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Updates in Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a chronic, immune mediated (T helper 2), inflammatory condition of the esophagus characterized by loss of barrier function, eosinophilic infiltration and subsequent remodeling of the esophagus. If left untreated this can lead to development of strictures and fibrostenotic disease. The clinical presentation varies depending on the age at time of diagnosis and chronicity of symptoms. The diagnosis of EoE requires clinical symptoms of esophageal dysfunction together with histologic evidence of esophageal eosinophilia (with ≥15 eos/hpf (about 60 eos/mm2)) without an alternative cause. Therapies for EoE include dietary (elimination diet, allergy testing-based diet, elemental diet) or pharmacologic (proton pump inhibitors (PPI), topical steroids, dupilumab) strategies coupled with esophageal dilation (balloon, bougie) if structuring disease is present. The goal of therapy is ultimately to achieve resolution of clinical symptoms coupled with endoscopic and histologic remission.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immunologic disease of the esophagus that has only been newly recognized over the past few decades. It was first characterized in the late 1970s[1,2] but more formally defined in the 1990s[3-5] and has evolved from being considered as rare case reports or as a feature of gastroesophageal reflux disease to now a common standalone clinical diagnosis. The first diagnostic guidelines for EoE were published in *Gastroenterology* in 2007 and has transformed over the following decade.[6] In this condition, the esophagus is infiltrated by eosinophils, resulting in an inflammatory reaction that leads to a variety of symptoms relating to esophageal dysfunction, including dysphagia, nausea, regurgitation, heartburn, and food impactions.

EoE has been reported in North and South America, Asia, Europe, and Australia. Within the United States, the prevalence of EoE has been estimated to be 1 to 5 patients per 10,000 and is increasing, from 2.7 to 5.2 per 10,000 in 2009 to 2013.[7] A systematic review of population-based studies from North America, Europe and

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Australia showed a pooled incidence rate of EoE of 3.7/100,000 people per year and pooled prevalence of 22.7/100,000 people.[8] EoE can affect people of all age groups, though there is a demonstrated bimodal age distribution with a peak at 12 years and at 41 years. It is more common in males compared to females, with a two- to three-fold increased prevalence in males.

There is a strong association between EoE and other atopic conditions including eczema, asthma, allergic rhinitis, and allergies, with about two-thirds of EoE patients having other allergic diseases.[9] EoE also has a strong familial component, and studies have explored genetic variants which confer a greater risk of developing the condition.[10] Alexander et al. showed a 57.9% ± 9.5% disease concordance in monozygotic twins compared with 36.4% ± 9.3% in dizygotic twins, a difference which did not reach statistical significance (p=0.11) but suggestive of genetic patterning.[11] Similarly, nuclear family heritability was 72% and twin combined gene-environment heritability 99.5%, but additive genetic heritability accounting for a common family environment was lowered to 14.5%, emphasizing the strong impact of environmental factors on development of EoE.

Pathogenesis

Ongoing research attempt to elucidate the pathophysiology of EoE, which is attributed to a complex intersection between genetic risk and environmental exposures. Certain types of food contain antigenic proteins that can trigger a T helper 2 (Th2) response triggering the release of cytokines (IL-4, IL-5, IL-13), which stimulate esophageal squamous cells to secrete eotaxin-3 to recruit eosinophils along with other granulocytes to the esophageal epithelium. The interleukins additionally work through inducing basal cell hyperplasia and dilated intracellular spaces and disrupting the epithelial barrier via inflammation and eventual fibrosis.[12-14]

Clinical Presentation

The presenting symptoms of EoE vary by age of onset. Young children often present with feeding difficulties, failure to thrive, nonspecific abdominal pain, and vomiting, whereas adolescents and adults tend to present with more localizing symptoms including dysphagia, food impaction, and chest or upper abdominal pain.[15-16] Both age groups can commonly present with gastroesophageal reflux. Dysphagia to solids is the most common symptom. 35% of patients in a Swiss Esophageal Esophagitis Database experienced food impactions requiring endoscopic bolus removal,[17] with likely higher rates of self-resolved food impaction that do not present to clinical care. Patients with undiagnosed EoE will often modify their diet and eating behavior which can contribute to delays in diagnosis, with one Swiss study showing a median delay in diagnosis of six years.[18] Some patients will present with esophageal strictures, an advanced feature of EoE. Schoepfer et al. found that diagnostic delay was the only risk factor for esophageal strictures at the time of EoE diagnosis. The prevalence of stricture formation significantly correlated in a time-dependent manner with the duration of undiagnosed and untreated disease, from 17.2% in a diagnostic delay of 0-2 years to 70.8% in a diagnostic delay of >20 years.

Diagnosis

When a suspicion of EoE is raised based on clinical symptoms, diagnosis is confirmed using a combination of endoscopic and histologic criteria. Updated international consensus criteria for EoE diagnosis were published following a conference held by A Working Group on PPI-Responsive Esophageal Eosinophilia (AGREE) in 2018.[19] Diagnosis of EoE requires all of the following criteria to be met: (1) clinical symptoms of esophageal dysfunction; (2) esophageal mucosal biopsies showing ≥15 eos/hpf (about 60 eos/mm^2); and (3) negative evaluation for non-EoE disorders which can contribute to esophageal eosinophilia (e.g., gastroesophageal reflux disease (GERD), Crohn's disease, drug hypersensitivity reactions). Previous iterations of diagnostic criteria required a trial of proton pump inhibitors (PPI) to distinguish EoE from GERD, or a hypothesized condition coined "PPI-responsive esophageal eosinophilia (PPI-REE)", but this criterion was removed in the most recent consensus guidelines as PPI-REE is now simply EoE, or at least along the same spectrum of disease.[20]

Endoscopic findings quantified using the Endoscopic Reference Score (EREFS) can support the diagnosis of EoE, although they are not

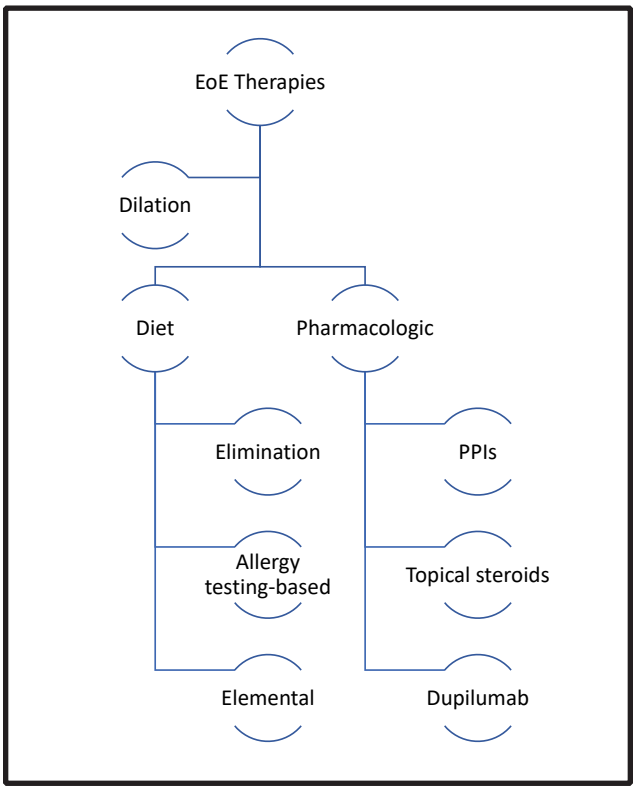

Figure 1. Treatment modalities for EoE. Dietary or pharmacologic therapies in conjunction with dilation (when stricture or narrow caliber esophagus present) have been shown to be effective treatment strategies.

diagnostic for the disease. Endoscopic appearance of the esophagus can be normal in 10-25% of patients with EoE.[21-22] EREFS is a composite of Edema, Rings, Exudates, Furrows, Stricture, with a score for each component based on either its presence or absence, or severity of the finding. It is integral to document the EREFS score when performing endoscopy on EoE patients to compare findings from one procedure to another. When obtaining esophageal biopsies, two to four biopsies should be obtained from at least two esophageal levels (e.g., proximal and distal esophagus) with the goal of increasing diagnostic yield when biopsies are performed on multiple levels.[23] EoE cannot be ruled out when there is a non-diagnostic amount of eosinophilia on esophageal biopsies in the context of active PPI use. Thus, at time of index endoscopy, it is integral that patients are off PPI so as not to mask endoscopic and histologic findings of EoE.

There is significant overlap between EoE and GERD despite being separate entities, and the two conditions can co-exist. Currently there is no single test that can be used to reliably distinguish between the two. Clinicians need to use a combination of patient's history and symptomatology, endoscopic clues (e.g., erosive esophagitis), histologic features, and at times, ambulatory reflux monitoring to come to a clinical diagnosis.

Treatment

EoE is a chronic condition that requires lifelong treatment. Untreated EoE can lead to esophageal fibrosis and remodeling that can result in stricture formation and food impactions. The goal of treatment is both symptomatic improvement and histologic reduction in eosinophil count to <15 eos/hpf. There are several treatment options with comparable efficacy that can be selected based on shared decision making between the clinician and the patient based on factors such as patient preference, drug availability, cost, and ease of therapy. Treatment modalities include dietary therapy, pharmacologic therapy, and dilation of esophageal strictures (Figure 1).

Dietary Therapy

Dietary therapy is an effective non-pharmacologic therapy option that involves eliminating food allergens from the diet. There are three major types of dietary therapy: empiric elimination diet, allergy testing-based diet, or elemental diet. Elimination diet is the most common first-line dietary therapy, and it involves eliminating foods that commonly cause immediate food hypersensitivity reactions. One approach is the six-food elimination diet (6FED) which excludes cow's milk, wheat, egg, soy, peanuts/tree nuts, and fish/shellfish. This diet has shown great efficacy rates in clinical and histologic remission.[24-27] However it is quite restrictive, so subsequent four-food (cow's milk, wheat, egg, soy) and two-food elimination diets (dairy and wheat) were proposed. Efficacy rates for less restrictive diets include 54% and 64% for four-food elimination diet in adults and children respectively and 43% for two-food elimination diet.[28] More recently, Kliewer et al. found that a one-food elimination diet (1FED) excluding only dairy showed no significant difference in histologic remission between 1FED and 6FED at 6 weeks in

a cohort of 129 patients (34% vs. 40%, p=0.58).[29] Therefore, elimination of dairy alone has become the most common initial elimination diet, with step-up therapy as needed.

Allergy testing-based diet and elemental diets are far less common treatment methods. In allergy testing-based elimination diet, dietary elimination is guided by results of common allergy tests such as skin prick test, serum immunoglobulin E (IgE) test, or atopy patch test. However, allergy testing is typically based on detecting IgE antibodies to identify allergens, but EoE is not an IgE mediated disease. This therapy has therefore shown mixed results, with pediatric studies and some adult studies showing effectiveness[30-32] but other adult studies showing lack of reliability of allergy testing predicting food triggers for EoE.[33-34] Elemental diet exclusively consists of an amino acid-based liquid formula, which eliminates all potential food triggers. Although an elemental diet is the most effective approach with a 91% remission rate[35], this is rarely recommended given its significant restriction, decreased quality of life, and high cost.

Pharmacologic Therapy

There are three major pharmacologic treatment options for EoE that come in various modes of administration, including oral PPI, topical swallowed steroids, and injectable biologic drugs.

Although not FDA approved for treatment of EoE, PPIs have been one of the mainstays of therapy since the condition was first defined. In addition to acid suppression, PPIs have anti-inflammatory effects that can treat esophageal eosinophilia. PPIs have been known to block eotaxin-3 expression, which is a key eosinophil chemoattractant in the pathophysiology of EoE.[36-37] Systematic reviews and meta-analyses of EoE patients on PPI have demonstrated a histopathologic remission rate of 42% compared to placebo, and 61% rate of symptomatic improvement.[38-39] Treatment with PPI typically begins with an eight-week trial of the highest dosage taken twice daily, followed by reassessment for symptomatic and histologic remission. Once remission is achieved, the patient can then taper the PPI to the lowest effective dose for chronic maintenance therapy.[40] An alternative strategy is to start with full dose taken once daily for four weeks, then increase to twice daily if symptoms do not improve. PPIs are a commonly preferred first-line therapy due to ease of administration, low cost, and favorable side effect profile.

Topical steroids are an effective pharmacological option, particularly for patients who are averse to systemic therapy. Budesonide (Eohilia™) became the first oral FDA approved medication for eosinophilic esophagitis in early 2024. Prior to recent FDA approval, various budesonide formularies were being used or swallowed fluticasone (metered dose inhaler) was used. Eohilia is a novel oral budesonide suspension that has thixotropic properties, meaning it is more liquid when shaken but becomes viscous when swallowed. Eohilia is supplied as 2 mg/mL single-dose packs while fluticasone comes in the form of a metered dose inhaler. These topical steroids have limited systemic absorption and thus are generally well tolerated while still being able to act directly on the gastrointestinal tract.[41] A systematic review of five studies including 174 patients with EoE showed complete histologic remission in adults and children with an overall effectiveness correlated to an OR of 25.12 (95% CI 5.46, 115.62) in fluticasone versus placebo and OR of 17.17 (95% CI 3.66,80.40) in budesonide versus placebo.[42] A more recent meta-analysis showed topical steroids induced complete histologic response compared to placebo with an OR of 35.82 (95% CI 14.98, 85.64).[43] With regards to Eohilia, there were two double-blind, parallel-group, randomized, placebo-controlled trials that lead to approval of the medication; in patients 11 to 56 years, histologic remission was achieved in 53% vs. 1% placebo and in patients 11 to 42 years, histologic remission was achieved in 38% vs. 2% placebo at 12 weeks.[44-45] It should be noted that Eohilia has not been proven to show benefit beyond 12 weeks and hence the maximum recommended duration of treatment advised by the FDA is 12 weeks.

Dupilumab (Dupixent®) is another FDA approved drug for treatment of EoE in patients ≥ 1 year of age; it is the only medication FDA approved in the pediatric population. It is a human monoclonal antibody that blocks interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling, which play key roles in multiple atopic conditions. It has been previously approved for atopic dermatitis, asthma, and rhinosinusitis with nasal polyposis. The

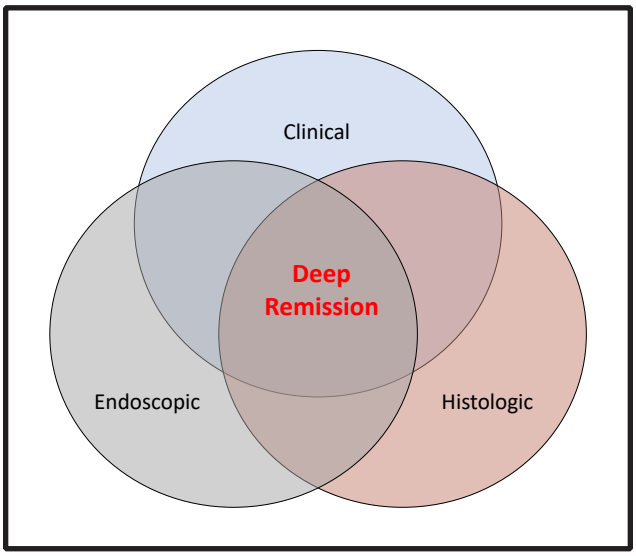

Figure 2. Treat to target approach. The goal of therapy remains obtaining deep remission, which entails clinical, endoscopic, and histologic (<15 eos/hpf) resolution of disease.

dosing for dupilumab varies based on the atopic condition; EoE dosing is 300 mg subcutaneous injection once weekly. Parts A and B of a phase 3 trial demonstrated histologic remission (defined as ≤6 eosinophils/hpf) at 24 weeks in: (A) 60% versus 5% in weekly dupilumab use compared to placebo; (B) 59% in weekly dupilumab use versus 60% in every two-week dupilumab use versus 6% in placebo.[46] Part C of the trial was continued up to 52 weeks demonstrating sustained treatment effects. 82% of patients who received weekly dupilumab in part A-C had <15 eosinophils/hpf at 52 weeks. In part B-C, the placebo group in part B was switched to either weekly or every two-week dupilumab dosing, and patients who had been on the weekly and every two-week dupilumab dosing were continued on their assigned therapy. At 52 weeks, histologic remission rates were 85% in weekly/weekly dupilumab group, 68% in the placebo/weekly dupilumab group, 74% in every 2 weeks/every 2 weeks dupilumab group, and 72% in the placebo/every 2 weeks dupilumab group.[47] It should be noted these studies were performed in PPI-refractory patients though the drug has been FDA approved for EoE independent of a PPI trial. Dupilumab has shown good efficacy on treatment of EoE with a favorable safety profile. The most common side effects include injection site reactions, conjunctivitis, upper respiratory tract infections, arthralgia, and herpes viral infections. Its injectable form and cost, however, may be barriers for some patients.

Esophageal Dilation

Although the primary goal of EoE treatment is to attain histologic remission, endoscopic dilation of the esophagus can provide symptomatic relief of dysphagia related to stenoses, such as strictures or rings, that can be a complication from the chronic inflammation in EoE.[48] Dilations may be particularly beneficial for those with fibrostenotic disease as opposed to an inflammatory phenotype. Dilation therapy alone is not recommended but should be used in conjunction with other medical therapies. Through-the-scope (TTS) balloon dilation can be considered for short-segment strictures, whereas bougie dilation can be used for long-segment strictures or multiple strictures. Often repeat dilations with gradual increases (typically no more than 3mm per session) in the dilation diameter may be necessary to safely achieve an adequate esophageal diameter and symptomatic remission. A goal esophageal diameter of 15 - 18mm is recommended.[49] Risks of dilation include esophageal tears and perforations, bleeding, and chest pain. There was earlier concern that the esophageal tissue is more fragile in EoE particularly when there is ongoing inflammation. However, dilations have been repeatedly shown to be a relatively safe therapeutic procedure, with reported perforation rates of 0.033%.[50]

Combination Therapy

There are currently no systematic guidelines for multimodal pharmacologic therapy. However, this can be considered in patients who are refractory to single agent therapy and have failed multiple single agents. Combination therapy may also be needed in patients who have concomitant GERD with EoE that is refractory to PPI therapy.

Goal of Therapy

Ultimately the goal of therapy is to not only minimize symptoms but a 'treat to target' approach as first proposed in the inflammatory bowel disease literature.[51] What has similarly been proposed in EoE is to achieve deep remission – meaning

resolution of clinical, endoscopic (improvement in EREFS score), and histologic findings (defined as <15 eos/hpf) identified at time of EoE diagnosis (Figure 2). Generally lifelong therapy (if pharmacologic, at the lowest effective dose; if dietary, must also continue) is indicated for this chronic condition. Clinical symptoms, however, do not always correlate with endoscopic or histologic findings, and so endoscopic surveillance is essential to assess response to therapy and confirm ongoing overall remission.[52]

CONCLUSION

EoE is a chronic atopic condition of the esophagus characterized by eosinophilic infiltration and subsequent remodeling of the esophagus which, if untreated, can lead to strictures, fibrosis, and food impactions. EoE is diagnosed when clinical symptoms of esophageal dysfunction are present with esophageal mucosal biopsies showing ≥15 eos/hpf (about 60 eos/mm2) without an alternative cause. Therapies for EoE include dietary (elimination diet, allergy testing-based diet, elemental diet), pharmacologic (PPI, topical steroids, dupilumab), and esophageal dilation (balloon, bougie). The goal of therapy is ultimately to achieve deep remission, with clinical, endoscopic, and histologic resolution of disease, though further data on this is needed. ■

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