HHS Public Access

Author manuscript

Immunol Allergy Clin North Am. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Immunol Allergy Clin North Am. 2018 February ; 38(1): 125–139. doi:10.1016/j.iac.2017.09.010.

Diagnosis and Management of Eosinophilic Esophagitis

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SYNOPSIS

Unlike traditional food allergies, IgE is not a key mediator of eosinophilic esophagitis (EoE). Nonetheless, foods antigens are important triggers of EoE, and allergists play an important role in management of this chronic disease. This review addresses insights into the diagnosis and management as it relates to our evolving understanding about the pathogenesis of EoE.

Keywords

Eosinophilic esophagitis; food allergy; elimination diet; IgG4; swallowed steroids

Introduction

Eosinophilic esophagitis (EoE) is defined as a chronic, local, immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation[1]. EoE was first defined as a clinicopathologic syndrome in the 1990s[2,3], and since this time, it has become an increasingly appreciated chronic inflammatory disease. EoE is now estimated to affect 10–50/100,000 children and adults in the United States, Canada, Europe, and Australia, and like other allergic conditions, the incidence appears to be increasing[4–9]. While the underlying pathophysiology of EoE remains unknown, it appears to be due to non-IgE mediated allergic inflammation to allergens, which have been shown to be predominantly food in both children and adults[10,11]. In this review, we will discuss recent advances as it pertains to the diagnosis and management of EoE.

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DISCLOSURE STATEMENT
The authors have nothing to disclose.

Symptoms

The presentation of EoE is not uniform across all ages. Young children and toddlers typically present with nausea, vomiting, feeding difficulties, abdominal pain, and failure to thrive[12,13]. In contrast, teenagers and adults with EoE tend to present with dysphagia, esophageal dysmotility, refractory reflux, or other sequelae related to esophageal remodeling, such as food impaction[14–17].

In addition to the symptoms directly related to EoE, there is a clear association of EoE with other atopic diseases, such as allergic rhinitis, asthma, atopic dermatitis, and IgE-mediated immediate food allergy[18,19]. Recent reports indicate that EoE is also more common in individuals with inflammatory and autoimmune diseases, such as chronic rhinosinusitis, ulcerative colitis, multiple sclerosis and systemic sclerosis[20,21]. There is also a possible association with connective tissue diseases such as Ehlers-Danlos, Marfan and Loeys-Dietz syndrome[22]. This suggests that the suspicion for EoE should be heightened in individuals with such diseases.

Pathophysiology

EoE shares many immunologic features with other atopic diseases. In addition to local eosinophilia, studies from human and animal models have shown that EoE is characterized by impaired epithelial barrier function[23,24] and infiltration of Th2 CD4+ helper T cells[25,26], mast cells[27], basophils[28], plasma cells[29], and group 2 innate lymphoid cells[30]. While allergen-specific IgE antibodies are also often detected, elimination diets based solely on IgE sensitization have had mixed success[31,32], and the use of anti-IgE treatment was not shown to be more efficacious in inducing EoE remission than placebo[29]. It has been shown, in both pediatric and adult populations, however, that food is a key trigger for EoE[33,34]. The strongest such evidence comes from trials with elemental diets, where histologic remission rates greater than 90% are observed, although focused food elimination diets also often lead to remission[10,11,34]. Taken together, EoE is often considered a non-IgE mediated food-antigen driven hypersensitivity[35], though the exact mechanism remains unclear.

Candidate and unbiased genetic approaches have identified a number of genes associated with EoE. These include the genes that encode for (or are involved in the regulation of): thymic stromal lymphopoietin (TSLP), filaggrin, desmoglein-1, calpain-14, eotaxin-3, and TGF-β[36]. Many of these genes are known to be involved in the regulation of barrier function, Th2 induction and tissue remodeling. Consistent with a Th2-related inflammatory milieu, the cytokines IL-4, IL-5 and IL-13 are also up-regulated in EoE[37]. Emerging data also shows abundant antigen-specific IgG4 in the esophageal mucosa and peripheral blood[29,38]. To date, the relative importance of these different cellular and molecular mediators in the pathogenesis of EoE remains to be established.

Diagnostic tests

EoE is a clinico-pathologic disease, and thus, the diagnosis depends on certain pathologic findings in individuals with an appropriate clinical history. As such, an esophagogastroduodenoscopy (EGD) is a required part of the work-up for EoE. At the

macroscopic level, a number of findings are associated with EoE, including esophageal rings, linear furrows, plaques, stenosis and strictures; however these findings are neither sensitive nor specific for the disease[39]. Histologic evidence of at least 15 eosinophils per high power field (hpf) on esophageal mucosal biopsy is required for diagnosis. Based on current guidelines, the diagnosis requires that the elevated eosinophils be limited to the esophagus and not be due to other underlying causes of eosinophilia. Furthermore, this esophageal eosinophilia must be present despite 8 weeks of empiric therapy with a protein-pump inhibitor (PPI)[40]. In those whom there is a favorable response to a PPI (i.e. – the eosinophils drop to less than 15/hpf on repeat endoscopy), the label PPI-responsive esophageal eosinophilia (PPI-REE) is applied. Previous studies, however, demonstrate similar clinical[41], histologic, immunologic[42,43], and molecular[44] characteristics between patients with PPI-REE and EoE, and thus there are currently conflicting opinions as to whether PPI-REE signifies a truly unique pathophysiologic state, or whether it should be considered within the spectrum of EoE[45,46]. As such, recently published European guidelines have eliminated the criteria for a PPI challenge prior to diagnosing EoE[1].

The role for allergy evaluation is important for both the management of EoE and that of comorbid atopic conditions, such as asthma, allergic rhinitis, IgE-mediated food allergy, and atopic dermatitis, which affect a majority of individuals with EoE[47–49]. Individuals with EoE frequently experience allergic rhinitis symptoms and may have seasonal exacerbations of their EoE[50–52], and thus a thorough evaluation of aeroallergen sensitization and treatment of allergic rhinitis symptoms is recommended. Furthermore, children with EoE frequently have concomitant IgE-mediated food allergy[19], and thus a careful evaluation of this condition, especially in light of possible elimination diets and food reintroduction, is essential.

As mentioned above, previous studies examining the use of elemental diets in both children and adults with EoE have demonstrated histologic remission in over 90% of patients[10,11], suggesting that exposure to certain foods are a key trigger for this condition. However, because elemental diets are burdensome and unappealing to many individuals, efforts have focused on the utility of allergy testing, such as skin prick tests, patch tests, and quantification of food-specific IgE, to design more tailored avoidance diets. In general, studies examining allergy-testing directed diets have shown mixed results, albeit with outcomes inferior to elemental diets (see Table 1). A recent meta-analysis demonstrated that 45% of individuals responded to diets guided by allergy testing, but there was considerable heterogeneity among the studies, which likely reflects different testing approaches[34].

The majority of studies examining allergy-testing directed diets have assessed the utility of using positive results from both skin prick and atopy patch testing (APT). APT involves the topical application of fresh food to the skin for 48 hours, with subsequent evaluation and follow-up at 72 hours. APT is an intuitive approach given that IgE-independent mechanisms are thought to be involved in EoE, but the testing is logistically challenging and has not been shown to be universally successful[53–55].

The predictive value of testing serum for food-specific IgE is less well studied than skin testing, but recent reports suggest that low-level specific IgE may be useful for dietary guidance[56,57]. The fact that testing for specific IgE by a multi-array component assay was

not helpful likely reflects important differences between traditional ImmunoCAP assays and multi-array component assays[14], with ImmunoCAP having greater sensitivity to many food allergens[58]. It has been theorized that this poor correlation may be due to assay inhibition by IgG4 blocking antibodies[59]. A role for food-specific IgG4 in identifying food triggers remains an open question, as a recent study also demonstrated that food-specific IgG4 levels of trigger foods decline significantly in patients with EoE after dietary elimination of these foods.[38]. However, whether this test may be used to predict causative foods remains unclear.

Differential diagnosis

The differential diagnosis for EoE includes a number of conditions that can cause esophageal eosinophilia and upper gastrointestinal symptoms. These include gastroesophageal reflux (GERD), parasitic or fungal infections, connective tissue disease, Crohn's disease, celiac disease, carcinoma, drug-related eosinophilia, congenital rings, achalasia, vasculitis and bullous pemphigoid. It is important to exclude these entities based on history and, in some cases, complementary testing.

Treatment

Evidence-based treatment options for EoE generally fall into one of the following categories: acid suppression, dietary avoidance, swallowed steroids, or esophageal dilation. With current guidelines requiring PPI failure as part of EoE diagnostic criteria, an obvious implication is that acid suppression by itself is inadequate therapy (with the exception of PPI-REE). However, as discussed above, recent European guidelines have eliminated the requirement of a PPI trial prior to diagnosis of EoE, and thus treatment with a PPI alone may be adequate in select patients[1]. The decision of whether to continue a PPI after confirming the diagnosis of EoE is not clear-cut, but may be considered if the PPI nonetheless improves symptoms such as reflux or dysphagia[61]. The decision to continue a PPI should be made after weighing the benefits versus the risks associated with the long-term use of these medications[62,63].

Most patients will initially start therapy with either dietary avoidance or a topical steroid. Oral steroids or immunosuppressants can be considered for severe cases, but these are not commonly used or recommended[64]. The advantage of dietary avoidance is that it avoids complications that can result from long-term topical steroid use, such as esophageal candidiasis[65,66], cataracts[67], and adrenal suppression[68]. A disadvantage is that long-term diet restrictions can be challenging, particularly if there are multiple trigger foods. There have been few head-to-head trials comparing food elimination and steroids, although a recent report by Philpott *et al* agrees with our clinical experience that steroids may be more likely to achieve remission than diet alone[69]. Often we find that patients have strong preferences for one option or the other, which helps guide initial management.

Approaches to dietary avoidance can be empiric elimination of the most common food triggers, allergy testing-directed diets, or elemental diets. The fact that allergy tests have not consistently proven useful for predicting trigger foods has led many providers to start with empiric diets. The classic six-food elimination diet (SFED) involves avoidance of milk,

wheat, egg, soy, fish/shellfish and peanuts/tree nuts. This diet was initially studied, in large part, as these foods are commonly associated with IgE-mediated food allergy;[70] however, numerous studies have shown that the SFED can be effective in EoE as well (see Table 2)[71]. Studies examining the SFED have generally shown histologic remission in 60–80% of cases[54,70,72], which is also supported by findings in the systematic review and meta-analysis by Arias and colleagues[34].

Two recent studies have evaluated the efficacy of an empiric four-food elimination diet (FFED). In the first study, which was performed in adults, avoidance of milk/dairy, gluten-containing grains, egg and legumes led to remission in 54% of patients[73]. It is important to note that this "FFED" also included avoidance of goat and sheep's milk, all gluten-containing grains, lentils, chickpeas, peas, beans, peanuts, and many tree nuts. More recently, avoidance of milk/dairy, wheat, egg, and soy was assessed in children with EoE, and a similar percentage of patients (65%) achieved histologic remission[74].

With the realization that milk and wheat are the most common triggers, some investigators have transitioned to a 'step-up' approach, which involves starting with avoidance of milk and gluten-containing cereals, and only restricting additional foods if there has been a response failure[75]. It is important to note, however, that foods that are not included in the SFED have also been implicated in some studies[19,31,76].

The topical steroid formulations that have been most studied are budesonide and fluticasone. While neither is approved by the Food and Drug Administration for the treatment of EoE, both have shown efficacy in controlled trials, and treatment with these medications is supported by American College of Gastroenterology (ACG) guidelines[40]. Fluticasone is usually administered twice a day with a metered-dose inhaler (MDI) without a spacer. While the optimal dose has not been established, commonly used doses are 176 μg/day in 1–4 year olds, 440 μg/day in children 5–10 years old and 880–1760 μg/day for those 11 years or older[77], though some investigators have used 1760 μg/day in children as young as 3 years old[78]. It is critical that the patient swallow and not inhale the medication. Some providers advocate ingesting the contents of individually wrapped foil-lined packets within the dry-powder inhaler (DPI) formulation of fluticasone for easier delivery[79]. Budesonide can be administered by ingestion of the nebulized formulation, but most providers favor using a viscous slurry. In this case, the content of a budesonide respule is added to a thickening agent, such as sucralose, though other vehicles including honey, agave nectar, Neocate Nutra, and applesauce are also frequently used[80,81]. Typically 1 mg of budesonide will be mixed with 0.5–1 teaspoons of sweetener[81]. The recommended oral viscous budesonide (OVB) dose in children (<10 years old) is 1 g once a day, while in those older than 10 years, it is 1 g twice a day. For both fluticasone and budesonide, it is recommended that food and drink be avoided for at least 30 minutes after administration. There have been no head-to-head trials comparing the two different steroid preparations, but an intriguing trial compared budesonide by the viscous versus nebulized formulations and found that viscous budesonide was superior for reducing eosinophilic inflammation[82]. Not unexpectedly, scintigraphy analysis demonstrated that the viscous formulation had extended contact with the esophageal mucosa compared to the nebulized version. Moreover, a recent retrospective comparison of the experience at a single center showed EoE subjects treated with OVB achieved histologic

remission (75%) more often than those treated with swallowed fluticasone (40%)[83]. Taken together, these studies suggest that budesonide viscous slurry may be of benefit in individuals who have failed fluticasone.

A final option to be considered in some cases is periodic esophageal dilation. Some individuals with esophageal strictures may require dilation as part of a multi-faceted treatment approach. In other cases, primarily when symptoms are restricted to dysphagia due to strictures, the symptoms may be addressed solely through periodic esophageal dilation. This approach is undertaken with the important caveat that the procedure is not addressing the underlying inflammation. Dilation has been shown to be successful in many studies, with a recent meta-analysis showing improvement in 75% of cases[84]. The possibility of adverse events including post-procedural chest pain, esophageal perforation, and hemorrhage must be considered when dilation is considered.[84]

Management

The natural history of EoE is not completely understood, but it is thought to be a chronic disease, and the development of fibrotic changes and strictures appears to be common in those with delayed diagnosis[85]. As symptoms and histologic inflammation have been shown to recur in individuals who stop treatment, continued management and surveillance of patients is recommended.[40] In particular, maintenance therapy with swallowed steroids or dietary management should be considered in patients with severe dysphagia, a history of food impaction, high-grade esophageal strictures, and a rapid clinical or histologic response with therapy[40].

While long-term outcomes are not well established, there is evidence that dietary elimination can lead to sustained remission in those who successfully avoid their food triggers[76]. In these patients, especially those avoiding multiple foods, it is important to monitor for nutritional deficiencies and to strongly consider referral or co-management with a dietitian.

Maintenance therapy with swallowed steroids was evaluated in a prospective study of 28 adults with EoE in remission who were treated with either twice daily budesonide (0.25 mg) or placebo for 50 weeks. While eosinophil counts increased in both groups during the study, the increase was statistically less among those treated with swallowed budesonide compared to those treated with placebo, and it was not associated with a significant increase in clinical symptoms[86]. In the absence of long-term data, the risks of treating with swallowed steroids remain largely theoretic, but emerging data suggests a need for careful monitoring of adverse effects. For example, in a prospective trial of children with EoE who were treated with topical steroids for a mean duration of 15 weeks, it was demonstrated that 66% of children developed adrenal suppression[87]. For this reason, periodic monitoring of a morning cortisol level or ACTH is suggested. To minimize the long-term risk of steroids, the dose should ideally be reduced to the minimum that will achieve ongoing remission of symptoms and inflammation, however this is complicated by emerging evidence that dose reduction often leads to a loss of response[78,88].

Future Considerations

Two key areas of ongoing investigation in EoE relate to the development of novel diagnostics and therapeutics. The current reliance on EGD for diagnosis and management of EoE has several pitfalls. An important one is that the inflammatory lesions in EoE are often patchy, which means that several samples are required to reduce the chance of a false negative. And while generally very safe, EGDs are invasive and expensive procedures that carry the risk of infection, perforation, and adverse effects from anesthesia. Novel approaches that may impact diagnosis and/or surveillance include a microarray gene expression diagnostic panel[89] and non-invasive techniques that utilize a capsule or sponge to measure luminal secretions[90,91]. Given the limitations of our current allergy testing, the development of novel assays to identify food and environmental triggers of EoE would further have an important role in guiding more personalized avoidance strategies.

From a therapeutic perspective, there is ongoing interest in targeting a number of mediators involved in eosinophil recruitment and Th2 inflammation. One of the most studied targets to date is IL-5, a cytokine important in the maturation and recruitment of eosinophils[92]. Mepolizumab[93–95] and reslizumab[96], both monoclonal antibodies targeting IL-5, have been shown in clinical trials to decrease esophageal eosinophilia, but clinical responses have not been uniform. Similarly, a monoclonal antibody targeting IL-13, a Th2 cytokine that is elevated in the esophagi of patients with EoE[97], was found to significantly decrease esophageal eosinophils, and there was a non-significant trend towards improved symptoms[98]. A clinical trial of an inhibitor of chemoattractant receptor-homologous molecule on Th2 cells (CRTH2), which is expressed by pathogenic effector Th2 cells[99], was also shown to reduce esophageal eosinophilia and improve clinical symptoms[100]. Potential future targets that may prove efficacious in treating EoE include monoclonal antibodies against IL-4 receptor alpha, a shared receptor for both IL-4 and IL-13, TSLP, and IL-9[101].

Summary

EoE is an emerging chronic inflammatory disease with significant associated morbidity. EoE is commonly food-triggered, and appropriate dietary avoidance is often sufficient for disease remission. Ongoing research holds great promise for the development of novel tools for disease diagnosis and management, as well as for the development of targeted therapies.

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KEY POINTS

- Eosinophilic esophagitis (EoE) is a chronic inflammatory disease that is commonly food-triggered.
- Mainstays of therapy involve the use of proton pump inhibitors, elimination of relevant food triggers, serial esophageal dilations, and topical steroids.
- Contemporary diagnosis and management relies on repeat endoscopy; however, emerging insights hold promise for the development of non-invasive approaches for disease monitoring and novel immune modulating therapies.

Table 1

Key Studies Assessing the Utility of Allergy Testing in EoE

Study (year)	Testing Modality	# of Subjects	Histologic Response	Additional Findings
Children				
Spergel *et al* (2002)[31]	SPT and APT	26	75%*	• Prospective study • Milk and egg were the most common positive foods by SPT • Wheat was the most common positive food by APT
Spergel *et al* (2005)[53]	SPT and APT	146	49%§	• Retrospective analysis of clinic population • Egg, milk, and soy were most common trigger foods identified by SPT • Corn, soy, and wheat were most common foods identified by APT
Spergel *et al* (2012)[32]	SPT and APT	319	53%§	• Retrospective analysis of clinic population • Of 941 patients, causative foods were identified in 319 • Similar histologic success for SPT/APT directed diets and SFED • Most common trigger foods were milk, egg, wheat, and soy
Al-Hussaini *et al* (2013)[102]	SPT and Food-specific IgE (ImmunoCAP >0.35 kU/L)	10	40%**	• Prospective study • Most common trigger foods were milk, soy, wheat, egg, and nuts
Henderson *et al* (2012)[54]	SPT and APT	23	65%**	• Retrospective comparison of elemental, SFED, and allergy-testing directed diets • Elemental diet was the most effective. • SFED and allergy-testing directed diets had comparable effectiveness
Adults				
Molina-Infante *et al* (2012)[55]	SPT, APT, and prick-prick testing	15	33%†	• Prospective trial • Foods that were positive by any form of testing were eliminated
Wolf *et al* (2014)[103]	SPT	22	32%*	• Retrospective study of clinic cohort • Milk, egg, and wheat were most common trigger foods
Rodriguez-Sanchez *et al* (2014)[56]	Food-specific IgE (ImmunoCAP >0.1 kU/L)	26	73%†	• Compared SFED to sIgE-targeted diets. • Fewer foods were removed and fewer EGDs were required in sIgE-directed diet. • Most common triggers: milk, wheat, egg, and legumes
Van Rhijn *et al* (2015)[104]	Component IgE (ISAC microchip)	15	7%‡	• Prospective trial of IgE-directed diet, based on ISAC assay.

Study (year)	Testing Modality	# of Subjects	Histologic Response	Additional Findings
				• Trial was prematurely terminated because only 1/15 patients showed improvement in the interim analysis.

SPT = Skin prick testing; APT = Atopy Patch Testing;

* Based on resolution of symptoms and biopsy results when available;

§ < 5 eosinophils/hpf;

** < 15 eosinophils/hpf;

† <14 eosinophils/hpf and clinical improvement;

‡ <10 eosinophils/hpf

Table 2

Key studies assessing utility of empiric diets in EoE

Study (year)	Empiric Diet	# of Subjects	Histologic Response	Additional Findings
Children				
Kagalwalla *et al* (2006)[70]	Six-food elimination	35	74%‡	• Retrospective observational study comparing SFED with elemental formula diet. • Established that the SFED is associated with clinical and histologic improvement in EoE
Henderson *et al* (2012)[54]		26	81%*	• Retrospective comparison of elemental, SFED, and allergy-testing directed diets, as outlined in Table 1
Kagalwalla *et al* (2017)[74]	Four-food elimination	78	64%	• Prospective observational study • Patients with detectable specific IgE (>0.35 IU/mL) were less likely to respond to diet
Kagalwalla *et al* (2012)[105]	Milk only	17	65%*	• Retrospective study of clinic cohort
Erwin *et al* (2016)[57]		21	62%*	• Prospective observational study • Demonstrated that patients with low, and even undetectable, specific IgE to milk responded to milk elimination diet.
Adults				
Gonsalves *et al* (2012)[72]	Six-food elimination	50	74%*	• First study of SFED in adults. • Most common triggers: wheat and milk • SPT only predicted trigger foods in 13%
Lucendo *et al* (2013)[76]		67	73%*	• Also excluded rice, corn, and legumes • 15 patients demonstrated remission at 2y • Most common triggers: milk, wheat, eggs, and legumes
Rodriguez-Sanchez *et al* (2014)[56]		17	53%*	• Compared SFED to sIgE-targeted diets, as outlined in Table 1
Philpott *et al* (2016)[69]		56	52%*	• Prospective, observational study in Australia comparing SFED to swallowed budesonide
Molina-Infante *et al* (2014)[73]	Four-food elimination	52	54%*	• SFED successful in 31% of FFED non-responders • Milk was the most common trigger (50%)

SPT = Skin prick testing; APT = Atopy Patch Testing

‡ <10 eosinophils/hpf;

* < 15 eosinophils/hpf