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An Allergist's Perspective to the Evaluation of Eosinophilic Esophagitis

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Abstract

Eosinophilic Esophagitis (EoE) is a classic atopic disease as it shares features with other atopic disease on all levels including pathogenesis, genetics, epidemiology, and treatment options. EoE has elements of Th2 pathogenesis with increase levels of Th2 cytokines (IL4, 5, and 13). In addition, it shares atopic genetic risk factors including thymic stromal lymphopoietin (TSLP) loci as a risk factor in genome wide association studies. EoE patients have a higher rate of other atopic disease (asthma, allergic rhinitis and food allergy) compared to the general population indicating their atopic phenotype. Like asthma, atopic dermatitis or food allergy, EoE has increased in the last 20 years. Treatment options include the basic principle of other atopic diseases include using topical steroids or avoidance of the triggers (food or pollen). An allergist provides a critical role as they are experts in the treatment of atopic disease including avoidance strategies.

Keywords

Eosinophilic Esophagitis; Skin prick testing; Atopy Patch testing; Aeroallergens; Food Allergy

Eosinophilic Esophagitis (EoE) is a chronic immune and antigen mediated clinicopathological disease, which is characterized by eosinophil infiltration into the esophageal epithelium and results in esophageal fibrosis and dysfunction.¹ EoE is emerging as an increasingly common cause of esophagitis in children and adults and requires intensive monitoring and treatment to prevent complications including poor growth, nutritional deficiencies, food impaction, stricture formation, and spontaneous esophageal perforation. In this review, we will briefly review why EoE is considered an atopic disease from a mechanistic, epidemiological, treatment standpoint and the role of allergist in the disease management.

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Conflict of Interest:

None

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Mechanistic Viewpoint-Why EoE is an atopic disease?

Overall, there is a chronic inflammatory infiltrate in EoE, which includes eosinophils, mast cells, basophils and T-cells that produce Th2 cytokines (i.e. IL-4 and IL-13) and promote additional inflammation and dysfunction. Similar to other atopic diseases, EoE is triggered by environmental irritants/allergens and food allergens, culminating in esophageal fibrosis or tissue remodeling.^{2,3} Like atopic dermatitis, there is an altered epithelial barrier dysfunction. Indeed, both gene expression profiling⁴ and immunolocalization studies⁵ have demonstrated a down-regulation in the expression of the cell adhesion protein desmoglein-1 (DSG-1) in the esophageal epithelium in actively inflamed EoE, which partially normalizes after clinical treatment.

Classic atopic cytokines and chemokines play an essential role in the inflammation associated with EoE, resulting in increased Th2 response, eosinophil survival, and fibrotic changes. For example, IL-4 promotes Th2-lymphocyte survival, eosinophil migration via induction of eotaxin-3 (CCL-26), and profibrotic changes by inducing periostin, collagen and β -actin. There are likely redundancies in cytokine function as anti-IL-5 leads to only partial reduction of esophageal eosinophilia in human trials.^{6,7} Thymic stromal lymphopoietin (TSLP) is an IL-7 like cytokine that is a master regulator of Th-2 type allergic inflammation. It is primarily secreted by cells of non-hematopoietic lineage such as epithelial cells, fibroblasts, and smooth muscle cells in response to atopic cytokines (IL-4, IL-13, TNF α) and environmental allergens. TSLP is increased in the esophageal biopsies of EoE subjects compared to non-EoE subjects⁸⁻¹⁰ and is overexpressed within epithelial barriers including the epidermis in atopic dermatitis.^{11,12} Polymorphisms in TSLP are linked to EoE, and deletion of TSLP in a murine model of EoE completely eliminates esophageal eosinophilia. In EoE, expression of TSLP may be induced by tissue injury or stimulation of the esophageal epithelium starting the Th2 cascade. TSLP has also shown to be pivot in the pathogenesis of asthma, allergic rhinitis and atopic dermatitis¹³⁻¹⁵. The same animal models that develop asthma or atopic dermatitis¹⁶ can develop EoE^{10,17} showing the link between atopic disease. Like most atopic diseases, T cells play a critical role as following eosinophils, intraepithelial T-lymphocytes are the most prominent infiltrating cell type in EoE. EoE patients have activated Th2 cells secreting IL-4, IL-5 and IL-13 in both the peripheral blood and active esophageal biopsies.^{18,19} These diverse evidence (animal, cytokine, histology) all indicate that EoE is an atopic disease.

Epidemiological Viewpoint: Why EoE is an atopic disease?

EoE has not only an atopic mechanism for disease progression. Like other atopic disease, the incidence and prevalence of EoE has increased dramatically in the last decade. The rise in EoE mirrors the increased prevalence of allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and food allergy) over the last few decades.²⁰⁻²² In our cohort at The Children's Hospital of Philadelphia, we have seen a 70-fold increase, from 1994 to 2011²³. This rise has also been observed in the adult population with increased prevalence from 2/100,000 in 1989 to 23/100,000 in 2004 in Olten Country, Switzerland²⁴. In addition, the patients are highly atopic with much high rate of asthma, allergic rhinitis and IgE-mediated food allergy compared to general population. Approximately 30-50% of individuals with EoE have

asthma compared to 10% in the normal population^{25,26}. Similar, 50-75% have allergic rhinitis compared to 30% in healthy children. In addition, 10-20% of children with EoE have IgE-mediated food allergy (urticaria and anaphylaxis) compared to 1-5% in normal children²⁵⁻²⁷. These rates of atopy (asthma, allergic rhinitis and atopic dermatitis) are approximately three times higher than what is expected in the general population. Other studies of pediatric and adult patients with EoE have confirmed the higher prevalence of environmental and/or food allergies, approximately fifty percent higher than the general population²⁸⁻³⁰. These data suggests EoE is a super-atopic phenotype.

Treatment Viewpoint: Why EoE is an atopic disease?

Like atopic disease, EoE is allergen driven disease. In most patients (both pediatric and adult patients), foods have shown to cause disease. Foods meet the classic Koch's postulate and removing food resolves disease and addition of same food causes disease. The major issue is how to determine what foods cause the disease. There have been two main approaches: empiric removal of the food or allergy test-driven removal of food.

For the dietary treatment of EoE, the alternate approach to select removal of foods is the total elimination of foods in elemental diets, which have demonstrated resolution of symptoms and normalization of biopsies in greater than 95% of pediatric and adult patients^{23,27,31}. This was original reported by Kelly and colleagues, who examined 10 children who had persistent GERD and esophageal eosinophilia refractory to pharmacotherapy and/or Nissen fundoplication as a treatment of medically resistant GERD. Following a 6-week trial of elemental formula, a significant decrease in esophageal eosinophils and clinical symptoms was observed in all of the patients, with 8 patients demonstrating complete resolution³². Others have reported that 97% of EoE patients treated with an elemental diet achieved symptom resolution and esophageal biopsy normalization both in children and adults^{23,27}. Because of the poor palatability of elemental formulas, elimination diets based on allergy testing (skin prick tests (SPTs) and atopy patch tests (APTs))^{33,34} or removal of the most common food allergens³⁵ have been tried²⁷.

Empiric Elimination of Foods

Kagalwalla and colleagues³⁵, demonstrated improvement of EoE after implementation of an empiric six-food elimination diet, selectively removing the 6 most common food allergens milk, soy, egg, wheat (all gluten grains), peanuts/tree nuts, and shellfish/fish without performing extensive skin testing. They found significant improvement in 74% of patients on the six-food elimination group, as compared with an 88% response in children treated with an elemental diet. However, removal of the most common food allergens did not reduce eosinophils to a normal range: 13.6 eosinophils/high power field (eos/hpf)³⁵ whereas elimination diets when effective based on SPT and APT testing reduce counts to 1.1 eos/HPF^{33,34} and elemental diets²⁷ reduced eosinophil counts to a normal range of 0 eos/HPF. In 50 adult patient, Gonsalves et al³⁶ showed similar effectiveness of a 6 food elimination diet in adults. After 6 weeks, 64% of patients had peak counts < 5 eos/HPF and 70% had peak counts of < 10 eos/HPF. Symptom scores decreased in 94% ($P < .0001$). After food reintroduction, esophageal eosinophil counts returned to pretreatment values ($P < .$

0001). Based on reintroduction, the foods most frequently associated with EoE were wheat (60% of cases) and milk (50% of cases).

Lucendo and colleagues examined a more restrictive diet with removal of nine food groups (milk [cow and goat], egg, wheat [all gluten grains+ oat], corn, rice, legumes, fish, shellfish and tree nuts).³⁷ In this prospective trial, they found resolution in 73% of the 67 adult patients. Milk, egg, wheat group and legume group were the most common foods with about 1/3 of the patient having one trigger group and 1/3 having two trigger food groups and 1/3 having three trigger food groups.³⁷

Based on these four food groups being the most common, Molina examined a “four-food elimination diet” in prospective trial in 52 adults patients.³⁸ They removed milk, egg, legumes and wheat. However, their definition of milk and wheat were very loose. For milk, their patients removed both cow’s and goat’s milk and for wheat, their patients removed all gluten containing grains and oat and for legumes, they remove all legumes including peas, beans, lentils and peanuts. Therefore, this is more a four food group elimination not four individual foods and much harder for a patient to do. In this restrictive diet, they had 54% patient respond.

In each study, milk was found to be the most common food; therefore, Kagalwalla examined the use of only milk elimination in pediatric population. They found 65% patients in a retrospective study responded to milk only elimination in a population of 17 patients.³⁹ However, when we looked at our larger population of over 1000 patients, we were only able to demonstrate 30% response rate to milk elimination.⁴⁰ The rate of single food causing symptoms and disease in EoE vary throughout studies and populations ranging from 30%^{37,40} to 74%. However, the 74% was a pre-selected group that responded to SFED already⁴¹. In their non-selective group, it was 65%. This difference could be due to size of the study, population going to allergist or gastroenterologist and age of the population. Additional studies are needed to better define this question; therefore, a large multi-center study will be done through Consortium for Eosinophilic Gastrointestinal Researchers (CEGIR) and PCORI grants to identified the rate of single food allergy in both pediatric and adult population.

Allergy Testing Directed Diets

One of the difficulties of empiric elimination is that patients are removing unnecessary foods and the diet can be difficult to manage. Therefore, various groups have examined a more scientific method of food removal based on allergy testing.⁴² There are three types of allergy testing, specific IgE testing (called RAST testing), skin prick testing or atopy patch testing. The major issue with any test is the reliability of testing including accuracy and reproducibility. For allergy testing, false and true predictive values as well as sensitivity and specificity have been examined extensively for classic IgE mediated reactions (hives, anaphylaxis), but less so for non-IgE mediated food reactions like EoE. For IgE-mediated reactions, the predictive values vary for each food and age of the population and clinical history. For example, specific IgE of 6 kU/L or wheal greater than 8 mm for egg has 95% positive predictive value for child (2-8 years of age), who has previous clinical reaction to

egg⁴³. In contrast, a specific IgE of 50 kU/L or wheal greater than 8 mm for wheat has less than 50% predictive value that child will react to wheat when re-exposed to the wheat products regardless of the history of previous reactions⁴⁴. In addition, the reproducibility of ⁴⁵ testing and specific IgE (blood) is good, but not perfect. For example, the size of skin test will vary based on location of skin test (arm vs back), season of the testing (in vs out-pollen season) or device used for skin testing⁴⁵. For atopy patch testing, predictive values have been calculated for atopic dermatitis and EoE with similar predictive values to skin prick testing for IgE-mediated reaction with have high negative predictive value for foods with the exception of milk. However, the reproducibility of the testing is poor as it is not as standardized as skin testing or specific IgE.

Specific IgE testing often called RAST testing measures serum specific IgE to individual food based on colorimetric assays. However, RAST is not right terminology, RAST is the old assay based on radioisotope measurement of specific IgE. The current assay uses various techniques to remove non-specific binding leading to false positives. There are various commercial assays that exist with variation on techniques to reduce non-specific binding⁴⁶. The new blood assay (Component Resolved Diagnostics) have examined individual epitopes for food For example for peanut allergy instead of measuring specific IgE to peanut, the assay measures specific IgE to individual parts of peanut (Ara H1, H2, H3, H8 and H9). This assay is useful to differential cross reactivity of peanut with birch pollen (positive to Ara H8) versus peanut anaphylaxis (positive to Ara H2).⁴⁷

There have a few studies that examined the use of specific IgE to guide dietary management of EoE. Most studies have examined retrospectively the predictive value of specific IgE to food causing the reaction. In these studies, they determine what food cause EoE based on empiric elimination and reintroduction of food into the diet. Then, they examine if that food was positive or negative on specific IgE testing. Gonsalves examined this in her adult population and found only 13% of the foods that caused EoE based on biopsy changes had corresponding positive specific IgE⁴⁸. Rodriquez-Sanchez examined the use of specific IgE to guide food elimination compared to empiric food elimination diet in 46 adults. They used a loose definition of positive Specific IgE with >0.1 kU/L instead of traditional 0.35 kU/L. In addition, if a patient had a specific IgE to wheat, they removed oat, rye, rice barley and corn due to possible cross-reactivity. Using these criteria, they had 50% response rate to specific IgE directed elimination diet compared 15% in empiric elimination diet. Erwin and colleagues compared skin testing, specific IgE and atopy patch testing for sensitization to foods in a pediatric population. They found the specific IgE was more sensitive for identifying sensitization to foods; however, they did not examine the specificity of the tests.⁴⁹

Skin prick test (SPT) should be performed using commercially available extract. Using a needle, operator should prick through a drop of the extract should which will be then absorbed. Positive histamine and negative diluents controls need also to be used. Reactions need to record on the basis of the largest diameter (in millimeters) of the wheal and flare at 15 minutes. A wheal of 3 mm greater than the negative control is considered positive. Fifteen studies involving 12 case series and 3 case reports have examined SPT in EoE patients. In adults, positive skin tests to food allergens were difficult to elicit, whereas

positive SPT to environmental allergens were more frequently found than positive reactions to food antigens.²⁹

The poor success rate of diet based completely on IgE testing (SPT or specific IgE0 is consistent with several lines of evidence indicate that IgE is not important in the pathogenesis of EoE. Murine models of EoE have shown that EoE-like disease can develop independent of IgE, as IgE-depleted mice develop food bolus impactions and esophageal eosinophilia equivalent to wild type mice.¹⁰ Although IgE-mediated food allergies are common (10-20%) in EoE, one small pilot study of 2 patients showed that anti-IgE therapy had no effect on esophageal eosinophilia⁵. Oral desensitization to foods is a very effective treatment for several IgE mediated food allergies but not for EoE. Indeed there is an increasing number of patients (5-15%) that resolve their IgE mediated food allergy using oral desensitization but develop EoE once the food is reintroduced in the diet, confirming that IgE mediated food allergy and EoE have a different mechanism^{50,51}. Therefore, I would not recommend IgE testing (skin prick test or specific IgE testing) to identify EoE specific food allergies. Nevertheless, IgE testing is necessary for 10-20% of the patients as they have IgE mediated food allergies.

Therefore, we examined an alternate looking for non-IgE mediated reactions, atopy patch test (APT). Patch testing was developed in the late 1800s for examination of contact dermatitis, a presumed T cell mediated disease. For food allergy, APT has been most extensively studied in atopic dermatitis. After the first controlled trial publication on patch testing in eczema published in 1982⁵², several studies have found that APT are better in identifying late reactions and GI reactions in children with atopic dermatitis⁵³⁻⁵⁵. APT involves prolonged contact of the allergen to the skin with the goal of mimicking a similar immune response to atopic dermatitis. In fact, biopsy specimens of the patch test sites typically show to an initial Th2 cell infiltration followed by a predominance of Th1 cytokines and eosinophils⁵⁶ similar to the biopsy findings that have been observed in the skin of atopic dermatitis patients during acute and chronic lesions³. The food to be tested is typically placed in aluminum cups (Finn Chambers on Scanpore; Alerter Laboratories, Inc. Petaluma, CA) and then applied to uninvolved areas of the patient's back in the 12-mm chambers³³. Similar to patch testing for contact dermatitis, a 48-hour occlusion time is used, and the patches are subsequently read at 24 hours after removal of the Finn chamber⁵⁷. The reading is different than the reading for contact dermatitis and is based on papules. Any food can be assessed with patch testing, although cow's milk, hen's egg, wheat, and soy have been studied most extensively⁵⁸. We have used APT diagnosis of food allergies in EoE extensively^{33,58}. We originally have examined 361 children with biopsy specimen-diagnosed EE and eliminated foods based on positive skin test and atopy patch test. We found that 77% of the patients had resolution of their esophagitis based on these results (including 14% that required elemental formulas because of the multiple positive food allergies). We expanded our patient pool to include all children with EoE seen at the Children's Hospital of Philadelphia between 2000 and 2011 identified 941 patients with EoE with a 50% success rate. We determined what food was triggering their EoE symptoms and biopsy changes as we examined single food elimination or addition. A food was considered a trigger food when biopsy normalized (<5 eos/hpf) when the food was removed or became abnormal (>15 eos/hpf) when the food was added. In our population, 30% had one food,

20% had two foods, 10% had three foods and 30% had more than three foods triggering their EoE.⁵⁹ These are individual foods, which contrasts with empiric elimination diets, which eliminate food groups. The negative predictive value for the combination of SPTs and APTs averaged 92%, with the exception of milk at 44%, and the positive predictive value averaged 44% (Table 1). An empiric 6-food elimination diet or removal of positive foods on allergy testing (SPTs/APTs) both had a histological success rate of 53% (Figure 1). Removal of foods identified on SPTs/APTs plus empiric elimination of milk leads to resolution in 77% of patients. We concluded that an elimination diet based on SPT/APT results leads to resolution of esophageal eosinophilia in a similar proportion of patients as empiric removal of foods (six-food elimination diet) but required that fewer foods be removed. These observations suggest that both methods are acceptable options.⁵⁹

Similar to other atopic disease, the basic non-avoidance treatment of EoE is the use of topical corticosteroids. This is the cornerstone of treatment in asthma, atopic dermatitis and allergic rhinitis. In EoE, the off-label use of topical steroids have shown to be highly effective in the treatment with success in 50-80% depending on the dose and formulation. The two most common topical steroids used are swallowed fluticasone or budesonide. Konikoff et al⁶⁰ conducted a randomized, double-blind, placebo-controlled trial of swallowed fluticasone at 220 mcg 2 puffs twice a day (880 mcg daily) for 3 weeks in pediatric patients with active EoE. Only fifty percent of fluticasone-treated patients achieved histological remission compared with 9% of patients receiving placebo ($P = .047$). Fluticasone decreased esophageal eosinophil levels from 84.6 ± 19.7 vs. 19.6 ± 12.9 eosinophils/high-power field in the distal esophagus. Resolution of vomiting occurred more frequently with fluticasone treated than placebo (67% vs. 27%). Oral viscous budesonide has also been shown to be effective. Children under the age of 10 yr received 1 mg daily and those who were 10 yr or over received 2 mg/day. Viscous budesonide is made by mixing each 1 mg Pulmicort RespuleTM with 10 g (10 packets) of sucralose (SplendaTM) to create a volume of approximately 8mL. Pulmicort RespuleTM is liquid budesonide intended for nebulized administration (0.5mg budesonide/2 mL)^{61,62}. In 20 children (mean age 5.5 yr, median age 4.1 yr) with EoE treated with oral viscous budesonide the mean highest eosinophil count was 87 eos/hpf (range 30–170) before and 7 eos/hpf (range 0–50, $P < 0.0001$) after therapy. There were 16 (80%) responders, 1 partial responder, and 3 no responders. Commonest pretreatment symptoms were nausea, vomiting, pain, and heartburn. The mean symptom score fell from 4.4 to 0.8 ($P < 0.0001$) and the mean endoscopy score from 3.6 to 0.8 ($P < 0.0001$). No significant adverse events were reported. Morning cortisol levels were within normal limits⁶¹. Further randomized placebo controlled study showed similar efficacy in children⁶² and adults⁶³.

The role of aeroallergens in EoE

EoE has been primarily thought to be driven by food allergens, most commonly milk, egg, soy, and wheat^{40,41}. Recently, however, there have been some studies suggesting that aeroallergens may play a role in the pathogenesis of EoE in certain individuals. The correlation between EoE and aeroallergens was first introduced by Mishra and colleagues, who described the development of esophageal eosinophilia in mice following intranasal exposure to *Aspergillus fumigatus*⁶⁴. They proposed a mechanism whereby allergen

sensitization in the respiratory tract via intranasal exposure followed by topical delivery of the allergens to the esophagus leads to EoE. We reported a clinically relevant case of aeroallergen-associated EoE as a 21 year old female with asthma and allergic rhinitis who had worsening symptoms and esophageal eosinophilia during the spring seasons with improvement in the winter seasons⁶⁵. Further evidence for seasonality of EoE symptoms has been described in other studies. Onbassi and his team who found that 26% of patients with allergic rhinitis without GERD had esophageal eosinophilia when biopsied during a time of active allergy symptoms⁶⁶. During pollen season there is an increased numbers of eosinophils in patient with AR compared to normal controls, although the number of eosinophils observed was lower than values typically seen in patients who have EoE^{23,66}. Retrospective analysis show decreased EoE diagnosis in the winter and increased diagnosis in the spring, summer, and fall in a total of 583 pediatric and adult patients with EoE⁶⁷. Similar results have been demonstrated with 330 cases of EoE reported in four additional studies with increase in the diagnosis of EoE in pollen seasons⁶⁸⁻⁷¹. Furthermore, Larson in a series of 313 esophageal bolus impactions found an increase in cases in the summer and fall⁷². However, Sorsen and colleagues evaluation of 753 endoscopies in adults with 44 patients having EoE did not find any seasonality to the diagnosis.⁷³ Overall, there are five reports of seasonality of diagnosis correlating with pollen season and one report that did not find any seasonality.^{68-71,74,75}

Direct evidence for the role of aeroallergen comes from a case report of three adults were recently reported to have developed EoE shortly after large allergen exposure to grass, mold, and dust⁷⁶. Interestingly, there have also been two reports of adult patients developing EoE after starting sublingual immunotherapy (SLIT) for pollen and grass allergies; in both cases, EoE resolved with the cessation of SLIT^{77,78}. These cases further support the potential relationship between EoE and aeroallergens and suggest that in some patients, aeroallergen sensitization underlies EoE as opposed to the more common pattern of food allergen sensitization. Furthermore, one pediatric patients had resolution of esophageal eosinophilia when 2 year treatment of subcutaneous immunotherapy to dust mite⁷⁹.

Of the 1180 patients seen in our EoE clinic, 145 or 12% were suspected of aeroallergen associated triggers based on symptoms. We were able to confirm that 40 patients had confirmed variation of eosinophilia triggered by aeroallergens. The majority of patients were male (80%), all had a history or exam consistent with allergic rhinitis, and most had a history of asthma (75%). Of those with seasonal variation, similar to previous studies^{69,72}, our data confirmed that summer had more flares than spring and fall. Of the 145 suspected cases of aeroallergen-triggered EoE, another 79 patients may in fact have aeroallergens trigger their EoE symptoms and/or esophageal eosinophilia, this could not be definitively confirmed secondary to concurrent alternations in diet or medication or because confirmatory biopsies were not performed. If this is true, the rate of aeroallergen induced EoE would be around 10%.

My personal approach to the role of aeroallergens in EoE is very clinical based and I treat empirical in three scenarios. If a patient has clear symptoms of allergic rhinitis by history or physical exam (for example pale nasal turbinates), I would treat them with antihistamines and nasal steroids. Also, if a patient has EoE symptoms that worsen during pollen season, I

would also recommend treatment. In the last scenario, if a patient fails SFED, I would also consider treating their allergic rhinitis especially if they are atopic; however, SFED does miss some major EoE food allergens such as meats and potato. For patients with significant aeroallergen symptoms, I would recommend skin testing to aeroallergens and consider subcutaneous immunotherapy as treatment options.

Role of the Allergist

Since EoE is an atopic disease, the role of the allergist in diagnosing and treating the disease is important. An allergist has formal training in atopic disease and understanding the pathogenesis of such diseases. The allergist will be able to determine if status of the patient's other atopic disease and help control them. These other atopic disease may affect EoE as atopic diseases in general have been shown not be tissue specific but affect the entire person. An allergist will be able to identify potential aeroallergen and /or food triggers and help design ideal avoidance methods if possible. As allergist have experience in treating atopic diseases with topical steroids or the "newer" biologics (anti-IgE, anti-IL4, 5, 4/13...). Therefore, they will help to manage this atopic disease of the GI tract. EoE will need to be partnership with both allergist and gastroenterologist co-managing this disease.

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Reference

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011; 128:3–20. e6. quiz 1-2. [PubMed: 21477849]
2. Robinson DS, Hamid Q, Jacobson M, Ying S, Kay AB, Durham SR. Evidence for Th2-type T helper cell control of allergic disease in vivo. *Springer Semin Immunopathol*. 1993; 15:17–27. [PubMed: 8103244]
3. Bieber T. Atopic dermatitis. *N Engl J Med*. 2008; 358:1483–94. [PubMed: 18385500]
4. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest*. 2006; 116:536–47. [PubMed: 16453027]
5. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Euro J Pediatric*. 2011; 170:1471–4.
6. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol*. 2006; 118:1312–9. [PubMed: 17157662]
7. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012; 129:456–63. 63, e1–3. [PubMed: 22206777]
8. Rothenberg ME, Spergel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet*. 2010; 42:289–91. [PubMed: 20208534]
9. Sherrill JD, Gao P, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010 (in press).
10. Noti M, Wojno ED, Kim BS, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nature medicine*. 2013; 19:1005–13.

11. Li M, Hener P, Zhang Z, Ganti KP, Metzger D, Chambon P. Induction of thymic stromal lymphopoietin expression in keratinocytes is necessary for generating an atopic dermatitis upon application of the active vitamin D3 analogue MC903 on mouse skin. *The Journal of investigative dermatology*. 2009; 129:498–502. [PubMed: 18650845]
12. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nature immunology*. 2002; 3:673–80. [PubMed: 12055625]
13. Harada M, Hirota T, Jodo AI, et al. Functional analysis of the thymic stromal lymphopoietin variants in human bronchial epithelial cells. *Am J Respir Cell Mol Biol*. 2009; 40:368–74. [PubMed: 18787178]
14. Torgerson DG, Ampleford EJ, Chiu GY, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat Genet*. 2011; 43:887–92. [PubMed: 21804549]
15. Ferreira MA, Matheson MC, Tang CS, et al. Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype. *J Allergy Clin Immunol*. 2014; 133:1564–71. [PubMed: 24388013]
16. Spergel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J Clin Invest*. 1998; 101:1614–22. [PubMed: 9541491]
17. Akei HS, Brandt EB, Mishra A, et al. Epicutaneous aeroallergen exposure induces systemic TH2 immunity that predisposes to allergic nasal responses. *J Allergy Clin Immunol*. 2006; 118:62–9. [PubMed: 16815139]
18. Lucendo AJ, Frigal-Ruiz AB, Rodriguez B. Boerhaave's syndrome as the primary manifestation of adult eosinophilic esophagitis. Two case reports and a review of the literature. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE*. 2011; 24:E11–5.
19. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut*. 2013; 62:824–32. [PubMed: 22580413]
20. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. *J Allergy Clin Immunol*. 2007; 120:491–503. quiz 4-5. [PubMed: 17689596]
21. Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol*. 1999; 103:559–62. [PubMed: 10200001]
22. Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: Data from 2 sequential cohorts. *J Allergy Clin Immunol*. 2002; 110:784–9. [PubMed: 12417889]
23. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *Journal of pediatric gastroenterology and nutrition*. 2009; 48:30–6. [PubMed: 19172120]
24. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol*. 2005; 115:418–9. [PubMed: 15696105]
25. Guajardo J, Plotnick L, Fende J, Collins M, Putnam P, Rothenberg M. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. *J Pediatr*. 2002; 141:576–81. [PubMed: 12378201]
26. Jyonouchi S, Brown-Whitehorn TA, Spergel JM. Association of eosinophilic gastrointestinal disorders with other atopic disorders. *Immunol Allergy Clin North Am*. 2009; 29:85–97. x. [PubMed: 19141344]
27. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol*. 2005; 3:1198–206. [PubMed: 16361045]
28. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol*. 2007; 119:731–8. [PubMed: 17258309]

29. Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol*. 2005; 115:1090–2. [PubMed: 15867873]
30. Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2008; 6:531–5. [PubMed: 18304887]
31. Gonsalves N. Food allergies and eosinophilic gastrointestinal illness. *Gastroenterology clinics of North America*. 2007; 36:75–91. vi. [PubMed: 17472876]
32. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterol*. 1995; 109:1503–12.
33. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2002; 109:363–8. [PubMed: 11842310]
34. Spergel JM, Brown-Whitehorn T. The use of patch testing in the diagnosis of food allergy. *Curr Allergy Asthma Rep*. 2005; 5:86–90. [PubMed: 15659270]
35. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006; 4:1097–102. [PubMed: 16860614]
36. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterol*. 2012; 142:1451–9. e1. quiz e14-5.
37. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. 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. *J Allergy Clin Immunol*. 2013; 131:797–804. [PubMed: 23375693]
38. Molina-Infante J, Arias A, Barrio J, Rodriguez-Sanchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. *J Allergy Clin Immunol*. 2014; 134:1093–9. e1. [PubMed: 25174868]
39. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. *Journal of pediatric gastroenterology and nutrition*. 2012; 55:711–6. [PubMed: 22820121]
40. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012; 130:461–7. e5. [PubMed: 22743304]
41. Kagalwalla AF, Shah A, Li BU, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *Journal of pediatric gastroenterology and nutrition*. 2011; 53:145–9. [PubMed: 21788754]
42. Greenhawt M, Aceves SS, Spergel JM, Rothenberg ME. The management of eosinophilic esophagitis. *The journal of allergy and clinical immunology In practice*. 2013; 1:332–40. quiz 41-2. [PubMed: 24565538]
43. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *The Journal of allergy and clinical immunology*. 1997; 100:444–51. [PubMed: 9338535]
44. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol*. 1998; 9:186–91. [PubMed: 9920216]
45. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test - European standards. *Clinical and translational allergy*. 2013; 3:3. [PubMed: 23369181]
46. Kam KL, Hsieh KH. Comparison of three in vitro assays for serum IgE with skin testing in asthmatic children. *Ann Allergy*. 1994; 73:329–36. [PubMed: 7944001]
47. Keet CA, Johnson K, Savage JH, Hamilton RG, Wood RA. Evaluation of Ara h2 IgE thresholds in the diagnosis of peanut allergy in a clinical population. *The journal of allergy and clinical immunology In practice*. 2013; 1:101–3. [PubMed: 24229831]

48. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors. *Gastroenterology*. 2012
49. Erwin EA, James HR, Gutekunst HM, Russo JM, Kelleher KJ, Platts-Mills TA. Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2010; 104:496–502. [PubMed: 20568382]
50. Sanchez-Garcia S, Rodriguez Del Rio P, Escudero C, Martinez-Gomez MJ, Ibanez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol*. 2012; 129:1155–7. [PubMed: 22236725]
51. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol*. 2011; 106:73–4. [PubMed: 21195949]
52. Mitchell EB, Crow J, Chapman MD, Jouhal SS, Pope FM, Platts-Mills TA. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet*. 1982; 1:127–30. [PubMed: 6119511]
53. Kalach N, Soulaïnes P, de Boissieu D, Dupont C. A pilot study of the usefulness and safety of a ready-to-use atopy patch test (Diallertest) versus a comparator (Finn Chamber) during cow's milk allergy in children. *J Allergy Clin Immunol*. 2005; 116:1321–6. [PubMed: 16337466]
54. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol*. 1996; 97:9–15. [PubMed: 8568142]
55. Kekki OM, Turjanmaa K, Isolauri E. Differences in skin-prick and patch-test reactivity are related to the heterogeneity of atopic eczema in infants. *Allergy*. 1997; 52:755–9. [PubMed: 9265992]
56. Darsow U, Drzezga A, Frisch M, et al. Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. *The Journal of investigative dermatology*. 2000; 115:1029–33. [PubMed: 11121137]
57. Rance F. What is the optimal occlusion time for the atopy patch test in the diagnosis of food allergies in children with atopic dermatitis? *Pediatr Allergy Immunol*. 2004; 15:93–6. [PubMed: 14998389]
58. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol*. 2005; 95:336–43. [PubMed: 16279563]
59. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012; 130:461–7. e5. [PubMed: 22743304]
60. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterol*. 2006; 131:1381–91.
61. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *The American journal of gastroenterology*. 2007; 102:2271–9. quiz 80. [PubMed: 17581266]
62. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterol*. 2010; 139:418–29.
63. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterol*. 2010; 139:1526–37. 37, e1.
64. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest*. 2001; 107:83–90. [PubMed: 11134183]
65. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol*. 2003; 112:796–7. [PubMed: 14564365]
66. Onbasi K, Sin AZ, Doganavsargil B, Onder GF, Bor S, Sebik F. Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. *Clin Exp Allergy*. 2005; 35:1423–31. [PubMed: 16297137]
67. Wang FY, Gupta SK, Fitzgerald JF. Is there a seasonal variation in the incidence or intensity of allergic eosinophilic esophagitis in newly diagnosed children? *Journal of clinical gastroenterology*. 2007; 41:451–3. [PubMed: 17450024]

68. Moawad FJ, Veerappan GR, Lake JM, et al. Correlation between eosinophilic oesophagitis and aeroallergens. *Alimentary pharmacology & therapeutics*. 2010; 31:509–15. [PubMed: 19925501]
69. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol*. 2009; 7:1055–61. [PubMed: 19577011]
70. Almansa C, Krishna M, Buchner AM, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *The American journal of gastroenterology*. 2009; 104:828–33. [PubMed: 19240704]
71. Iwanczak B, Janczyk W, Ryzko J, et al. Eosinophilic esophagitis in children: frequency, clinical manifestations, endoscopic findings, and seasonal distribution. *Advances in medical sciences*. 2011; 56:151–7. [PubMed: 22008313]
72. Larsson H, Bergquist H, Bove M. The incidence of esophageal bolus impaction: is there a seasonal variation? *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2011; 144:186–90. [PubMed: 21493413]
73. Sorser SA, Barawi M, Hagglund K, Almojaned M, Lyons H. Eosinophilic esophagitis in children and adolescents: epidemiology, clinical presentation and seasonal variation. *Journal of gastroenterology*. 2013; 48:81–5. [PubMed: 22618806]
74. Elitsur Y, Aswani R, Lund V, Dementieva Y. Seasonal distribution and eosinophilic esophagitis: the experience in children living in rural communities. *Journal of clinical gastroenterology*. 2013; 47:287–8. [PubMed: 23164688]
75. Schlegel CR, Quintanilla NM, Olive AP, Minard CG, Davis CM. Relationship of pediatric eosinophilic esophagitis diagnosis to pollen and mold counts. *Ann Allergy Asthma Immunol*. 2014; 113:321–2. [PubMed: 24996994]
76. Wolf WA, Jerath MR, Dellon ES. De-novo onset of eosinophilic esophagitis after large volume allergen exposures. *Journal of gastrointestinal and liver diseases : JGLD*. 2013; 22:205–8. [PubMed: 23799220]
77. Miehlke S, Alpan O, Schroder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case reports in gastroenterology*. 2013; 7:363–8. [PubMed: 24163646]
78. Antico A, Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. *J Allergy Clin Immunol*. 2014; 133:1482–4. [PubMed: 24636095]
79. Ramirez RM, Jacobs RL. Eosinophilic esophagitis treated with immunotherapy to dust mites. *J Allergy Clin Immunol*. 2013; 132:503–4. [PubMed: 23763975]
80. Pucci S, Incorvaia C. Allergy as an organ and a systemic disease. *Clinical and experimental immunology*. 2008; 153(Suppl 1):1–2. [PubMed: 18721320]

Summary

Eosinophilic Esophagitis (EoE) is an atopic disease; it shares features with other atopic disease: pathogenesis (Th2 cytokines and features), epidemiology (general increase and increase incidence and prevalence of other asthma, allergic rhinitis and food allergy), treatment options (avoidance or topical steroids), and triggers: food and aeroallergen. From the viewpoint of an allergist, these common features indicate that EoE is a classic atopic disease and needs to be treated from that standpoint. Like other atopic disease, EoE does not only have isolated Th2 pathogenesis in the esophagus, but there is atopic features systemically like peripheral eosinophilia, increased sensitization to aeroallergens and elevated Th2 cytokine⁸⁰. These general atopic features seen in EoE indicates that it is important to not only treat the esophagus, but the entire individual with all of their atopic tendencies to get optimal control of their disease.

Practice Points

- Eosinophilic Esophagitis is an atopic disease
- Food Allergies are the cause for the vast majority of patients
- Aeroallergens can exacerbate symptoms in approximately 10% patients
- It is important to control other atopic conditions to control EoE.
- Food elimination by empiric elimination or allergy testing directed therapy are valid and accepted treatment options

Research Agenda

- The role of subcutaneous immunotherapy to pollens in the treatment of Eosinophilic Esophagitis needs to be elucidated
- The optimal dietary therapy for EoE (allergy testing vs empiric elimination) needs to be determined
- The optimal food allergy testing to determine what the causative foods in EoE needs to be developed.

Success rate of various diet therapies in patients with EoE. Retrospective examination of various diets in the EoE definitive food cohort patients (319 patients). Diet successes were defined as identification of all of the causative foods in patients with EoE that led to normalization of esophageal biopsy specimens. Adapted from Spergel et al.⁴⁰

Table 1Negative and Positive Predictive Values for Allergy Testing in EoE³⁸

Food	NPV	PPV
Milk	45%	82%
Egg	93%	61%
Wheat	88%	42%
Soy	93%	33%
Peanut	99%	22%
Beef	96%	31%
Corn	99%	42%
Potato	99%	36%
Chicken	98%	33%

NPV-negative predictive value; PPV-positive predictive value