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Motility (T Lembo, Section Editor)

Current Approach to the Management of Eosinophilic Esophagitis in Adults

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Opinion statement

Eosinophilic esophagitis (EoE) is an increasingly diagnosed, immune-mediated disease characterized by inflammation of the esophagus in both children and adult, causing significant morbidity. Adults typically present with dysphagia and a history of food impaction. Diagnosis should be considered in patients with histological evidence of eosinophilia (≥15 eosinophils per high-power field) on esophageal biopsy. More recently, it has been observed that a significant percentage of patients with esophageal eosinophilia respond both clinically and histologically to PPI therapy. This disorder has been named PPI-responsive esophageal eosinophilia (PPI-REE). Recent studies suggest that patients with PPI-REE have similar clinical and endoscopic features of patients with EoE. Specifically, both PPI-REE and EoE patients have a strong disposition to allergy compared to patients without eosinophilia. As such, PPI-REE may represent a subset or variant of EoE. Effective treatment of EoE requires a multidisciplinary approach with gastroenterologists, pathologists, allergists, and nutritionists. Treatments include elimination and elemental diets, topical glucocorticoids (fluticasone and budesonide), and endoscopic dilation.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus that affects both children and adults. While the pathogenesis is not completely understood, it is thought to be related

to genetic, immunologic, and environmental factors. EoE should be suspected in patients with typical esophageal symptoms and characteristic endoscopic and histologic findings of esophageal eosinophilia. This condition was first reported in the late 1960s. It was initially thought to be a manifestation of gastroesophageal reflux disease (GERD), given their histologic similarities [1]. This association was later questioned, however, as patients often did not have evidence of reflux on objective testing, such as a 24-hour pH monitoring [2]. More recently, population-based studies have demonstrated an increasing incidence of EoE, most commonly among young men in their teens to 30's [3–6]. Affected adults often present with solid food dysphagia and food impaction. Less common clinical symptoms include refractory heartburn, abdominal pain, and chest pain [6–8]. Esophageal strictures have been demonstrated in a substantial percentage of patients with EoE, and esophageal perforations, both spontaneous or procedure related, have also been reported [9–12]. High prevalence of a variety of allergic conditions has also been observed in the EoE population, including food, environmental, and medicinal allergies, asthma, positive radioallergosorbent test (RAST), and positive pinprick skin tests [13–15].

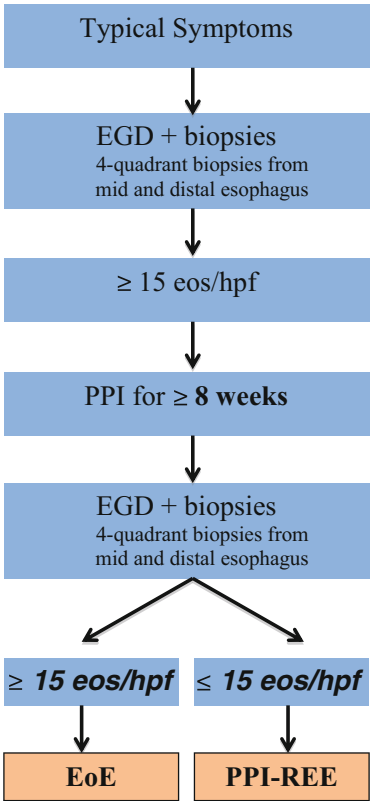

Fig. 1. Diagnostic algorithm for esophageal eosinophilia: EoE versus PPI-REE.

Pathogenesis

To date, the pathogenesis of EoE is incompletely understood, but genetic, immunologic, and environmental factors have been implicated. The underlying immune reactions in EoE is mediated by both immunoglobulin E-dependent and independent mechanisms and may involve several different cell types including mast cells, T cells, and eosinophils [16]. Triggers of the immune reaction, such as food and environmental allergens, may stimulate a T helper 2 (Th2) cell-mediated response, driven by the constitutively expressed chemokine eotaxin-3 [17, 18].

Diagnosis of EoE

Esophageal eosinophilia is defined by an increased infiltration of eosinophils in the squamous epithelium of the esophagus. Recently, a subset of patients with esophageal eosinophilia has been found to respond, both histologically and symptomatically, to PPI therapy. This group of patients with esophageal eosinophilia is now distinguished from those who do not respond to PPI therapy and is termed PPI-responsive esophageal eosinophilia (PPI-REE). Therefore, two

similar yet distinct disease processes are now classified under the umbrella condition of esophageal eosinophilia: EoE and PPI-REE, with the distinction being whether or not there is resolution of eosinophilia in response to PPI therapy. Two consensus guidelines have helped establish diagnostic criteria, with ≥15 eosinophils per high-power field being defined as increased esophageal eosinophilia [19, 20]. The American College of Gastroenterology clinical guideline published in 2013 emphasized the distinction between PPI-REE and EoE as an initial step. From these guidelines, criteria for EoE diagnosis include: ≥15 eosinophils per high-power field, eosinophilia confined to the esophagus despite at least 8 weeks of PPI therapy, exclusion of secondary causes of esophageal eosinophilia, and typical esophageal symptoms (Fig. 1). Treatment response to dietary elimination or glucocorticoids, while not a requirement, helps support EoE diagnosis [19]. Despite the consensus guidelines, the current eosinophil cutoff of 15 eosinophils per high-power field and the length and dose of PPI trial need further study and validation.

Whether PPI-REE is a distinct disease process from EoE or a variant remains uncertain. Studies have shown no significant differences in clinical and endoscopic findings between EoE and PPI-REE [21, 22] or no predictive characteristics to distinguish between the PPI-REE and EoE prior to a PPI trial [23–25]. Given the possible involvement of eosinophils in reflux-induced inflammation of the esophagus, PPI-REE was initially believed to represent GERD-related eosinophilia, due to its response to acid suppression. However, more recent studies, including those from our group, have provided evidence that PPI-REE may be distinct from GERD and more closely resemble EoE. We have also recently demonstrated that PPI-REE patients have similar allergy profiles to EoE patients, but are significantly different from erosive esophagitis patients without eosinophilia [26]. Additionally, levels of eotaxin-3, a chemokine chemotactic for eosinophils, have been shown to be similar between EoE and PPI-REE [27•, 28]. These findings suggest that PPI-REE likely represents a variant or subtype of EoE.

Clinical characteristics

In adults, solid food dysphagia (up to 80 %) represents the most common symptom, while children often present with abdominal pain (26 %) and vomiting (26 %) [29, 30]. A significant proportion of adults with solid food dysphagia experiences food impaction, which often serves as the inciting event leading to ultimate diagnosis [7]. Less commonly, adults may also report reflux [31].

Endoscopic findings

Several characteristic findings on endoscopy have been associated with EoE, including linear furrows, rings, strictures, whitish exudate, edema, narrow esophagus, and crepe paper-like appearance [32–34]. Endoscopic findings, while reportedly highly specific, are not sensitive. An increased risk of esophageal perforation, both spontaneous (Boerhaave's syndrome) and after endoscopy, has also been reported among EoE patients [35–37]. A new classification and grading system for endoscopic findings in EoE has been developed through

rating the major features of EoE including fixed rings, exudates, furrows, and edema, with good interobserver agreement [33].

Histology

Patients with EoE demonstrate at least 15 eosinophils per high-power field on esophageal mucosal biopsies both before and after a trial of PPI, without eosinophilic infiltration in gastric or duodenal biopsies. Two to four biopsies should be obtained from both the proximal and distal esophagus to increase the sensitivity for diagnosis [38]. The characteristic histologic finding in EoE is eosinophilic microabscesses. Other histologic findings include high levels of tryptase-staining mast cells, increased papillary size, and basal cell hyperplasia [25, 39, 40].

Esophageal motility studies

To date, no characteristic motility pattern for EoE has been identified; however, dysmotility can be present in patients with EoE when eosinophilic infiltration invades the muscular propria. Patients with EoE undergoing esophageal manometry may show signs of esophageal body hypercontractility, ineffective peristalsis, or incomplete relaxation of the lower esophageal sphincter [41]. Panesophageal pressurization secondary to decreased esophageal compliance has also been reported. Notably, up to 40 % of patients with EoE have normal manometry. Therefore, there is currently no defined role for esophageal motility studies in the evaluation and management of EoE.

Laboratory studies

While there are no laboratory findings specific to EoE, up to 50 % of patients may demonstrate peripheral eosinophilia and increased IgE levels [20, 42]. There is currently no clear consensus on whether and when EoE patients should be referred for allergy evaluation. However, allergists can play important roles in the management of EoE, both in assessing and treating food allergies, and in testing for other comorbid allergic conditions. In our practice, all patients with confirmed EoE are evaluated by an allergist with skin prick testing and atopy patch testing for both food and environmental allergies given the high prevalence of EoE patients and atopy [43]. Such testing may help identify potential allergens that may trigger disease or symptoms.

Emerging research

Experimental modalities including multiphoton fluorescence microscopy, narrow band imaging, and confocal microscopy capsule may lead to less-invasive approaches to diagnose EoE. The functional luminal imaging probe, an endoscopically administered device that measures esophageal compliance, is a potential promising new technique in the evaluation of EoE since decreased compliance has been related to risk of food impaction [44–46]. An esophageal string test has been designed as a minimally invasive clinical device for

measuring eosinophilic inflammation via eosinophil-derived proteins in luminal secretions [47]. Another recently developed molecular diagnostic test may be used to diagnose patients with EoE, although further research is needed [48].

Treatment

Prior to treatment initiation, other diagnoses that may be clinically similar to EoE must be excluded, including GERD and PPI-REE. This is accomplished with a trial of PPI therapy for at least 8 weeks, followed by a repeat endoscopy demonstrating persistent eosinophilia, defined by greater than 15 eosinophils per high-power field. After confirmation of primary EoE diagnosis, treatment options then include dietary, pharmacologic, and endoscopic therapy, with the goal of both symptomatic and histologic improvement.

Proton pump inhibitor

Since one third to one half of the patients with esophageal eosinophilia respond both clinically and histologically to PPI therapy, a trial of PPI should be attempted after initial identification of esophageal eosinophilia [49]. We recommend high-dose (twice daily) PPI therapy for a minimum of 8 weeks followed by a repeat endoscopy to assess for histologic response. Repeating an endoscopy to document resolution of eosinophilia is important since symptom improvement does not necessarily correlate with improvement in eosinophilia [50]. The benefit of PPI therapy in esophageal eosinophilia may be due to a number of different mechanisms, such as a protective effect on injured hypersensitive esophageal mucosa when exposed to acid [51].

Dietary therapy

Resolution of esophageal eosinophilia with elemental diets (amino acid-based formulas) provided early evidence that food allergens may be a trigger for EoE [52]. Food allergy is derived from both IgE and non-IgE-mediated reactions to chronic immune processes via T cells. In EoE, non-IgE-mediated reactions to ingested allergens appear to be the main mechanism for dysfunction [53, 54]. Removal of allergic triggers from the diet has been shown to induce both clinical and histologic remission, including subepithelial fibrosis [55]. However, identification of the culprit dietary allergens is often difficult on routine skin testing. Moreover, the diets are strict and, especially in children, can lead to behavioral changes such as increased anxiety [56]. Other concerns include cost and adherence [57]. Interestingly, foods that often induce anaphylaxis (e.g., peanuts, shellfish) do not frequently cause EoE. Milk and wheat appear to be the most common EoE triggers [54, 58]. Approaches to dietary therapy for EoE include empiric elimination diet, exclusion of potential allergens according to allergy testing, and amino acid-based elemental formulas. Of these, elemental diets and an empiric six-food elimination diet (SFED) appear to be the most effective in achieving histologic remission [59].

An amino acid-based elemental diet completely eliminates all food allergens and has demonstrated high efficacy in inducing remission. However, adherence

to the diet is often challenging, as the formulas are costly and unappealing in taste, and a large volume may be required to meet daily caloric need. SFED, which excludes milk, soy, egg, wheat, peanut/tree nut, and seafood, is the most commonly used and does not require allergy testing. Allergy testing-based elimination diet may be preferred over an empiric elimination diet to start for patients at a center where allergy testing is readily available, as their regimen may be simplified if a culprit can be identified. However, some EoE patients may test negative on routine skin testing. Even if potential allergens are identified on testing, they may not be the sole trigger of the patients' EoE. The potential benefits and role of routine allergy testing in dietary therapy for EoE needs further evaluation.

After at least 1 month of a diet and improvement in symptoms, repeat biopsies should be performed to establish histologic remission. If biopsies are normal, foods should then be reintroduced from least allergenic to the most while symptoms are carefully monitored. There is currently no consensus on the optimal approach in assessing response to food reintroduction. Some have recommended repeat endoscopy to be performed 3 months after reintroduction of each food to demonstrate histologic remission before adding back the next one. If symptoms recur with any specific food within a group, that specific food should be avoided and another food within the same group should be trialed before repeat endoscopy [56]. This approach, however, would potentially require a large number of endoscopic procedures. Other dietary approaches necessitating fewer endoscopies include simultaneous reintroduction of combinations of similar foods, endoscopy after every two foods, and a four-food, rather than six-food elimination diet. If symptoms persist despite implementation of a diet, reasons for failure must be explored including adherence, environmental triggers, other food allergies, or other causes of eosinophilia [60•].

Medical therapy

Corticosteroids

Topical glucocorticoids are the mainstay of medical treatment. They are the only drugs proven to induce clinical and histologic remission and potentially reduce esophageal remodeling [61]. Fluticasone, budesonide, and ciclesonide are all used, though none have been approved by FDA for the treatment of EoE (Table 1). Budesonide may be administered as an oral viscous slurry or via a nebulizer. Viscous slurry has demonstrated improved histologic response

Table 1. Initial topical steroid dosing for treatment of EoE. This table is adapted with permission from Dellon ES et al. [19]

Medication	Age	Dosing
Budesonide[a]	Children	1 mg/day
	Adults	2 mg/day, divided dose
Fluticasone[b]	Children	88–440 mcg/day, divided dose
	Adults	880–1760 mcg/day, divides dose

[a]Oral viscous budesonide preparation: aqueous solution of 1/2 ml budesonide mixed with 5 g of sucralose
[b]Multidose inhaler preparation: puff into mouth during breath hold and swallowed, minimizing inhalation

compared to placebo or nebulized budesonide, and less dysphagia compared to placebo but not nebulized budesonide [62, 63]. Fluticasone, given via a metered dose inhaler without a spacer, is sprayed into the mouth and swallowed without inhalation. Similar to budesonide, it has demonstrated improved histologic and clinical response compared to placebo [64]. Candidal esophagitis is the most commonly encountered adverse effect, and one case of herpes esophagitis has also been reported [49, 65]. Ciclesonide has also been used but data is limited. The optimal length of therapy remains debated, but may range from 1 to 3 months. Maintenance therapy should be considered in patients with severe symptoms including a history of food impaction and severe endoscopic findings, and in patients who have relapsed after therapy [19]. Maintenance therapy with low-dose swallowed budesonide has been shown to be more effective than placebo in maintaining histologic and clinical remission in EoE patients [66]. Predictors of non-response to steroid therapy found on previous studies include esophageal dilation and decreased level of mast cells and eotaxin-3 [67•]. Systemic corticosteroids also result in clinical and histologic improvement, although their use is often limited by side effects, as well as symptom recurrence with tapering [68]. Therefore, they are reserved for patients with severe symptoms necessitating rapid recovery or those who failed topical therapies.

Other treatments

Early studies demonstrated improved symptoms in patients with EoE treated with montelukast, although later studies have shown mixed results [69, 70]. Monoclonal antibodies against IL-5 (mepolizumab and reslizumab) have been found to result in histologic improvement but little symptomatic improvement to date [71, 72]. Other emerging therapies currently under investigation include OC000459 (a prostaglandin D2 receptor antagonist), monoclonal antibodies against eotaxin 3 and interleukins, and angiotensin receptor blockers [73].

Endoscopic therapy

Esophageal dilation has been demonstrated to improve dysphagia in most patients with esophageal strictures, with a mean symptom-free duration of nearly 2 years. However, dilation is also associated with postprocedural pain in a proportion of patients and does not alter the underlying eosinophilic inflammation [74]. Therefore, endoscopic dilation is reserved for patients with persistent symptoms and endoscopic findings after medical and/or dietary therapy, unless a history of food impaction is reported or a high-grade stricture is found [20]. A variety of methods for esophageal dilation exists. Through-the-scope balloon dilation allows for the inspection and monitoring of the esophageal mucosa in real time, while bougie dilation offers the ability to dilate multiple and long strictures [20]. Regardless of approach, given the fragility of esophageal mucosa in EoE, the endoscopist should aim for small increments in diameter with careful and continuous assessment of the mucosa. This conservative approach may require multiple sessions to reach the dilation target. The size of the initial dilator should be just above that of a regular adult upper gastroscope (approximately 9–10 mm), and each dilation should be limited to a maximum of 3 mm per session, with an ultimate goal of 15–18 mm in esophageal diameter [20, 37, 74, 75]. A recent meta-analysis demonstrated only

a 0.1 to 2 % perforation rate in patients with EoE, which is similar to that in patients without EoE, suggesting that previous concerns for esophageal perforation in EoE may have been overstated [35, 76].

Conclusion

EoE is a chronic inflammatory disorder affecting the esophagus in both children and adults. It causes significant morbidity and presents with a number of different upper gastrointestinal symptoms, the most common of which is dysphagia. Diagnosis is based on typical esophageal symptoms, endoscopic findings, and ≥15 eosinophils per high-power field on esophageal biopsies after at least 8 weeks of PPI therapy, in patients where secondary causes of eosinophilia have been excluded. Treatment of EoE includes diet (elimination or elemental) and drugs (topical glucocorticoids). Endoscopic esophageal dilation is reserved for patients with a critical stricture, history of food impaction, or persistent esophageal symptoms and endoscopic findings after medical therapy. Both diagnosis and treatment of EoE require a multidisciplinary approach from gastroenterologists, nutritionists, allergists, and pathologists given the complexities of the disease and the treatment implications.

Compliance with Ethics Guidelines

Conflict of Interest
Alison H. Goldin declares that she has no conflict of interest.
Walter W. Chan declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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