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Diagnosis and Treatment of Eosinophilic Esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is an eosinophil rich, Th2 antigen mediated disease of increasing pediatric and adult worldwide prevalence.[1] 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 due to strictures. Therapies include proton pump inhibitors, elimination diets and topical corticosteroids. Effective treatment canreverse tissue fibrosis in some patients as well as decrease the rate of food impactions. Esophageal dilation may be required to increase luminal patency. The chronic nature of EoE necessitates long-term therapy in order to avoid disease recurrence and complications. This review serves the function of providing our current state of the art diagnostic criteria and disease management for adult and pediatric EoE.

Keywords

Eosinophil; Dysphagia; Stricture; Fibrosis; Corticosteroid; Diet; Remodeling

Introduction

Eosinophilic esophagitis (EoE) is a Th2, antigen driven disease in which chronic, eosinophil rich inflammation causes symptoms of esophageal dysfunction.[2] Esophageal symptoms due to 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 esophageal eosinophilia. Untreated EoE progresses to esophageal remodeling, rigidity, and luminal narrowing.[3–5] EoE diagnosis rests on the

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presence of esophageal eosinophilia greater than or equal to 15 eosinophils per high power field under routine light microscopy following hematoxylin and eosin staining.[2] The diagnosis and management of EoE continues to be updated as new concepts and literature evolve. There have been 4 consensus guideline reports from the U.S. since 2006.[2, 6–8] The goal of this article is to provide an up to date review of the current knowledge for EoE diagnosis and its management.

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 clinicopathological disease characterized by (a) esophageal symptoms including but not limited to dysphagia and food impaction in adults and feeding intolerance and gastroesophageal reflux disease (GERD) symptoms in children and (b) eosinophil predominant inflammation of ≥15 eosinophils per high power field in the esophageal tissue after exclusion of other disorders associated with similar clinical, histologic, or endoscopic features.[2]

While the initial consensus recommendations recommended a failure of twice daily or high dose proton pump inhibitor (PPI) therapy prior to diagnosing EoE, the latest consensus guidelines have removed this recommendation.[2, 8] Although PPIs primarily provide acid blockade, they also can have anti-inflammatory effects, including decreasing IL-13 induced eotaxin-3 production.[9, 10] In clinical alignment with this finding, a subgroup of patients (30–50%) who meet EoE diagnostic criteria respond clinically, histologically, and endoscopically to two months of high dose PPI therapy.[11–13] Transcription profiling using the EoE Diagnostic Panel (EDP) also shows that gene expression is identical, but less severely dysregulated, in PPI-responsive and PPI-resistant EoE.[14] For these reasons, PPI responsive esophageal eosinophilia is now considered an EoE sub-phenotype and PPI is considered a therapeutic option for EoE.[15]

Clinical features

Age-related differences in clinical presentation have been identified in children and adults.[16, 17] The most common presenting symptoms in adults are dysphagia, food impaction, heartburn, and chest pain with as many as 50% of adult patients initially presenting with food impaction having a final diagnosis EoE.[7] In contrast, children present more commonly with vomiting, heartburn, regurgitation, emesis, and abdominal pain. While younger children rarely present with dysphagia and food impaction typical of adult complaints, these presentations are commonly seen in older individuals over the age of 12 years.[18] Several validated tools are now available to gauge symptoms in adults and children.[19–22] A multicenter study demonstrates that the pediatric symptom scoring tool PEESSv2.0 can correlate with histologic changes including eosinophilia.[15] The Eosinophilic Esophagitis Activity Index (EEsAI) adult metric has good correlations between symptoms, histology and patient reported outcomes.[21] 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%).[23] 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%).[24] Endoscopic features can be subtle and missed on endoscopy so multiple esophageal biopsies are required in all patients suspected of having EoE irrespective of endoscopic appearance.[2] The endoscopic reference scoring tool EREFS has been validated to objectively characterize endoscopic abnormalities in children and adults with EoE.[25, 26]

Making the diagnosis of EoE

The gold standard for EoE diagnosis remains the biopsy findings demonstrating increased intraepithelial esophageal eosinophils without concomitant eosinophilic infiltration in the stomach or duodenum.[8] Since eosinophilic infiltration of the esophagus may not be evenly distributed, biopsies should be obtained from the proximal and distal esophagus to increase the diagnostic yield.[27] At least five biopsies should be obtained at multiple esophageal levels to maximize the sensitivity based on a diagnostic threshold of ≥15 eosinophils per high power field.[27] In addition to biopsies performed during elective endoscopy for evaluation of above symptoms, biopsies are suggested in all patients undergoing endoscopy for food impaction due to high prevalence of EoE in this subset of patients.

Other histologic features of EoE include superficial layering of the eosinophils, eosinophilic micro-abscesses (clusters of ≥4 eosinophils), epithelial hyperplasia, intercellular edema or spongiosis, and eosinophil degranulation. Subepithelial fibrosis may be seen in biopsies of both children and adults with EoE.[28] Recent investigationshave developed and validated the EoE histologic severity scoring index (HSS), a newer histologic scoring system which takes into account additional inflammatory features rather than focusing solely on the eosinophil number.[29]

The presence of eosinophilia is the key factor for a diagnosis of primary EoE so 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 extra-esophageal eosinophilic gastrointestinal disorders. In some of these cases, it is important to treat the potential primary disease, for example, GERD, Crohn’s or celiac disease, appropriately and evaluate for the remission of esophageal eosinophilia.[7] If still present, then a diagnosis of concurrent EoE and EoE-directed therapy are warranted. While eosinophils in the esophagus can be attributed to primary EoE as well as GERD, this distinction is made by 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 may be environmental or iatrogenic.[30] A diagnosis or exacerbation of EoE during a pollen season in which a patient is exposed to a triggering antigen may resolve spontaneously. Approximately 3–5% of patients on oral immunotherapy

for the treatment of food anaphylaxis are also at risk for EoE. Removal of the immunotherapeutic antigen usually results in EoE remission.[30]

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 healthcare 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 (EST) 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.[31] The Cytosponge is another capsule based technology originally designed for assessment of esophageal mucosa in Barrett's esophagus and has recently been used to assess inflammation in EoE in adults.[32] Unsedated transnasal endoscopy has been used in children and adults to assess esophageal mucosal inflammation via biopsy.[33, 34] 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 assessing of tissue inflammation.[35] Each of these modalities show promise in being able to assess inflammation without the use of standard endoscopy. While 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 using endoscopic ultrasound.[36, 37] 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.[37, 38] 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.[39–41] While esophageal diameter does not correlate with eosinophilic inflammation in adults, two pediatric studies have demonstrated that esophageal cross sectional area and compliance can align with eosinophilic inflammation, epithelial remodeling, and subepithelial fibrosis in children.[40, 41] EndoFLIP can be a helpful adjunctive tool in both stricture identification and assessment when planning for esophageal dilations in adults (Gonsalves, unpublished) and esophageal rigidity can improve after treatment with either diet or medication.[42]

While histologic assessment is the gold standard in diagnosing in EoE, there have been cases in which patients with a high pretest probability of EoE have had biopsies which do not meet the diagnostic eosinophil threshold for EoE. Tissue staining for eosinophil products such as eosinophil peroxidase (EPX) may be of utility in such cases since the eosinophil "footprint" can be detected in the absence of eosinophils.[43] While EPX staining remains a research tool, if EoE is suspected in a patient due to ancillary testing such as endoFLIP or by clinical symptoms, this can trigger a request for EPX staining by the local pathologist.

The EoE diagnostic panel (EDP) is a molecular tool which may help further identify and risk stratify patients. This test assesses the expression of 96 genes that are dysregulated in EoE and has high sensitivity and specificity for diagnosis.[44] Further, the EDP has distinguished molecular phenotypes in EoE.[45] Both EPX staining and the EDP can be assessed using archived tissue, allowing a post-hoc analysis. While these tests are mainly research focused tools at present, there may be clinical applicability of these tools in the future, especially in unclear or borderline EoE cases.

Therapeutic options in EoE

Dietary therapy—Amino acid formula was first described as an effective therapy in children with EoE, thereby implicating dietary antigens in its pathogenesis.[46] Further studies have confirmed the common causative food antigens.[47] Three distinct diet approaches have evolved and elimination diet has emerged as a non-pharmacologic, first-line approach for EoE management. However, the order and number of specific antigens to avoid and the order of re-introduction remains an active area of investigation.

Elemental Diet—The first study to show improvement in EoE after treatment with an elemental or amino acid based diet in EoE was a case series of 10 children with suspected GERD and esophageal eosinophilia.[46] In this landmark study, administration of an elemental diet led to symptom and inflammatory resolution in children who had failed acid blockade. Subsequently, pediatric series from several institutions confirmed an overall >90% histologic remission in EoE using amino acid formula.[48] 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 drop out due to palatability.[49] Overall, meta-analysis showed superiority of the elemental diet over specific food elimination diets.[48] 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 utilized a combination of skin prick and atopy patch testing to detect potential EoE triggers.[50] These diets have met with limited success, especially in adults.[51, 52] Current studies demonstrate that omalizumab is not effective for EoE, suggesting that IgE is not required for triggering EoE[53] and consistent with disease mechanisms that rely on cellular immunity and epithelial barrier disruption (see accompanying reviews in this issue of the JACI). As such, IgE based testing does not reflect the triggering mechanism in EoE and, although validated for anaphylaxis, is insufficient for guiding EoE therapy. Atopy patch testing, while reflecting the delayed type hypersensitivity mechanism of EoE, is not standardized or validated. Milk, the most common EoE trigger, has the poorest predictive values.[50]

In general, the negative predictive values for food testing in EoE are superior to the positive predictive values. Generally, the positive predictive values fall in the 44% range.[48, 54] 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.[55, 56] Despite this, skin prick testing to foods should be considered, especially in children. The empiric removal of a food in a specific food antigen IgE sensitized child can result in immediate hypersensitivity reactions upon food reintroduction.[57] For this reason, skin prick testing, epinephrine dispensation, and office food challenge upon reintroduction should be considered.[51] While food IgE testing may not delineate the causative antigen, the presence of food allergy/sensitization can align with more severe histologic disease in the context of TGFβ1 genotype.[58] 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 EoE.[59] Other testing modalities for causative foods, such as intra-esophageal injections, should not be used routinely unless proven to be safe.[60]

Empiric Elimination Diet—Given the difficulties of an elemental diet and the variable response rates to testing based diets, several studies have utilized an empiric elimination diet. The foods eliminated are the most common food allergens in the U.S. The six 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.[61] Similar histologic response rates were found in prospective adult EoE studies from the US and Spain.[62, 63] In both adult and pediatric populations, milk, wheat, egg and soy have been identified as the most common food triggers for EoE leading to the investigation of the "four food elimination diet" with efficacy equivalence to SFED. Empiric elimination of single (milk) and two (milk and wheat) foods are also being actively investigated as alternatives to the SFED.[64, 65]

Empiric elimination diets still allow the continued consumption of a restricted number table foods including fruits, vegetables, meat, poultry, rice, beans and non-wheat grains. Typical duration for empiric elimination diets is 6–8 weeks followed by a repeat endoscopy. In patients demonstrating histologic response, eliminated food groups are sequentially reintroduced while monitoring for disease recurrence using endoscopic biopsies. While there is no standardized approach to food reintroduction and follow up endoscopy after an empiric elimination diet, typically a repeat endoscopy is performed after the introduction of 1–2 foods.[65] The current requirement for repeated endoscopies during the reintroduction is a considerable drawback to this approach particularly in pediatric patients who are exposed to general anesthesia.[1] Practically, the elimination diet can be onerous due to concerns with dietary contamination, psychosocial impact of restricted diets, and 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 may make the process of diet reintroduction more palatable.[32, 67]

Since there are no controlled studies directly comparing diet to steroid therapy in 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 utilizing 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 non-dietary first line approach. Once a food trigger has been identified, complete avoidance is recommended, especially in children who have positive IgE testing to the food, due to the potential for loss of tolerance. In contrast, in patients with negative skin prick testing to foods, occasional dietary "indiscretion" may 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 EoE.[63, 64]

Topical corticosteroids (TCS)—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 utilized in randomized, placebo controlled pediatric and adult EoE trials.[69–73] There are no FDA approved drugs for EoE in the U.S. but an orodispersable budesonide tablet is now available in Europe.[72, 73] As such, patients in the U.S. are still faced with significant challenges such as proper mixing/swallowing technique and insurance coverage when using TCS for EoE.

Meta-analyses of esophageal TCS in the form of fluticasone or budesonide demonstrate the superiority of TCS to placebo for esophageal eosinophilia, endoscopic findings, and symptoms.[74] A recent meta-analysis of budesonide showed overall efficacy for all clinical endpoints with a histologic response of budesonide to placebo that demonstrated efficacy of budesonide over placebo generated an overall relative risk of 11.93 ($p<0.001$) in 245 pediatric and adult patients.[75] Long term TCS therapy is indicated in EoE due to frequent recurrence with TCS removal. However, spontaneous increases in esophageal eosinophils despite continued therapy is not uncommon.[76, 77] Side effects from TCS can include oral and/or esophageal candidiasis and adrenal insufficiency.[2] However, adrenal crisis is not common and there have been no reported adverse effects on height.[78]

PPI treatment in EoE—The reported response rates to PPI therapy in the EoE population can vary widely from 30–70%.[2] 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. Since 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 resistant EoE remain to be determined in depth. Molecular transcriptomics demonstrate that expression of transcript for the potassium channel, Kir2.1 (gene KCNJ2) is lower in PPI responsive patients. If validated, this could provide a potential screen for personalized therapeutics.[13] Patients with allergic rhinitis and CYP2C19 rapid metabolizers are at higher risk for loss of EoE control despite continued PPI therapy.[13]

Esophageal Dilation—Esophageal dilation has primarily been used in adult EoE patients with strictures. This approach when done conservatively is safe with a low complication rate.[79] While diet and TCS can treat the inflammatory EoE, dilation treats the 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 higher levels of esophageal eosinophilia.[38] Since atopic diatheses can influence one another, it is reasonable to speculate that EoE control may 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.[30]

Treatment of remodeling

EoE progresses to esophageal remodeling and stricture when left untreated or when the patient is unresponsive to therapy.[3–5] 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 control of complications such as food impactions and subepithelial fibrosis can be controlled in a subset of adults and children.[38, 84, 85] Mechanisms for preventing the onset of stricture appear to include treatment early in disease course and longitudinal retention of eosinophilic inflammatory control.[38, 85] For those patients who have a stricture at diagnosis, therapy can be difficult with poor response to TCS 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, as well as the optimal histologic, symptom, or endoscopic endpoints, 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 non-invasive assessments of the esophagus.

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Abbreviations

EoE	eosinophilic esophagitis
endoFLIP	endoscopic luminal imaging probe
GERD	gastroesophageal reflux disease
Hpf	high power field
PPI	proton pump inhibitor
SFED	six food elimination diet
TCS	topical corticosteroid

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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 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 EoE?

Are there clinical or genetic predictors of response to therapy or progression of this disease?

What are the most effective maintenance therapies?

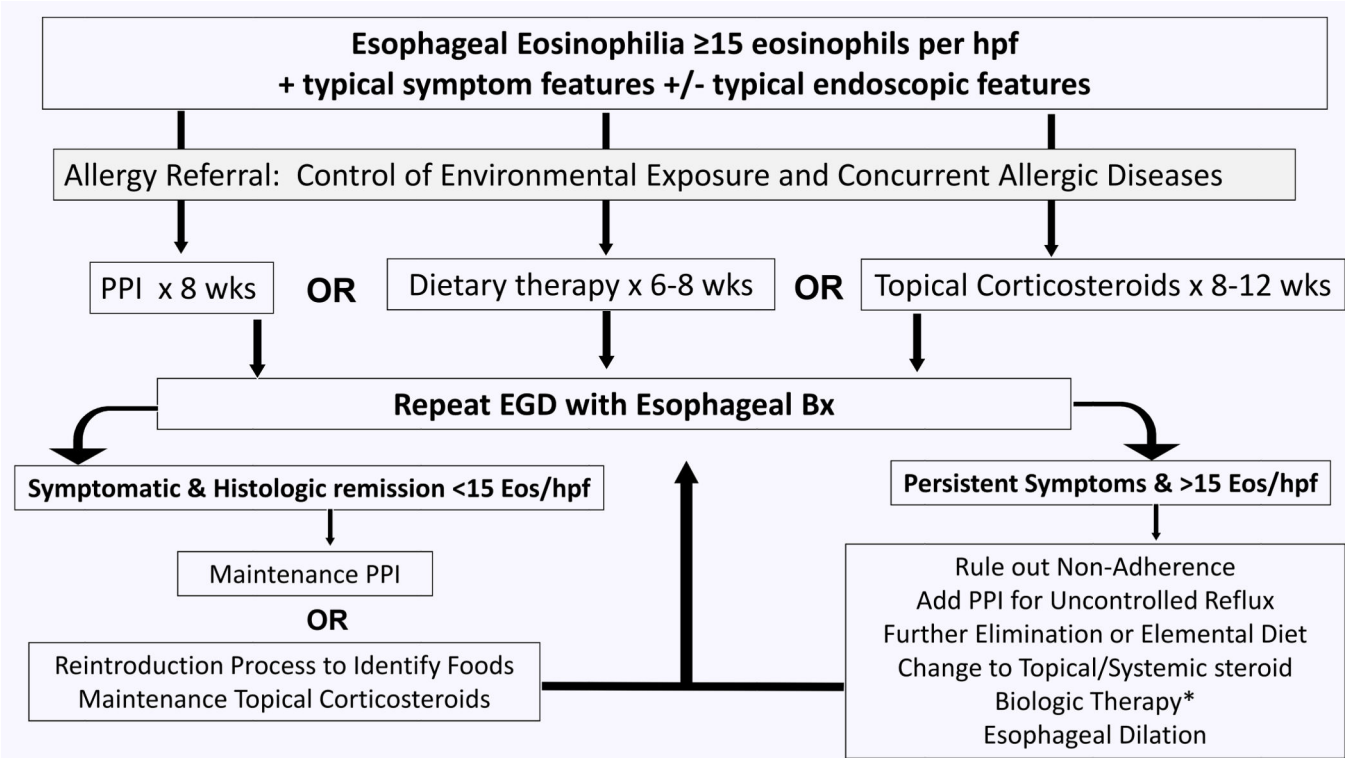

Figure 1:
Suggested algorithm for EoE management. *See Dellon and Hirano article in this issue for further information on emerging biologic therapy.