallergen immunotherapy could represent a new or adjunct treatment option in EoE or both remain to be systematically evaluated, but this issue may well warrant controlled trials and further study. In addition, recent animal model studies have documented that *Aspergillus*-induced EoE can be reduced in mice that lack invariant natural killer T (iNKT) cells (see further discussion below) [16¹¹]. As such, shifts in the compartments of NKT and other T-cell subsets such as regulatory and effector T cells may occur using aeroallergen-specific immunotherapy.

THE ROLE OF FOOD ANTIGENS AS EOSINOPHILIC ESOPHAGITIS TRIGGERS AND FOOD ALLERGY TESTING IN EOSINOPHILIC ESOPHAGITIS

The role of food allergens in instigating EoE is clear. Animal models definitively demonstrate that food antigens such as ovalbumin (egg) and peanut delivered to the stomach or the esophagus can cause eosinophilic esophageal inflammation [17,18¹¹,19]. Animal models have demonstrated many of the histologic features of human EoE including basal zone hyperplasia of the esophageal epithelium as well as subepithelial fibrosis and angiogenesis [11,18¹¹,20]. Recent data using murine models show that decreasing pathways such as acidic mammalian

chitinase AMCase, which is involved in tissue remodeling, will improve features of food antigen EoE including fibrosis [20]. In addition, mice that do not have canonical TGFβ1 pathway signaling due to blocking antibodies to phosphorylated Smad2/3 also have improvements in esophageal remodeling features such as fibrosis and angiogenesis in egg-induced EoE [18¹¹]. As such, animals with food-induced EoE and remodeling provide preclinical models for understanding potential future therapies to decrease EoE complications.

Recent studies have also demonstrated the importance of immune cells and factors involved in other allergic disorders. For example, thymic stromal lymphopoietin and basophils have been shown to be integral to EoE induction [21]. Mast cells have been shown to be necessary for smooth muscle hyperplasia in EoE, whereas eosinophils and IL-13 have been shown to drive fibrosis and strictures [22,23]. Human data also demonstrate that eosinophils make IL-9, and that eosinophils live in couplets with mast cells in the EoE esophagus [5¹¹]. This points to a mechanism by which eosinophils could actively maintain or instigate other pathogenic features of EoE.

Although antigen-specific T cells have been demonstrated to exist in the peripheral blood of a small number of adult individuals with eosinophilic gastrointestinal disorders (EGID), the presence of food-specific T cells still requires systematic documentation in EoE. Interestingly, recently a number of groups have shown changes in the numbers of iNKT cells in EoE individual esophageal biopsies and peripheral blood [16¹¹,24,25¹¹]. Rather than being antigen specific, these cells are CD1d restricted and recognize certain patterns of antigens such as α-Gal-Cer. iNKT cells are increased in esophageal biopsy specimens but decreased in the peripheral blood of EoE individuals, suggesting that there is increased trafficking of iNKT cells into the esophagus in EoE [16¹¹,24]. Neutralization of iNKT populations in mice was therapeutic for experimental EoE, and activation of iNKT caused murine EoE [16¹¹]. While one group documented the presence of iNKT cells that could be activated by milk sphingolipid, another demonstrated that younger EoE children (<6 years old) had higher levels of esophageal iNKT cells and responded to dietary elimination [25¹¹]. As such, iNKT cells may be potentially important in disease pathogenesis and serve as a potential new therapeutic target in EoE.

Food antigens can induce EoE in both pediatric and adult patients [26¹¹,27]. Indeed, it is intriguing that the same food groups cause disease through all ages of EoE individuals. One study of young children found that isolated milk elimination had success

rates of 65% for complete or partial histologic remission [26[¶]]. In children and adults, milk and wheat are the most common EoE triggers [27–29]. In addition, it is clear that EoE individuals commonly have positive testing for food-specific IgE, demonstrating high rates of food sensitization when testing is done using serum or skin to detect the presence/function of food-specific immunoglobulin E (IgE) [30^{¶¶}]. Although sensitization, that is, the presence of IgE, is common, sensitization does not necessarily connote actual food allergy. Food allergy is constituted when there is a repeatable and predictable reaction upon ingestion of the food antigen. In the case of IgE, these reactions are immediate in nature, usually occurring within minutes of ingesting the triggering food. While it is clear that IgE is the mechanism for immediate hypersensitivity to foods, there is no clear clinical evidence that IgE or immediate food hypersensitivity functions in EoE. In fact, animal models demonstrate that IgE is expendable in murine EoE models [31]. It is clear, however, that there are increased numbers of IgE receptor-positive cells in human EoE individuals, as well as experimental evidence of class switch to IgE in the EoE esophagus [32]. As such, food or aeroallergen-specific IgE may be important in propagating EoE or may allude to a specific clinical EoE phenotype.

In humans, the most convincing evidence for food allergen-driven EoE comes from food antigen elimination and re-introduction trials. As in IgE-mediated food allergy, it is likely that the most commonly consumed foods will be the most common EoE food triggers. As such, it is likely that there will be population differences in EoE triggers that depend on the common foods consumed in any given region of the world. Indeed, in both pediatric and adult populations, amino acid-based formulas that eliminate all food antigens can be highly effective therapy for controlling epithelial histologic changes [30^{¶¶},33,34^{¶¶}]. It is interesting that in children, food antigen elimination can result in control of both epithelial inflammation and subepithelial fibrosis [35,36]. Adults treated with elemental formula had decreased esophageal eosinophilia and improvements in endoscopic features that reflect inflammation, such as plaques and pallor, but this was not the case for those endoscopic changes that represent esophageal remodeling, for example, strictures and narrowing [33]. Also in contrast to pediatric individuals who have symptom control with elemental formula, adult EoE individuals did not necessarily have adequate symptom control with amino acid-based formulas [33].

While empiric elimination of common antigens such as milk, wheat, egg, soy, peanuts/nuts, and

fish/shellfish is effective in controlling adult and pediatric EoE, it would be appealing to create a targeted elimination diet with good predictive values that were based on allergy testing. Such a regimen would allow the removal of only those offending foods and allow for the continued ingestion of nontriggering foods. Current large, pediatric studies demonstrate that the combination skin prick and patch testing can be helpful in creating a successful food elimination diet. However, this may not be the case in adult individuals [37]. Currently, the ideal food allergy test to predict antigenic triggers in EoE does not exist. As such, there is no effective management strategy that bypasses the use of endoscopy with biopsy in order to assess the effects of antigen elimination and re-introduction on esophageal inflammation. Indeed, the only way to definitively document a food trigger for EoE is to remove the food antigen, demonstrate clinico-pathologic EoE resolution, and then re-introduce the food and demonstrate that the histologic, endoscopic, and symptom features of EoE recrudescence.

In an attempt to predict food antigen triggers in EoE, food prick and patch testing have been utilized. Skin prick testing (SPT) demonstrates immediate immunologic hypersensitivity via food-specific IgE on mast cells and basophils. Skin patch tests are geared to demonstrate cell mediated, delayed hypersensitivity to food antigens. Data published in the last year support the use of combined skin prick and patch testing in pediatric EoE individuals. Studies in 98 pediatric EoE individuals showed that sensitivity and specificity rates can vary by food, but specificity of the testing is usually in the range of 78–90% while sensitivity is in the 65–95% range [34^{¶¶}]. Similar to the data on IgE-mediated anaphylaxis, negative predictive values (NPVs) exceed positive predictive values for food testing in EoE. Data from the Children's Hospital of Philadelphia demonstrated NPV of >93% using combined skin prick and patch testing for all foods except milk (NPV = 44%) and wheat (NPV = 88%) [30^{¶¶}]. In contrast, adult data demonstrated that prick/patch test-based dietary elimination has poorer predictive values with only 26% of individuals reaching partial histologic resolution when using a testing-based diet [37]. When evaluating these studies, it is important to note that adult studies do not have nearly the numbers of individuals that the pediatric studies do, with total numbers in testing based elimination adult trials of 15 individuals as opposed to combined pediatric trials that have over 400 individuals.

Although building the perfect allergy test for EoE food triggers has not yet occurred, it is exceedingly clear that EoE individuals have significant rates of food sensitization with positive tests on

specific serum IgE as well as SPT. Seventy-seven percent of children have at least one positive SPT while, overall, 50% of adults will have a positive food test [30²²,38]. There can also be differences in the rates of positive testing depending on the type of extract used, with fresh foods having higher positive rates as compared with food extracts [37]. Using serum-based testing, it is even more common to have positive tests [39]. However, the clinical utility or predictive indexes for serum food-specific IgE are not clear in EoE. As such, the ideal food allergy test remains to be determined.

THE ROLE OF THE ALLERGIST IN EOSINOPHILIC ESOPHAGITIS PATIENT MANAGEMENT

The allergist can play an important and integral role in the management of EoE. The allergist/immunologist has multiple skills and expertise that function synergistically with the gastroenterologist and pathologist for EoE care. First, as noted above, the interpretation and management of food test results can be complex. In addition, individuals should be adequately counseled regarding the risks and benefits of allergen avoidance. For example, there is a substantial amount of research ongoing in food allergy and novel mechanisms for desensitization that have provided relevant information for EoE. Oral desensitization trials have demonstrated that EoE can be induced during desensitization to an IgE-mediated food allergy, and the natural history of milk allergy may progress from IgE-mediated reactions to EoE [40,41,42²³]. However, the rate at which this occurs and whether there are certain individuals who are at higher risk for such events are not clear currently.

With respect to the management of food elimination, allergic issues such as loss of tolerance to a food for which IgE is present must be taken into consideration. Patients who avoid food for weeks to months in the context of sensitization to that food can lose their clinical ability to tolerate that food antigen [43]. In this scenario, the reintroduction of the previously tolerated food can lead to symptoms of immediate hypersensitivity such as hives, angioedema, and respiratory distress. As such, the decisions of whether to prescribe injectable epinephrine during food avoidance and whether to perform a food challenge in an allergist's office when the food is to be reintroduced are important, and potentially life-saving, decisions. For these reasons, patient education regarding food avoidance is important and best done by an allergist.

The high rates of concurrent atopy and the clear interplay between these diseases in an individual

patient warrants skin testing to aeroallergens and their potential avoidance as EoE triggers. In addition, pulmonary function testing may be warranted in EoE individuals, for example, those who present with cough. It is typical that allergic diseases often go hand in hand and this is clearly evidenced in EoE individuals who commonly have more than one allergic diathesis. It is also important to remember that allergic diseases flare in concert. For example, viruses can concurrently flare both asthma and eczema. In addition, avoidance of the same allergic trigger can be integral to management of more than one atopic disease. As a parallel, house dust mite avoidance is important for controlling of both asthma and eczema in the same individual [44]. Indeed, as alluded to in the case report of EoE management with house dust mite-specific immunotherapy, dust mite avoidance or therapy that is tolerogenic for aeroallergens may help to control EoE [15]. Given the potential and documented role of aeroallergens in EoE pathogenesis, it is also possible that EoE flares based on pollen seasons occur. As such, it would be of utility to know if an individual has aeroallergen sensitization. If, for example, an individual with ragweed sensitization has seasonal EoE flares in the fall, medical management could be increased or instituted just during this time frame.

The use of therapies such as chronic, topical corticosteroids is routinely managed by allergists who are familiar with the long-term potential side-effects that vary from one corticosteroid to another, as well as from one formulation to another. As such, the allergist can be of help in making decisions regarding topical steroid choices and formulations, especially because the currently utilized formulations are FDA approved for asthma but not EoE.

CONCLUSION

In conclusion, EoE is an allergic disease of increasing prevalence and for which we are still learning the most common allergic triggers and the most efficient way in which to manage these triggers. As such, it is a disease that is best managed by the concerted efforts of gastroenterology, allergy/immunology, and pathology physicians.

Acknowledgements

S.A. is supported by NIH/NIAID AI 092135 and DOD FA100044.

Conflicts of interest

There are no conflicts of interest.

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