Diagnosis and treatment of eosinophilic esophagitis

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Activity Objectives:

1. To discuss the new consensus definition of eosinophilic esophagitis (EoE), including updates on the role of proton pump inhibitors.
2. To describe the relative effectiveness of the different therapies for EoE.

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Eosinophilic esophagitis (EoE) is an eosinophil-rich, T_H2 antigen–mediated disease of increasing pediatric and adult worldwide prevalence. Diagnosis requires greater than or equal to 15 eosinophils per high-power field on light microscopy. Symptoms reflect esophageal dysfunction, and typical endoscopic features include linear furrows, white plaques, and concentric rings. Progressive disease leads to pathologic tissue remodeling, with ensuing esophageal rigidity and loss of luminal diameter caused by strictures. Therapies include proton pump inhibitors, elimination diets, and topical corticosteroids. Effective treatment can reverse tissue fibrosis in some patients, as well as decrease the rate of food impactions. Esophageal dilation might be required to increase luminal patency. The chronic nature of EoE necessitates long-term therapy to avoid disease recurrence and complications. This review serves the function of providing the current state-of-the-art diagnostic criteria and disease management for adult and pediatric EoE. (J Allergy Clin Immunol 2020;145:1-7.)

Key words: *Eosinophil, dysphagia, stricture, fibrosis, corticosteroid, diet, remodeling*

Eosinophilic esophagitis (EoE) is a T_H2 antigen–driven disease in which chronic eosinophil-rich inflammation causes symptoms of esophageal dysfunction.[1] Esophageal symptoms caused by EoE can manifest in multiple ways, including heartburn/regurgitation, vomiting, dysphagia, food impactions, and even abdominal pain. The differential diagnosis for EoE is broad and can include gastroesophageal reflux disease (GERD), parasitic and fungal infections, inflammatory bowel disease, allergic vasculitis, connective tissue disease, and other disorders associated with

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Abbreviations used
EDP: EoE Diagnostic Panel
endoFLIP: Endoscopic functional luminal imaging probe
EoE: Eosinophilic esophagitis
EPX: Eosinophil peroxidase
GERD: Gastroesophageal reflux disease
PPI: Proton pump inhibitor
SFED: Six-food elimination diet
TCS: Topical corticosteroid

esophageal eosinophilia. Untreated EoE progresses to esophageal remodeling, rigidity, and luminal narrowing.[2-4] The diagnosis of EoE rests on the presence of esophageal eosinophilia greater than or equal to 15 eosinophils per high-power field under routine light microscopy after hematoxylin and eosin staining.[1] The diagnosis and management of EoE continue to be updated as new concepts and literature evolve (Fig 1). There have been 4 consensus guideline reports from the United States since 2006.[1,5-7] The goal of this article is to provide an up-to-date review of the current knowledge for EoE diagnosis and its management (Fig 1).

CLINICOPATHOLOGIC DEFINITION OF EoE

Recent consensus recommendations based on a systematic review of the literature and expert opinion led to the diagnostic criteria that EoE is a clinicopathologic disease characterized by (1) esophageal symptoms, including but not limited to dysphagia and food impaction in adults and feeding intolerance and GERD symptoms in children, and (2) eosinophil-predominant inflammation of 15 or more eosinophils per high-power field in the esophageal tissue after exclusion of other disorders associated with similar clinical, histologic, or endoscopic features.[1]

Although the initial consensus recommendations recommended a failure of twice-daily or high-dose proton pump inhibitor (PPI) therapy before diagnosing EoE, the latest consensus guidelines have removed this recommendation.[1,7] Although PPIs primarily provide acid blockade, they also can have anti-inflammatory effects, including decreasing IL-13–induced eotaxin-3 production.[8,9] In clinical alignment with this finding, a subgroup of patients (30% to 50%) who meet EoE diagnostic criteria respond clinically, histologically, and endoscopically to 2 months of high-dose PPI therapy.[10-12] Transcription profiling using the EoE Diagnostic Panel (EDP) also shows that gene expression is identical but less severely dysregulated in patients with PPI-responsive and PPI-resistant EoE.[13] For these reasons, PPI-responsive esophageal eosinophilia is now considered an EoE subphenotype, and PPI is considered a therapeutic option for EoE.[14]

Clinical features

Age-related differences in clinical presentation have been identified in children and adults.[15,16] The most common presenting symptoms in adults are dysphagia, food impaction, heartburn, and chest pain, with as many as 50% of adults initially presenting with food impaction having a final diagnosis EoE.[6] In contrast, children present more commonly with vomiting, heartburn, regurgitation, emesis, and abdominal pain. Although younger children rarely present with the dysphagia and food impaction typical of adult complaints, these presentations are commonly seen in older subjects over the age of 12 years.[17]

Several validated tools are now available to gauge symptoms in adults and children.[18-21] A multicenter study demonstrates that the pediatric symptom scoring tool Pediatric Eosinophilic Esophagitis Symptom Scores (PEESSv2.0) can correlate with histologic changes, including eosinophilia.[14] The Eosinophilic Esophagitis Activity Index adult metric has good correlations between symptoms, histology, and patient-reported outcomes.[20] Despite this, symptoms do not provide adequate EoE diagnostic or management capacity, and EoE patient care requires repeated biopsy to assess for esophageal inflammation.

Endoscopic features

Characteristic features seen during endoscopic examination can suggest an EoE diagnosis. The most common endoscopic features in adults with EoE include linear furrows (80%), mucosal rings (64%), small-caliber esophagus (28%), white plaques and/or exudates (16%), and strictures (12%).[22] In a large clinical series of 381 children, the most common endoscopic features were normal appearance (32%), linear furrows (41%), esophageal rings (12%), and white plaques (15%).[23] Endoscopic features can be subtle and missed on endoscopy, and therefore multiple esophageal biopsies are required in all patients suspected of having EoE, irrespective of endoscopic appearance.[1] The endoscopic reference score (EREFS) has been validated to objectively characterize endoscopic abnormalities in children and adults with EoE.[24,25]

MAKING THE DIAGNOSIS OF EoE

The gold standard for EoE diagnosis remains biopsy findings demonstrating increased intraepithelial esophageal eosinophil counts without concomitant eosinophilic infiltration in the stomach or duodenum.[7] Because eosinophilic infiltration of the esophagus might not be evenly distributed, biopsy specimens should be obtained from the proximal and distal esophagus to increase the diagnostic yield.[26] At least 5 biopsy specimens should be obtained at multiple esophageal levels to maximize the sensitivity based on a diagnostic threshold of 15 or more eosinophils per high-power field.[26] In addition to biopsies performed during elective endoscopy for evaluation of the above symptoms, biopsies are suggested in all patients undergoing endoscopy for food impaction because of the high prevalence of EoE in this subset of patients.

Other histologic features of EoE include superficial layering of the eosinophils, eosinophilic microabscesses (clusters of ≥4 eosinophils), epithelial hyperplasia, intercellular edema or spongiosis, and eosinophil degranulation. Subepithelial fibrosis can be seen in biopsy specimens of both children and adults with EoE.[27] Recent investigations have developed and validated the EoE histologic severity scoring index, a newer histologic scoring system that takes into account additional inflammatory features rather than focusing solely on eosinophil numbers.[28]

The presence of eosinophilia is the key factor for a diagnosis of primary EoE, and therefore it is essential to rule out secondary causes of esophageal eosinophilia. EoE can be associated with other inflammatory intestinal diseases, including inflammatory bowel disease, celiac disease, GERD, and extraesophageal eosinophilic gastrointestinal disorders. In some of these cases, it is important to treat the potential primary disease, such as GERD, Crohn disease, or celiac disease, appropriately and evaluate for remission of esophageal eosinophilia.[6] If still present, then a diagnosis of concurrent EoE and EoE-directed therapy are warranted. Although eosinophils

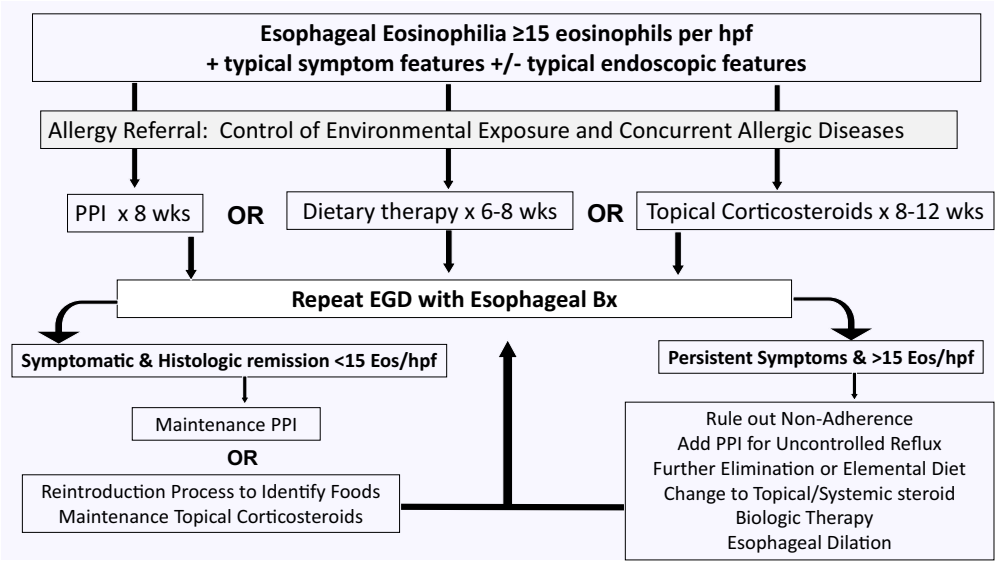

FIG 1. Suggested algorithm for EoE management. *Bx,* Biopsy; *Eos/hpf,* eosinophils/high-power field.

in the esophagus can be attributed to primary EoE, as well as GERD, this distinction is made based on clinical judgement. For instance, if a patient has erosive esophagitis, hiatal hernia, typical reflux symptoms, and esophageal eosinophilia, the primary contribution in this patient is likely reflux versus EoE.

In addition, it is imperative to understand EoE triggers that might be environmental or iatrogenic.[29] A diagnosis or exacerbation of EoE during a pollen season in which a patient is exposed to a triggering antigen might resolve spontaneously. Approximately 3% to 5% of patients receiving oral immunotherapy for the treatment of food anaphylaxis are also at risk for EoE. Removal of the immunotherapeutic antigen usually results in EoE remission.[29]

Less invasive techniques to evaluate the esophagus

Upper endoscopy is a procedure that requires general anesthesia in children and, usually, conscious sedation in adults. As such, upper endoscopy is an invasive procedure that costs health care dollars, as well as lost work and school time. For these reasons, research has focused on the development of less invasive tools to assess esophageal inflammation. The esophageal string test is a capsule-based technology that captures eosinophil-associated proteins from the esophageal lumen and has shown good correlation with eosinophilic infiltration in esophageal biopsy specimens in both children and adults.[30] The Cytosponge (Medtronic, Minneapolis, Minn) is another capsule-based technology originally designed for assessment of the esophageal mucosa in patients with Barrett esophagus and has recently been used to assess inflammation in adults with EoE.[31] Unsedated transnasal endoscopy has been used in children and adults to assess esophageal mucosal inflammation through biopsy.[32,33] More recently, a tethered confocal microscopy capsule has been piloted in adults with EoE, with preliminary data suggesting that comprehensive cellular data can be gathered for assessment of tissue inflammation.[34] Each of these modalities show promise in being able to assess inflammation without the use of standard endoscopy. Although these modalities are unlikely to replace the diagnostic or therapeutic benefits of endoscopy when a diagnosis or dilation is needed, they could have an important role in replacing repeated endoscopies for disease surveillance after treatment interventions.

Additional diagnostic modalities

Thickening of the deeper layers of the esophagus has been demonstrated by using endoscopic ultrasonography.[35,36] Mucosal and submucosal fibrosis and smooth muscle hypertrophy are likely to drive decreased esophageal compliance and to contribute to dysphagia symptoms in the absence of an identifiable stricture.[36,37] A newer technique called the endoscopic functional luminal imaging probe (endoFLIP) has demonstrated altered esophageal wall compliance in adults and children with EoE, further supporting the concern for esophageal remodeling.[38-40] Although esophageal diameter does not correlate with eosinophilic inflammation in adults, 2 pediatric studies have demonstrated that esophageal cross-sectional area and compliance can align with eosinophilic inflammation, epithelial remodeling, and subepithelial fibrosis in children.[39,40] endoFLIP can be a helpful adjunctive tool in both stricture identification and assessment when planning for esophageal dilation in adults (Gonsalves, unpublished data), and esophageal rigidity can improve after treatment with either diet or medication.[41]

Although histologic assessment is the gold standard in diagnosing EoE, there have been cases in which patients with a high pretest probability of EoE have had biopsy specimens that do not meet the diagnostic eosinophil threshold for EoE. Tissue staining for eosinophil products, such as eosinophil peroxidase (EPX), might be of utility in such cases because the eosinophil "footprint" can be detected in the absence of eosinophils.[42] Although EPX staining remains a research tool, if EoE is suspected in a patient because of ancillary testing, such as endoFLIP, or based on clinical symptoms, this can trigger a request for EPX staining by the local pathologist.

The EDP is a molecular tool that might help further identify and risk stratify patients. This test assesses the expression of 96 genes that are dysregulated in patients with EoE and has high sensitivity and specificity for diagnosis.[43] Furthermore, the EDP has distinguished molecular phenotypes in EoE.[44] Both EPX staining

and the EDP can be assessed by using archived tissue, allowing a *post hoc* analysis. Although these tests are mainly research-focused tools at present, there might be clinical applicability of these tools in the future, especially in cases of unclear or borderline EoE.

THERAPEUTIC OPTIONS IN PATIENTS WITH EoE

Dietary therapy

Amino acid formula was first described as an effective therapy in children with EoE, thereby implicating dietary antigens in its pathogenesis.[45] Further studies have confirmed the common causative food antigens.[46] Three distinct dietary approaches have evolved, and an elimination diet has emerged as a nonpharmacologic, first-line approach for EoE management. However, the order and number of specific antigens to avoid and the order of reintroduction remain active areas of investigation.

Elemental diet

The first study to show improvement in EoE after treatment with an elemental or amino acid–based diet in patients with EoE was a case series of 10 children with suspected GERD and esophageal eosinophilia.[45] In this landmark study, administration of an elemental diet led to symptom and inflammatory resolution in children in whom acid blockade had failed. Subsequently, pediatric series from several institutions confirmed an overall greater than 90% histologic remission in EoE using an amino acid formula.[47] Two prospective adult studies of elemental diet reported a lower histologic response of approximately 75%; however, both trials were limited by a 4-week treatment period and high patient nonadherence and dropout because of palatability.[48] An overall meta-analysis showed the superiority of the elemental diet over specific food elimination diets.[47] However, significant obstacles limit the use of amino acid formula, including taste, limited meal variety, lack of insurance coverage, and the number of endoscopies required to identify specific triggers during food reintroduction.

Allergy testing–directed elimination diet

Allergy testing–based elimination diets have used a combination of skin prick and atopy patch tests to detect potential EoE triggers.[49] These diets have met with limited success, especially in adults.[50,51] Current studies demonstrate that omalizumab is not effective for EoE, suggesting that IgE is not required for triggering EoE[52] and consistent with disease mechanisms that rely on cellular immunity and epithelial barrier disruption (see accompanying reviews in this issue of the *Journal*). As such, IgE-based testing does not reflect the triggering mechanism in patients with EoE and, although validated for anaphylaxis, is insufficient for guiding EoE therapy. Atopy patch testing, although reflecting the delayed-type hypersensitivity mechanism of EoE, is not standardized or validated. Milk, the most common EoE trigger, has the poorest predictive values.[49]

In general, the negative predictive values for food testing in patients with EoE are superior to the positive predictive values. Generally, the positive predictive values fall in the 44% range.[47,53] Additional methodologies, including serum IgE testing, patch testing, and component-resolved diagnosis, have been attempted but have not been successful in pinpointing triggering food antigens.[54,55] Despite this, skin prick testing to foods should be considered, especially in children. Empiric removal of a food in a specific food antigen IgE-sensitized child can result in immediate hypersensitivity reactions on food reintroduction.[56] For this reason, skin prick testing, epinephrine dispensation, and office food challenge on reintroduction should be considered.[50] Although food IgE testing might not delineate the causative antigen, the presence of food allergy/sensitization can align with more severe histologic disease in the context of TGF-β1 genotype.[57] In addition, children with a predisposing single nucleotide polymorphism for EoE in the thymic stromal lymphopoietin gene have more food allergen triggers, demonstrating the interaction between foods and genetics in patients with EoE.[58] Other testing modalities for causative foods, such as intraesophageal injections, should not be used routinely unless proved safe.[59]

Empiric elimination diet

Given the difficulties of an elemental diet and the variable response rates to testing-based diets, several studies have used an empiric elimination diet. The foods eliminated are the most common food allergens in the United States. The 6-food elimination diet (SFED) eliminates cow's milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish and has been used the most extensively. SFED has shown consistent effectiveness in the treatment of EoE, with histologic remission in 74% of children.[60] Similar histologic response rates were found in prospective adult EoE studies from the United States and Spain.[61,62] In both adult and pediatric populations, milk, wheat, egg, and soy have been identified as the most common food triggers for EoE, leading to investigation of the "4-food elimination diet" with efficacy equivalence to SFED. Empiric elimination of single foods (milk) and 2 foods (milk and wheat) are also being actively investigated as alternatives to the SFED.[63,64]

Empiric elimination diets still allow continued consumption of a restricted number of table foods, including fruits, vegetables, meat, poultry, rice, beans, and nonwheat grains. The typical duration for empiric elimination diets is 6 to 8 weeks, followed by a repeat endoscopy. In patients demonstrating a histologic response, eliminated food groups are sequentially reintroduced while monitoring for disease recurrence by using endoscopic biopsies. Although there is no standardized approach to food reintroduction and follow-up endoscopy after an empiric elimination diet, typically, a repeat endoscopy is performed after introduction of 1 to 2 foods.[64] The current requirement for repeated endoscopies during reintroduction is a considerable drawback to this approach, particularly in pediatric patients exposed to general anesthesia.[65] Practically, the elimination diet can be onerous because of concerns with dietary contamination, the psychosocial effect of restricted diets, and the costs of allergen-free food products.[66] Incorporation of a dietician and allergist to provide patient education and dietary monitoring likely improves the success of the elimination diet approach. The less invasive methods for esophageal sampling might make the process of diet reintroduction more palatable.[31,67]

Because there are no controlled studies directly comparing diet with steroid therapy in patients with EoE, the choice of treatment approach is currently individualized and based on patient preference. The dietary approach requires a highly motivated patient and physician, as well as available nutritionist resources. Conversations regarding the limited timeframe required for strict elimination, the goal of ultimately liberalizing the eliminated

foods, the ability to discern a causative agent, and the appeal of not using a pharmaceutical agent can help bring an elimination diet into perspective for the patient. In contrast, patients with failure to thrive or an already restricted diet should consider a nondietary first-line approach.

Once a food trigger has been identified, complete avoidance is recommended, especially in children who have positive IgE test results to the food, because of the potential for loss of tolerance. In contrast, in patients with negative skin prick test responses to foods, occasional dietary "indiscretion" might be acceptable and non–life-threatening. Indeed, small case series have described tolerance to baked milk in pediatric patients with cow's milk–mediated EoE.[68] Dietary therapy can be an effective long-term treatment in patients with EoE.[62,63]

Topical corticosteroids

Initial reports began as case studies using asthma metered-dose inhalers with a puff-and-swallow technique for esophageal deposition. Since that time, a number of formulations have been used in randomized, placebo-controlled pediatric and adult EoE trials.[69-73] There are no US Food and Drug Administration (FDA)–approved drugs for EoE in the United States, but an orodispersable budesonide tablet is now available in Europe.[72,73] As such, patients in the United States are still faced with significant challenges, such as proper mixing/swallowing technique and insurance coverage when using topical corticosteroids (TCSs) for EoE.

Meta-analyses of esophageal TCSs in the form of fluticasone or budesonide demonstrate the superiority of TCSs to placebo for esophageal eosinophilia, endoscopic findings, and symptoms.[74] A recent meta-analysis of budesonide showed overall efficacy for all clinical end points, with a histologic response of budesonide to placebo that demonstrated that efficacy of budesonide over placebo generated an overall relative risk of 11.93 ($P < .001$) in 245 pediatric and adult patients.[75]

Long-term TCS therapy is indicated in patients with EoE because of frequent recurrence with TCS removal. However, spontaneous increases in esophageal eosinophil counts despite continued therapy is not uncommon.[76,77] Side effects from TCSs can include oral and/or esophageal candidiasis and adrenal insufficiency.[1] However, adrenal crisis is not common, and there have been no reported adverse effects on height.[78]

PPI treatment in patients with EoE

The reported response rates to PPI therapy in the EoE population can vary widely from 30% to 70%.[1] This is likely due to distinct clinical scenarios, but there are currently no clinical features that clearly discern a patient who will respond to PPI monotherapy. Because high-dose PPI is now considered an EoE-directed therapy but the natural history of PPI-responsive EoE is unclear, it is imperative to continue to follow patients. Differences in the pathophysiology between PPI-responsive and PPI-resistant EoE remain to be determined in depth. Molecular transcriptomics demonstrate that expression of transcript for the potassium channel Kir2.1 (*KCNJ2* gene) is lower in patients with PPI-responsive EoE. If validated, this could provide a potential screen for personalized therapeutics.[12] Patients with allergic rhinitis and CYP2C19 rapid metabolizers are at greater risk for loss of EoE control despite continued PPI therapy.[12]

Esophageal dilation

Esophageal dilation has been used primarily in adults with EoE and strictures. This approach, when done conservatively, is safe, with a low complication rate.[79] Although diet and TCSs can treat inflammatory EoE, dilation treats structural alterations. Esophageal dilation is well tolerated by patients and can provide long-lasting symptomatic relief but does not improve histologic changes.[80]

Environmental allergy testing and control of concurrent atopic diatheses

Abundant data demonstrate the ability of aeroallergens to trigger and/or exacerbate EoE.[81,82] Given this, it is reasonable to test patients with EoE for aeroallergen sensitization and to educate patients about simple avoidance measures. Placebo-controlled trials of subcutaneous immunotherapy for aeroallergens are not feasible for EoE, but case reports document the success of aeroallergen immunotherapy for EoE, and aeroallergen immunotherapy could be a reasonable adjuvant EoE therapy.[83]

There is a close link between the airway and the esophagus. Asthmatic children with EoE have greater levels of esophageal eosinophilia.[37] Because atopic diatheses can influence one another, it is reasonable to speculate that EoE control might be improved by optimizing the management of concurrent asthma, allergic rhinitis, and eczema. To this end, it is the responsibility of the practicing allergist to treat EoE in the context of the entire allergic person.[29]

TREATMENT OF REMODELING

EoE progresses to esophageal remodeling and stricture when left untreated or when the patient is unresponsive to therapy.[2-4] Long-term studies in adults and children suggest that predictors of therapeutic response are female sex and initial response to therapy.[77,84] Current studies demonstrate that sustained response and decreased complications, such as food impactions and subepithelial fibrosis, occur in a subset of adults and children who are responsive to therapy.[37,84,85] Mechanisms for preventing the onset of strictures appear to include treatment early in the disease course and long-term control of esophageal eosinophilic inflammation retention.[37,85] For those patients with a stricture at diagnosis, therapy can be difficult with poor response to TCSs and requirement for repeated dilation.[86]

GOALS OF TREATMENT

When treating EoE, it is critical to remember that it is a chronic disease that requires chronic therapy in most patients. The best maintenance regimens, the ability to sustain therapeutic response, and the optimal histologic, symptomatic, or endoscopic end points remain under investigation. What is clear is that the goal of therapy of EoE is not only to improve clinical symptoms but also to prevent disease progression and ensuing complications.[77] Both medical and dietary therapy can accomplish these goals. Critical areas that need to be further defined in this field are understanding the natural history and predictors of the different phenotypes of the disease, identification of better food trigger identification tools, and development of noninvasive assessments of the esophagus.

What do we know?

- **EoE is a chronic immune-mediated disorder characterized by symptoms related to esophageal dysfunction and eosinophilic histologic inflammation.**
- **Untreated disease can lead to esophageal remodeling and strictures, and maintenance therapy is advised.**
- **Both dietary and medical therapy for this condition have been shown to effectively reduce histologic inflammation, improve clinical symptoms and endoscopic abnormalities, and improve remodeling in a subset of patients.**

What is still unknown?

- **Is there a way to better identify food allergens in identification of food triggers in patients with EoE?**
- **Are there clinical or genetic predictors of response to therapy or progression of this disease?**
- **What are the most effective maintenance therapies?**

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