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Advances in Clinical Management of Eosinophilic Esophagitis

Evan S. Dellon, MD MPH[1,2] and **Chris A. Liacouras, MD**[3]

[1]Center for Esophageal Diseases and Swallowing, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

[2]Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

[3]Center for Pediatric Eosinophilic Disorders, Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia PA

Abstract

EoE is a chronic immune/antigen-mediated clinicopathologic condition that has become an increasingly important cause of upper gastrointestinal morbidity in adults and children over the past 2 decades. It is diagnosed based on symptoms of esophageal dysfunction, the presence of at least 15 eosinophils/high-power field in esophageal biopsies, and exclusion of competing causes of esophageal eosinophilia, including proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE). We review what we have recently learned about the clinical aspects of EoE, discussing the clinical, endoscopic, and histologic features of EoE in adults and children. We explain the current diagnostic criteria and challenges to diagnosis, including the role of gastroesophageal reflux disease and PPI-REE. It is also important to consider the epidemiology of EoE (current incidence of 1/10,000 new cases per year and prevalence of 0.5-1/1,000 cases per year) and disease progression. We review the main treatment approaches and new treatment options; EoE can be treated with topical corticosteroids such as fluticasone and budesonide, or dietary strategies, such as amino acid-based formulas, allergy test-directed elimination diets, and non-directed empiric elimination diets. Endoscopic dilation has also become an important tool for treatment of fibrostenostic complications of EoE. There are number of unresolved issues in EoE, including phenotypes, optimal treatment endpoints, the role of maintenance therapy, and treatment of refractory EoE. The care of patients with EoE and the study of the disease span many disciplines—EoE is ideally managed by a multidisciplinary team of gastroenterologists, allergists, pathologists, and dieticians.

Corresponding Author: Evan S. Dellon MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Rd. UNC-CH, Chapel Hill, NC 27599-7080, Phone: (919) 966-2513, Fax: (919) 843-2508, edellon@med.unc.edu.

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Eosinophilic esophagitis (EoE) has received increasing attention over the past 2 decades.[1–3] It was rarely recognized before the 1990s, when the presence of intraepithelial eosinophils in the esophagus was thought primarily to indicate reflux esophagitis.[4] Between 1993 and 1995, however, the disease, as it is currently recognized, was described in 3 seminal studies.[5–7] Since then, there has been a nearly exponential increase in the number of publications related to EoE;[8] the first consensus guidelines for EoE were published in 2007,[1] with revisions in 2011[2] and 2013.[3]

Definition

EoE is a chronic, immune-mediated clinicopathologic disease.[1–3] The following criteria are required for diagnosis: symptoms of esophageal dysfunction; eosinophilic inflammation localized to the esophagus, with at least 15 eos/high-power field (hpf) in esophageal mucosal biopsies; and exclusion of other recognized causes of esophageal eosinophilia, including proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE).[2, 3] To fulfil the last criterion, patients must be placed on PPI therapy prior to confirming the diagnosis of EoE—those with esophageal eosinophilia who respond do not have EoE as it is currently defined. Additionally, EoE is diagnosed by clinicians using all available clinical and histopathologic information.

Clinical Presentation

Features in children

Children typically present with 1 or more symptoms such as vomiting, regurgitation, nausea, epigastric or abdominal pain, chest pain, water brash, globus, or decreased appetite.[9] Less-common symptoms include growth failure and hematemesis. Infants and toddlers are more likely to present with difficulty feeding, manifest as gagging, choking, food refusal, and vomiting. Dysphagia is not commonly seen until adolescence.[10, 11] The evaluation of young children is necessarily affected by interpretation and reporting by an observer (the parent or caregiver), and symptoms are often non-specific (e.g., poor feeding). Symptom frequency and severity can vary substantially among patients, and do not always correlate with the degree of esophageal eosinophilia. The presence of systemic symptoms such as fever or weight loss should promote evaluation for a disease process other than EoE.

Children with eosinophilic esophagitis have a higher rate of atopy (asthma, eczema, or rhinitis) than children without EoE.[12] Approximately 30%-50% of children with EoE have asthma and 50%-75% have allergic rhinitis, compared to 10% and 30%, respectively, in the general pediatric population, and environmental allergies are approximately 50% more common in children with EoE.[13, 14] Similarly, 10%-20% of children with EoE have immunoglobulin (Ig)E-mediated food allergy (urticaria and anaphylaxis) compared to 1%-5% of children without EoE; more than 50% of patients have another family member who has a history of allergy.[15]

Children who have other inflammatory bowel disorders including celiac disease or Crohn's disease can have eosinophil-predominant esophageal inflammation.[2, 16] However, it is not appropriate to make a diagnosis of EoE when there is another condition that could account

for the histologic changes. In these cases, treatment should be initiated for the presumed primary etiology, with monitoring of the esophageal inflammation. If esophageal eosinophilia persists after the primary disease is controlled, then in certain cases EoE can be diagnosed as an overlapping condition. EoE has been associated with connective tissue diseases, so there may be a shared pathogenic mechanism.[17] In contrast, EoE can occur in children who have other unrelated medical conditions such as trachea-esophageal fistula, Down syndrome, Pfeiffer syndrome, VATER syndrome (vertebral, anal, tracheal, esophageal, and renal abnormalities), or CHARGE syndrome (coloboma, heart defects, atresia of nasal choanae, retardation of growth/development, genital/urinary abnormalities, and ear abnormalities or deafness) without sharing an underlying pathophysiology.[2]

Features in adults

In contrast to children, the most common presentation of EoE in adults is solid food dysphagia.[18, 19] Depending on the study design, 60%-100% of patients report dysphagia.[8, 20–24] EoE is now the most common cause of food impaction among patients who visit the emergency department, comprising more than 50% of cases;[25–27] more than a quarter of adults with EoE reported past food impaction.[20, 21, 23, 24] When taking a history from a patient with suspected EoE, it is important to ask not only if they are having trouble swallowing, but also about dietary modification. Many adults with EoE have adapted their eating behaviors to minimize symptoms. A patient may not report dysphagia, but will recount being the last person at the table to finish meals, chewing food into a mush, lubricating foods, drinking copious amounts of water after each bite, swallowing repeatedly to push food down, avoiding foods that tend to get stuck, and crushing or avoiding pills.

In addition to dysphagia, other symptoms are observed in adults with EoE. Heartburn may be present in 30%-60% of patients with EoE.[20, 21, 23] Among adults with PPI-refractory reflux symptoms, EoE is the cause in 1%−8%.[23, 28–30] Non-cardiac chest pain has been reported in 8%−44% of adults with EoE;[21, 23] one study found EoE to be the cause in 6% of subjects with this symptom.[31] Abdominal pain, nausea, vomiting, diarrhea, and weight loss are not typically associated with EoE in adults—patients with these features should be evaluated for other disorders, including a more diffuse eosinophilic gastrointestinal disorder.

Atopic diseases, such as food allergies, asthma, allergic rhinitis and sinusitis, and atopic dermatitis, are also frequent co-morbidities in adult patients with EoE. Although this strong association has long been recognized in children with EoE, it was reported more recently in 20%-80% of adults with EoE, with even higher rates of allergen sensitization upon testing. [21, 23, 32–34] Because of this high prevalence of atopic disease, allergists often collaborate with gastroenterologists to identify and manage extra-esophageal allergic conditions, food allergies, and dietary changes. Allergy referral is appropriate if these conditions are detected.[2, 3]

Endoscopic features in adults and children

There are a number of esophageal structural changes associated with EoE (Figure 1).[1, 2, 35] Fixed esophageal rings are the prototypical finding, but rings can also be transient, called felinization. Strictures often develop in patients with EoE as a result of chronic

inflammation and fibrosis. In some cases, the esophageal lumen is diffusely narrowed, termed small-caliber esophagus. This can be difficult to appreciate during endoscopy, but can be detected on a barium esophagram.[36] Linear furrows and white plaques or exudates are also frequently seen. A more subtle finding is a decrease in the normal vascular pattern due to congestion of the mucosa, termed edema. Crêpe-paper mucosa describes the splitting of the esophageal mucosa with passage of the scope. Many of these endoscopic findings occur together, but are not all seen in every patient with EoE. For example, the esophagus may appear normal in 7%−10% of cases,[35] and if biopsies are not analyzed, EoE will be missed.

Additionally, there are differences in the endoscopic findings between children and adults.[21, 35] Children more commonly have either a normal-appearing esophagus or findings of plaques or edema, whereas adults more commonly have rings and strictures. Dilation is uncommonly performed in children.[9, 21] These differences in endoscopic presentation by age has led to the concept that some features of EoE are directly attributable to inflammation (furrows, plaques, edema), while others represent fibrosis (rings, strictures, narrowing) resulting from chronic inflammation.[18, 19]

Endoscopic features of EoE do not identify patients with this disease with high levels of sensitivity or specificity, and therefore cannot be used alone to confirm or refute a diagnosis.[35] However, a new classification system has been validated for describing EoE-related endoscopic findings and severity.[37] It is called the EoE endoscopic reference score (EREFS)—the acronym also reflects the major components of the score: exudates, rings, edema, furrows, and strictures. The EREFS can be used in reporting endoscopic findings of EoE, and might be used as an outcome measure in clinical trials.

Histologic features in children and adults

The histologic changes of EoE are the same in children and adults. There is a prominent eosinophilic infiltration of the esophageal epithelium, which can be detected by standard hematoxylin and eosin staining (Figure 2).[38] At least 15 eosinophils/hpf must be present to consider a diagnosis of EoE, in most cases.[1–3] Although this threshold was set to increase the uniformity of EoE diagnosis,[8] it is somewhat arbitrary—clinical judgment is required to interpret the significance of borderline counts. Other histopathologic findings that are associated with EoE include eosinophilic degranulation, eosinophil micro-abscesses, basal layer hyperplasia with concomitant elongation of the rete pegs, dilated intracellular spaces or spongiosis, and, if subepithelial tissue is present for analysis, lamina propria fibrosis (Figure 2). Of note, none of these findings are pathognomonic for EoE, and histopathologic findings alone cannot diagnose EoE.

Because biopsies obtained with conventional forceps sample the esophageal epithelium and rarely obtain tissue deeper than the lamina propria, most of the histologic characterization of EoE is limited to the mucosa. However, rare esophagectomy specimens from patients with EoE have shown transmural eosinophilic inflammation.[39, 40] These samples corroborate findings from endoscopic ultrasound studies reporting a thickened esophageal wall in patients with EoE.[41, 42]

Diagnosis

Challenges

Although the criteria for diagnosis of EoE seem straightforward, there are a number of challenges in diagnosing this disorder. Esophageal eosinophilia is not specific to EoE, so other disorders on the differential diagnosis must be considered (Table 1).[1–3] Eosinophilic gastroenteritis with esophageal involvement should be assessed by analysis of gastric and duodenal biopsies. Hypereosinophilic syndrome is a concern when the peripheral blood eosinophil count is above 1500×10^9 cells/L. Many other causes of esophageal eosinophilia are relatively uncommon and can be excluded by collecting a thorough clinical history and routine lab tests. However, gastroesophageal reflux disease (GERD) and PPI-REE are the most frequently encountered competing conditions.

Many symptoms of GERD and EoE overlap. GERD can also cause high levels of infiltration of the esophagus by eosinophils,[28] making it particularly difficult to distinguish between EoE and GERD. The relationship between these conditions may be even more complicated.[43] GERD and EoE can simply overlap, EoE might cause GERD (because of impaired esophageal clearance of physiologic reflux), and GERD could cause EoE (if reflux leads to a leaky epithelial barrier, through which antigens induce an allergic response). Therefore, although the presence of GERD does not preclude a diagnosis of EoE, it is important to determine the contribution of reflux to the symptoms of patients with EoE. Unfortunately, pH monitoring has not been shown to distinguish between these conditions.[44, 45]

Over the past several years, PPI-REE has been described.[2, 3, 46] In this condition, patients suspected of having EoE (based on symptoms, associated endoscopic findings, and ≥ 15 eosinophils/hpf in esophageal biopsies) undergo clinical and histologic resolution following PPI therapy. It is currently not clear if PPI-REE is a subtype of GERD, a variant of EoE, or a different condition altogether.

Since the first report of PPI-REE in a case series,[47] studies in children and adults have shown that 33%−74% of patients with esophageal eosinophilia respond to PPIs.[30, 44, 46, 48–50] Clinical, endoscopic, and histologic features of EoE and PPI-REE overlap—[30, 46, 48, 49] they cannot be distinguished by pH monitoring[44, 46, 48] and are associated with production of similar cytokines and tissue biomarkers.[51, 52] PPIs reduce secretion of eotaxin 3 (CCL26) in response to T-helper (Th)2 cytokine stimulation in EoE cell lines at physiologic levels,[53, 54] and appear to restore the barrier function of the esophageal mucosa.[55] This area of research is developing rapidly; although PPI-REE and EoE are now separate disorders, their relationship might eventually be redefined.

Another diagnostic challenge involves proper tissue sampling from the esophagus. Because endoscopic features of EoE are not pathognomic, biopsies must be obtained; guidelines recommend collecting at least 2–4 biopsies from 2 separate locations in the esophagus (distal and mid/proximal). This is because the infiltration of eosinophils is patchy throughout the esophagus,[20, 39, 56, 57] and PPIs can have different effects, based on the location of eosinophilia,[58] so it might not be sufficient to collect a biopsy from 1 site.[20, 57, 59] On

histopathologic analysis, the convention is to report peak, rather than the average, eosinophil counts, and also to report the size of the microscope's high-power field.[2, 3, 8, 38, 60]

Emerging modalities

Development of more-efficient and less-invasive methods of EoE diagnosis is an active area of investigation. Symptom scores and predictive models have been described,[21, 61–63] but not validated. Techniques such as narrow-band imaging,[64] confocal microscopy,[65] multiphoton fluorescence microscopy,[66] and tethered capsule endoscopy[67] have been described but are largely still in experimental phases. Similarly, there is proof of concept that nuclear scintigraphy[68] and positon emission topography might be used in diagnosis.[69] The functional luminal imaging probe, which measures esophageal compliance, has led to a new understanding of changes in the mecahnical properties of the esophagus in patients with EoE, as a result of remodeling. This probe is likely to measure esophageal distensibility and caliber with greater accuracy than endoscopy.[70] Decreased compliance was associated with subsequent risk of food impaction,[71] so this technique might also be used to assess treatment outcomes. The esophageal string test and cytosponge are novel and minimally invasive approaches under investigation.[72–74]

Biomarkers of EoE are also being investigated. Several studies have shown that staining biopsies for eosinophil granules,[75–77] mast cells,[78] or cytokines,[77, 79, 80] can specifically identify EoE. A recent study validated that levels of major basic protein, eotaxin 3, and mast cell tryptase could distinguish patients with EoE from patients with GERD,[81] but EoE could not be distinguished from PPI-REE.[52] Blood and stool biomarkers have been studied, but as of yet have no proven utility.[80, 82, 83]

A particularly exciting new diagonstic technique involves analysis of gene expression patterns in esophageal tissues of patients with suspected EoE. The initial description of the EoE-associated transcriptome was a major advance;[84] changes in expression of a subset of 94 genes can identify patients with EoE with high levels of sensitivity and specificity.[85] Although additional studies are required to confirm the utility of this test, EoE might one day be diagnosed based on genetic rather than clinicopathologic features.

Epidemiology and Natural history

Epidemiology

EoE is a global disease, with large numbers of cases reported in North and South America, Western and Eastern Europe, and Australia; fewer cases have been reported in Asia and the Middle East, and, as of yet, none in India or Sub-Saharan Africa.[86] EoE affects patients of any age, though is more common in children and adults under the age of 50 years.[2, 8, 12, 87, 88] Men are affected more commonly than women, consistently in a ratio of 3–4:1; most patients with EoE have been reported to be White, though EoE is found among all races and ethnicities.[2,8, 21, 23, 88–91]

The incidence of EoE is approximately 1/10,000 new cases/year,[11, 89, 92, 93] although some investigators believe this to be an underestimate. Incidence has increased steadily over the past 1–2 decades in multiple locations.[11, 93, 94] This increase in incidence cannot be fully

explained by increasing awareness of the condition or higher rates of endoscopies and biopsies.[21, 89, 95] In a recent analysis of a large administrative database, the prevalence of EoE in the United States was estimated to be 0.5-1/1,000 cases/year.[88] This is consistent with other reports of EoE prevalence in the general population.[89, 93, 96–98]

It is intriguing to speculate about why the incidence of EoE is increasing so rapidly[86]—these types of changes usually indicate an environmental, rather than a genetic, cause. A number of potential risk factors have also been proposed, including the decreased prevalence of *Helicobacter pylori* infection,[99] increased use of PPIs,[100] and early life exposures, such as to antibiotics.[101] Additionally, EoE has been found to more common in cold and arid climates,[102] as well as in rural areas.[103] EoE has also been associated with connective tissue and autoimmune diseases.[17, 104] The hygiene hypothesis, alterations in the esophageal microbiome, changes in food sources, addition of antibiotics or fertilizers to plant and animal foodstuffs, and plastic or synthetic food packaging have all been proposed as causes.[105] It is not known whether one or all of these factors, or some unidentified factor, accounts for the risk for EoE.

Natural history

Multiple studies have shown that EoE is a chronic disorder—eosinophilic infiltration and associated endoscopic features persist.[1–3, 9, 12, 13, 21, 24, 106–114] However, there have not been any reports of EoE progressing into a more general eosinophilic gastrointestinal disorder, hypereosinophilic syndrome, or eosinophilic leukemia. There are also no reports of EoE causing neoplasia, but follow-up times are likely not sufficient yet to fully exclude this possibility.

EoE might progress from an inflammatory phenotype, characterized by younger age, symptoms of failure to thrive, abdominal pain, heartburn, and endoscopic findings of white plaques/exudates and mucosal edema, to a fibrostenotic phenotype, characterized by older age, symptoms of dysphagia and food impaction, and endoscopic findings of esophageal rings, strictures, and narrowing. Three recent studies all showed that increasing symptom length before diagnosis of EoE (a proxy for persistent eosinophilic inflammation without treatment) was strongly associated with increasing development of strictures over time.[18, 19, 115] These findings provide not only important prognostic information, but indicate the need to treat the inflammation associated with EoE.

Treatment

Treatment of EoE is based on its pathogenesis.[116] In brief, EoE is believed to be a Th2 cell-mediated immune response (involving interleukin (IL)4, IL5, and IL13) to food and/or environmental allergens. IL5 supports eosinophil differentiation and maturation, and IL5 and IL13 stimulate the esophageal epithelium to produce eotaxin 3—a potent chemokine that recruits eosinophils into the esophagus. Activated eosinophils release multiple factors that promote local inflammation and tissue injury, including transforming growth factor β. This key mediator of tissue remodeling, including subepithelial fibrosis and epithelial proliferation, can also cause smooth muscle dysfunction.[117, 118] In addition to eosinophils,

other inflammatory cells, including T cells, mast cells, basophils, and natural killer cells, are also involved.[119–121]

There are 3 major treatment approaches to EoE, often referred to as the 3 Ds: drugs, diet, and dilation. Drugs and dietary changes target the inflammation associated with EoE pathogenesis, whereas dilation treats esophageal remodeling and fibrotic complications. Choice of treatment depends on patients' clinical features, patient and provider preferences, local expertise, and costs. In general, drugs and diet are typical first line agents, whereas dilation is reserved for patients with esophageal strictures or narrow-caliber esophagus. No drugs have been approved by the Food and Drug Administration for treatment of EoE, so all medications are used to treat this disorder are off label. However, there are strong data to support the use of some pharmacologic agents.

Corticosteroids

Corticosteroids are the only pharmacologic therapy shown to improve the clinical and histologic features of eosinophilic esophagitis, and are a mainstay of treatment for children and adults with EoE. These drugs have been shown to reduce tissue fibrosis and esophageal remodeling in patients with EoE.[118, 122]

Systemic corticosteroids—Systemic corticosteroids such as prednisone or methylprednisolone rapidly resolve esophageal eosinophilia and improve symptoms; this class of medications was one of the first to be used in patients with EoE. It became clear, however, that after the steroid therapy was tapered, symptoms and esophageal eosinophilia recurred rapidly.[123] Most experience with systemic steroids has been in children. Because of concern over long-term side effects, these medications are reserved for patients with severe symptoms or growth failure who require therapy for rapid improvement.

Topical corticosteroids—Because of potential side effects from systemic steroids, techniques for delivering corticosteroids topically to the esophagus were developed. A case series showed that dispensing fluticasone or beclomethasone from a multi-dose inhaler (MDI) directly into the patient's mouth and having the patient swallow, rather than inhale, produced excellent effects.[124] Larger observational studies showed that this approach was effective in a high proportion of patients,[9, 125–128] and a number of randomized controlled trials (RCTs) have evaluated these drugs.[106–109, 111, 129–133] The best studied medications are fluticasone, dispensed from an MDI, and budesonide, administered either as a viscous slurry or as a swallowed nebulized vapor.

There have been 3 RCTs of fluticasone vs placebo (1 in children, 1 in adults, and 1 enrolling children and young adults),[106, 109, 133] 1 RCT of fluticasone vs prednisone in children,[129] and 2 RCTs of fluticasone vs esomeprazole in adults.[130, 134] In each of the placebo-controlled trials, patients in the fluticasone group had significant reductions in esophageal eosinophil counts compared to the placebo group (Figure 3). Doses for fluticasone typically range from 440 to 880 mcg/day in children and 880 to 1760 mcg/day in adults. Findings from the 2 most recent fluticasone trials indicate that an initial dose of 1760 mcg/day might be optimal for all patient age groups.[109, 133]

Most studies of budesonide provided it in a slurry mixed with sucralose, termed oral viscous budesonide.[128, 135] There have been 2 RCTs of budesonide vs placebo in children,[107, 111] 1 RCT of swallowed nebulized budesonide vs placebo in adults,[108] and 1 RCT of budesonide vs swallowed nebulized budesonide.[131] All have shown great efficacy in decreasing or normalizing eosinophil counts (Figure 3). The usual dose of budesonide ranges from 1 mg/day in children to 2 mg/day in adolescents and adults. When the aqueous solution is used, 3–5 gm of sucralose are required per 2 mL of aqueous solution to achieve the desired thickened consistency. Preliminary results from an RCT showed that an effervescent budesonide tablet was also effective compared to placebo.[132]

When prescribing these medications, it is important to instruct the patients and their families in the proper technique to optimize esophageal deposition and minimize pulmonary delivery.[131] For MDIs, the medication should be administered at end expiration during a breath hold. For all topical steroids, administration should be after meals, and patients should not eat or drink anything for 30–60 minutes after swallowing the drug.

No study has shown adrenal axis suppression after an 8–12 week course of topical steroids,[107, 109, 111, 131] and complications caused by systemic steroids (mood changes, weight gain, etc) are rarely observed. However, there have been no long term follow-up studies of topical corticosteroid use in patients with EoE. Budesonide might have increased absorption from the gastrointestinal tract in patients with active inflammation, such as those with EoE.[136] Additionally, because grapefruit inhibits the CYP3A enzyme pathway responsible for the high first-pass effect of budesonide, patients taking this drug should not ingest grapefruit or its juice.[137] Oral candidiasis is uncommon, but esophageal candidiasis was identified in follow-up endoscopies of 15%-20% of patients treated with topical steroids.[106–109, 111, 129, 131, 132] Patients that develop candidiasis should be treated with nystatin or fluconazole. Herpes esophagitis has also been reported as a complication of topical steroid treatment of EoE.[138]

Biologics—Antibodies against IL5 (mepolizumab and reslizumab) have been studied for treatment of EoE. These antibodies were initially tested in a case series and a small pilot RCT.[139, 140] Findings from larger RCTs of both antibodies were recently reported. Despite encouraging histologic improvements, the clinical response was disappointing compared to placebo.[110, 112] Because of these mixed results, further studies are in progress.

Omalizumab, an antibody against IgE that is used to treat allergic asthma and chronic urticaria, has been examined in 1 RCT of EoE. There were no differences in outcomes of patients given the omalizumab or placebo.[141] Infliximab, an antibody against tumor necrosis factor, was tested in 3 patients and not found to produce a consistent effect.[142] Neither of these medications are recommended for treatment of EoE.

Leukotriene antagonists and mast cell stabilizers—The data on montelukast are mixed. In an initial case series, high doses (in the 20–40 mg range) appeared to be clinically effective,[143] but follow-up studies in adults and children have not confirmed this finding.[144, 145] Similarly, cromolyn does not appear to provide any benefit to patients.[9] Therefore, these medications are not recommended for treatment in routine practice.

Immunomodulators—A case series reported treatment of 3 patients with the immunomodulators 6MP or azathioprine.[146] Although patients appeared to respond to these medications, the disease flared after patients stopped taking them, and then improved again after patients restarted them. However, there are no corroborating data to support these observations. Because of the potential toxicity of these agents, further experience is required before immunomodulators can be recommended for EoE.

Emerging pharmacologic therapies—Our increased understanding of the pathogenesis of EoE has identified several other therapeutic targets,[116] increasing candidate pharmacologic approaches.[147] OCT000459 is an oral agent that blocks the effects of prostaglandin D2. In a small RCT, its use was associated with a mild, but significant decrease in eosinophil count, compared to placebo.[148] This agent is available for research purposes only. A number of new biologic agents, including monoclonal antibodies against IL13, IL4, and eotaxin 3, are under investigation but not yet available for use. Because angiotensin receptor blockers are thought to inhibit transforming growth factor β, an early-phase study is planned to investigate whether this drug is effective against EoE. Finally, new topical steroid formulations, including a viscous budesonide suspension and a dissolving fluticasone tablet, are being tested.

Dietary therapy

The identification and removal of allergic dietary antigens is also a mainstay of treatment for EoE. Although corticosteroids may temporarily improve symptoms, when they are discontinued, the disease returns. In contrast, when foods that induce symptoms are eliminated from the diet, patients undergo long-term remission without medication. Dietary therapy has also been shown to improve esophageal fibrosis and remodeling.[122]

Dietary approaches to treat EoE include elemental diets with an amino acid-based complete liquid formulation,[9, 149] directed elimination diets based on allergy test results,[150] and non-directed elimination diets (in which common food antigens are empirically excluded from the diet).[151] A recent meta-analysis of studies of adults revealed that elemental diets were effective for 91% of patients, non-directed diets for 72%, and allergy test-directed diets for 46%.[152] The type of diet selected should be tailored to the needs of the patient and depends on the presence or lack of anaphylactic food allergies, the age of the patient, and the acceptance of the diet by the patient or family. Furthermore, patients should be referred to a dietician with experience treating patients with EoE, to ensure adequate nutrition and maximize compliance.

Amino acid-based formulas—Strict elemental diets have been reported to induce remission in 88%-96% of children with EoE[9, 149, 151] and 72% of adults.[153] These outcomes, which are better than those from dietary or medical interventions, were achieved without any reported complications. Disadvantages of this approach are palatability, a need for enteral feeding tubes for some patients, and patient compliance. Elemental formulas are expensive and not always covered by traditional insurance plans, so they can pose a significant financial burden. Although a strict diet of an amino acid-based formula can

initially be difficult for patients (and parents) to accept, there is rapid symptom improvement, so the benefits may outweigh the risks of other treatments.

Once histologic remission is established, based on a repeat endoscopic evaluation after patients have been on elemental diets for 4–6 weeks, foods are reintroduced. The least allergenic foods (vegetable or fruit groups) should be tried first, followed by foods that are more likely to cause a response, such as grains, meats, nuts, fish, shellfish, soy, and dairy.[149] A chart with foods organized from least to most allergenic (A to D) can be used to help guide food reintroduction, and single foods from a specific food group can be reintroduced in the diet every 5–7 days (Figure 4).[154] If symptoms do not recur after reintroduction of food(s) from 1 group, endoscopy and biopsy are performed 2–3 months later, to provide histologic evidence for remission before the next single food from the next food group is introduced. However if patients develop symptoms following ingestion of any specific food, that food is excluded from the diet and the patient proceeds to the next food in that group, once their symptoms have resolved.

Directed elimination diets based on results of allergy testing—Children treated with elimination diets based only on results from radio-allergosorbent and/or skin prick tests (SPTs) have not been found to induce clinical and histological remission.[125] The same was true for adults; rates of response were low and the predictive value of the SPT in identifying foods that cause symptoms ranged from only 13% to 22%.[155, 156] However, when children were evaluated by the SPT and atopy patch test (APT), and then placed on elimination diets based on the combination of results, 78% had significant clinical and histological remission.[150] Soy, wheat, chicken, and beef were the foods most frequently identified by the APT and SPT. Interestingly, although dairy often produced negative test results, it was the most commonly identified inducer of EoE. Most allergists therefore restrict dairy from the diet without a test. The APT has not been standarized for food allergies, and is not universally available, so it cannot be recommended for all children with EoE.[157] Children and adults who seek a directed elimination diet require referral to an allergist with knowledge of EoE.

Non-directed (empiric) elimination diet—The advantage of a non-directed elimination diet is that it does not require allergy testing. This approach was first used to study the effects of a 6-food elimination diet in 35 children.[151] Cow's milk protein, soy, wheat, egg, peanut/tree nut, and fish/shellfish were the only foods excluded; 74% of subjects made significant clinical and histological improvements. This treatment approach has since been validated by 2 additional prospective studies in adults. In these studies, 70% to 73% of subjects had histological improvements;[155, 156] there have been comparable results from retrospective studies.[158]

Once clinical and histological remission is achieved in patients on 6-food elimination diets, single food groups can be reintroduced. Patients are evaluated by endoscopy and biopsy 4–6 weeks after each new food is introduced. The next food is reintroduced after the histology examination establishes remission.[159]

The primary advantage of the empiric elimination diet over an elemental formula is that it allows patients to eat a variety of foods, including meats, grains, fruits, vegetables, and legumes. In situations where allergy testing is not easily accessible, and where an elemental diet is not a consideration, the empiric diet is the dietary treatment of choice, and may not be a significant financial burden. However, there can be a significant endoscopic burden to the food re-introduction process, depending on the number of repeat endoscopies needed. As many as 10 endoscopic examinations have been required, over the course of 12–18 months, in some strict protocols.[156] Therefore, the efficacy of empiric diets requiring elimination of fewer food groups is also under investigation.[160]

Dilation

Esophageal dilation of patients with EoE was initially associated with complications—perforation rates were as high as 8% and many patients developed deep mucosal tears and underwent hospitalization for post-procedural chest pain.[161–163] The 2007 Guidelines for EoE therefore took a cautious approach, with dilation to be considered only after drug or dietary therapy.[1] Since that time, however, it has been shown that dilation can be performed safely in patients with EoE, and that it can improve symptoms.[164–168] A recent meta-analysis calculated the risk of perforation from EoE to be 0.3%[169]—similar to the rate of dilation in patients without EoE.[170]

Although dilation has become an acceptable treatment strategy in recent EoE Guidelines,[2, 3] it does not affect the eosinophil-induced inflammation that causes the disease.[166] Also, the safety data on which the Guidelines are based were collected from expert centers that are familiar with dilation therapy for EoE. It is not clear whether low-volume centers have the same safety profiles.

Wire-guided bougie, through-the-scope balloons, and non-wire guided bougies have all been reported to be effective dilation techniques.[165, 171, 172] There have been no head-to-head comparisons of the techniques—the dilator is selected based on the preference of the endoscopist. Most published studies used either balloons or wire-guided bougies. The goal of the dilation is a mucosal tear, defined as a break in the esophageal mucosa in the area of the stricture (Figure 5), which is not considered a complication.

Dilation improves symptoms of dysphagia. In a large multicenter series, almost half of patients were symptom free 1 year after a single dilation, and more than 40% remained symptom free for 2 years.[166] However, after dilation, approximately 75% of patients reported chest pain or discomfort, rated as moderate or severe in about 20%. It is therefore important to counsel patients to expect post-dilation pain and to manage it with reassurance and analgesics as needed. This pain rarely requires emergent evaluation to exclude esophageal perforation.

Emerging concepts and unresolved issues

EoE is a dynamic field, and for a recently recognized disease, the pace of knowledge acquisition has been astounding. The fact that 3 practice guidelines have been published

within the last 6 years illustrates this point. As such, it is understandable that many questions remain.

Phenotypes

One question concerns the phenotypes of EoE. Many investigators believe that EoE has several phenotypes. Clinical phenotypes and symptoms of EoE can vary between children and adults; endoscopic phenotypes can be characterized either by inflammation or fibrostenosis. There could also be phenotypes associated with atopic status, sex, or race/ethnicity. No one knows whether EoE might progress from one phenotype to another, or whether the phenotypes are static. The different phenotypes have yet to be fully characterized, so it is not clear how disease progression and treatment responses vary among phenotypes.

Treatment endpoints and symptom-histology discordance

The ideal treatment endpoint in EoE would be complete resolution of clinical symptoms, eosinophilic inflammation, and esophageal remodeling. A stringent treatment outcome response such as this, however, might be hard to achieve in practice—significant improvement in these areas might be a more realistic goal. Additionally, treatment outcomes have varied among clinical trials, with nearly every study having a different threshold of histologic response (Figure 3).[106–109, 111, 129–134] The most appropriate treatment outcome is of clinical, research, and regulatory interest, and multiple studies are underway to help define this.

Further complicating the picture is that in some cases of EoE, there is often a dissociation between symptomatic and histologic response.[173] This dissociation may be explained based on the balance of inflammatory and fibrostenotic disease activity. For example, a patient with a critical stricture that is dilated can have rapid symptom response, but without dietary or pharmacologic therapy will still have marked esophageal eosinophilia. In contrast, a patient with a stricture who is treated with steroids or diet may achieve histologic normalization, but if the stricture does not improve, symptoms of dysphagia will persist. Modification of eating behavior to avoid foods that induce dysphagia may also have a role. A combination of these factors could explain results of RCTs of topical steroids or anti-IL5 agents, in which eosinophil counts significantly decreased in the active compared to the placebo group, but symptoms improved in both.[109, 111, 112]

Maintenance therapy and treatment-refractory patients

When treatment is stopped EoE typically recurs,[9, 12, 42] raising questions about whether treatment should be continued for all patients. The most recent guidelines recommend considering maintenance treatment for all patients with EoE—particularly for those with severe or rapidly relapsing symptoms, history of food impaction, strictures that require dilation, or history of esophageal perforation.[3] If a patient has been successfully treated with dietary elimination and food triggers have been identified, ongoing elimination of the dietary elements should be used as maintenance therapy. However, there is controversy about whether topical steroids should be continued indefinitely, particularly in light of the potential side effects and lack of long-term data. An approach where the dose is

progressively decreased to the lowest dose that keeps the disease in remission seems reasonable until more data are available.

A related question is how to approach treatment-refractory disease. Little has been published on this topic,[174, 175] but it is clear from RCTs of topical steroids and findings from studies of selective dietary therapies (not amino acid-based formulas) that between a quarter and half of patients with EoE might not respond.[106, 109, 155, 158]

The first thing to assess is whether a patient is adhering to the prescribed therapy. If so, it is important to determine which component of the disease has failed to respond: symptoms, inflammation, or remodeling. If eosinophilia persists, then it would be reasonable to switch from steroids to diet, or vice versa, expand an elimination diet or consider elemental formula, increase topical steroid doses, or consider systemic steroids. If there is a persistent stricture, then dilation is appropriate. Superimposed infection should be excluded. If the esophagus is patent, inflammation has resolved, but symptoms persist, other causes should be pursued. There has been limited experience with second- or third-line pharmacologic agents, or with combination therapies. Overall, approximately 50% of patients refractory to initial treatment strategies eventually respond to second or third-line agents,[175] but this observation highlights the need for more effective therapies for EoE.

Conclusions

EoE is a chronic immune/antigen-mediated clinicopathologic condition that has become an increasingly important cause of upper gastrointestinal morbidity in adults and children over the past 2 decades. A management algorithm is presented in Figure 6. Diagnosis is based on symptoms of esophageal dysfunction, demonstration of ≥15 eosinophils/hpf in esophageal biopsies, and exclusion of competing causes of esophageal eosinophilia, including PPI-REE. Esophageal eosinophilia in and of itself does not indicate EoE. The mainstays of EoE treatment are drugs, diet, and dilation. Topical corticosteroids and dietary elimination are each acceptable first line treatment approaches. Esophageal dilation can be used for treatment of the fibrostenotic complications of EoE. No drugs have been approved by the Food and Drug Administration for treatment of EoE, so pharmacologic agents are prescribed off label, increasing costs and barriers to access for patients. Similarly, dietary treatments and elemental formulas are rarely covered by insurances.

Approved medications and access to nutritional formulas are key milestones for treatment. The care of patients with EoE, and the study of the disease, is multidisciplinary and involves gastroenterologists, allergists, pathologists, and dieticians. These teams, working with patients and advocacy groups, have made great strides in increasing our understanding this disease, and ongoing collaborations hold great promise for the future.

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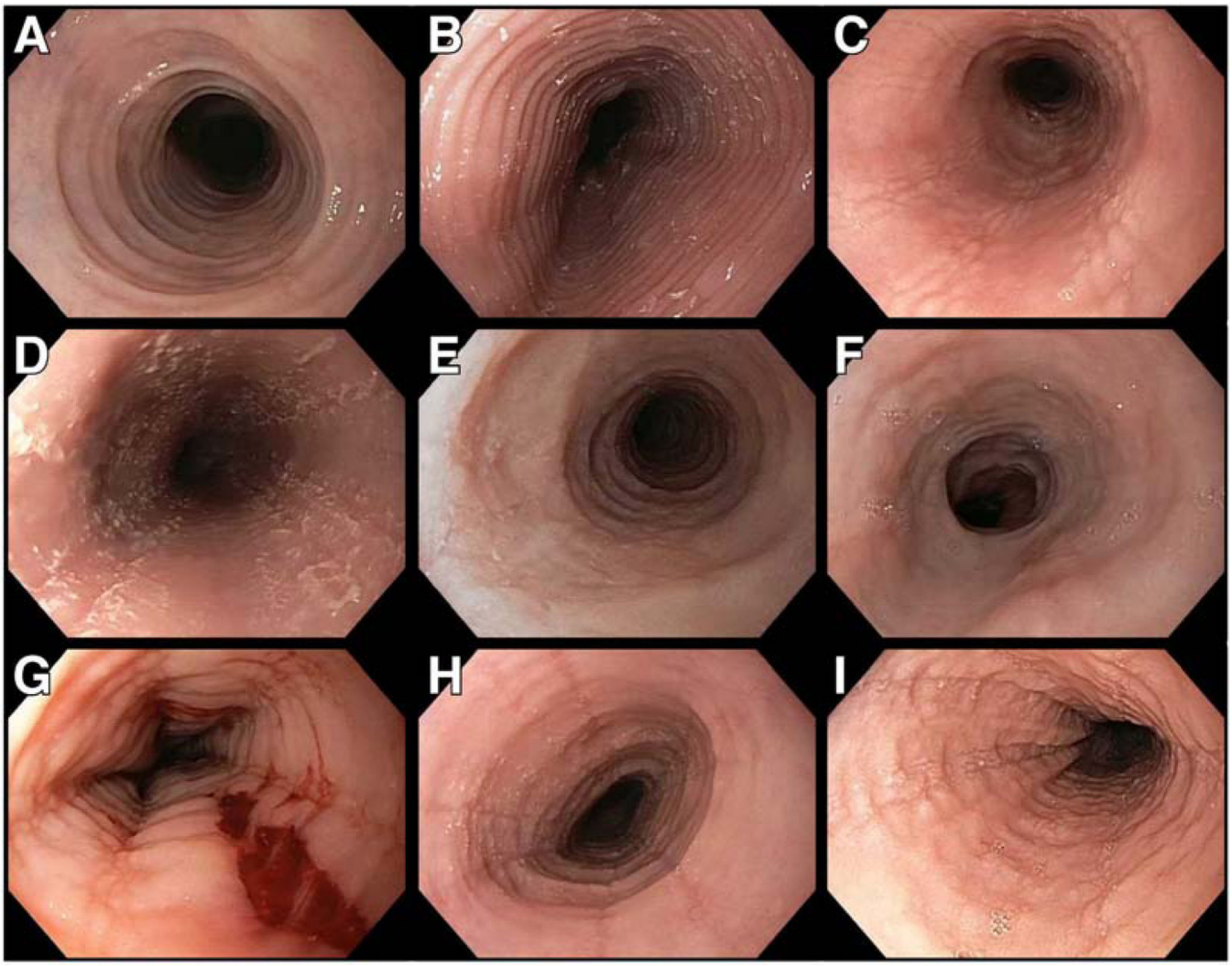

Figure 1.

Endoscopic findings in EoE. **(A)** Fixed esophageal rings, previously called trachealization. Rings can vary in severity from subtle ridges to tight fibrotic bands, and full insufflation of the esophagus is required to appreciate their extent. **(B)** Transient esophageal rings, also called felinization. **(C)** Linear furrows, which are fissures that run parallel to the axis of the esophagus and have a train track appearance. **(D)** White plaques/exudates, which are eosinophilic micro-abscesses that can be confused with candidal esophagitis; brushings from this patient were negative for candida. **(E)** Esophageal narrowing with mucosa edema and decreased vascularity. Of note, decreased vascularity and mucosal edema are also visible in images C, D, G, H, and I, and can be a subtle finding in EoE. **(F)** A more focal stricture in the distal esophagus. Strictures can be located at any location in the esophagus, however. **(G)** Crêpe-paper mucosa, in which there is a mucosal tear with passage of the endoscope in a narrowed esophagus. **(H)** A combination of multiple findings including rings, furrows, plaques, narrowing, and decreased vascularity. **(I)** A combination of several findings including rings, deep furrows, plaques, and mucosa edema.

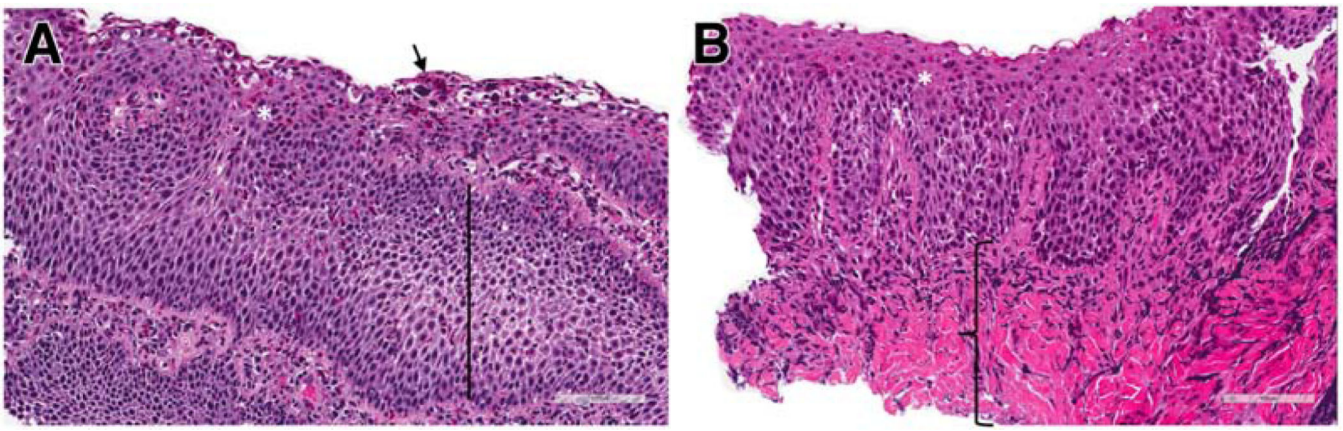

Figure 2.

Histologic findings in EoE (40x images). **(A)** Mucosal biopsy of the esophagus showing a marked eosinophilic infiltrate. Additional findings of note include eosinophil degranulation (white asteric), which often indicates eosinophil activation; eosinophil microabscesses, defined as clusters of at least 4 eosinophils and superficial layering with sloughing of the apical epithelial cells (arrow); and basal cell hyperplasia, frequently occupying 50% or more of the epithelium, with spongiosis, a result of dilated intracellular spaces reflecting leaky mucosal barrier (black bar). **(B)** In addition to the eosinophilic infiltrate and degranulation (white asterisk), this specimen shows lamina propria fibrosis (black bracket).

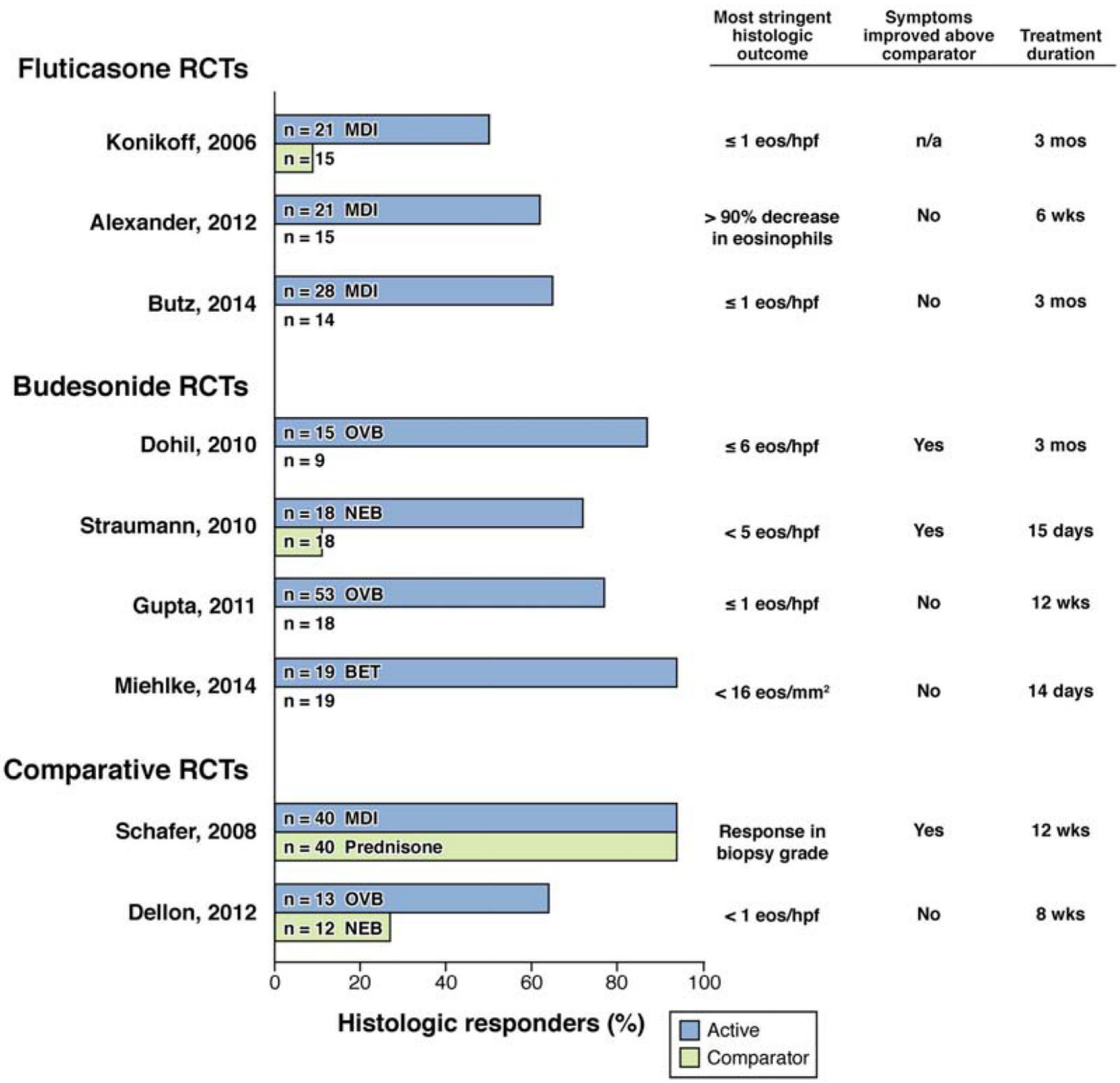

Figure 3.

Overview of response rates and treatment outcomes in clinical trials of topical corticosteroids for EoE. The histologic response rate for the active (blue bars) and comparator (green bars) treatments are shown, for the most stringent outcome measure reported for each trial. MDI indicates use of a multi-dose inhaler in all three of the placebo-controlled fluticasone trials, and in one of the comparative trials.[106,109,133] Budesonide indicates use of a viscous budesonide suspension or slurry,[107,111,131] NEB indicates use of swallowed nebulized budesonide,[108,131] and BET indicates use of a budesonide effervescent [132] The studies listed under the fluticasone RCTs and budesonide RCTs headers are all placebo controlled.

(Add several foods over a period of time)

(Add one food over a period of time)

A	B	C	D
Vegetables (non-legume) Carrots, squash (all types, sweet potato, white potato, string beans, broccoli, lettuce, beets, asparagus, cauliflower, brussel sprouts	**Citrus fruits** Orange, grapefruit, lemon, lime	**Legumes** Lima beans, chickpeas, white/black/red beans	**Fish/shellfish**
Fruit (non-citrus, non-tropical) Apple, pear, peaches, plum, apricot, nectarine, grape, raisins	**Tropical fruits** Banana, kiwi, pineapple, mango, papaya, guava, avocado	**Grains** Oat, barley, rye, other grains	**Corn**
Vegetables Tomatoes, celery, cucumber, onion, garlic, any other vegetables	**Melons** Honeydew, cantaloupe, watermelon	**Meat*** Lamb, chicken, turkey, pork	**Peas**
	Berries Strawberry, blueberry, raspberry, cherry, cranberry	***Progress from well-cooked to rarer**	**Peanut**
	Grains Rice, millet, quinoa		**Wheat**
			Beef
			Soy
			Egg
			Milk

Figure 4.

Dietary reintroduction of food allergens (Modified with permission from Dr. Spergel and colleagues[154]).

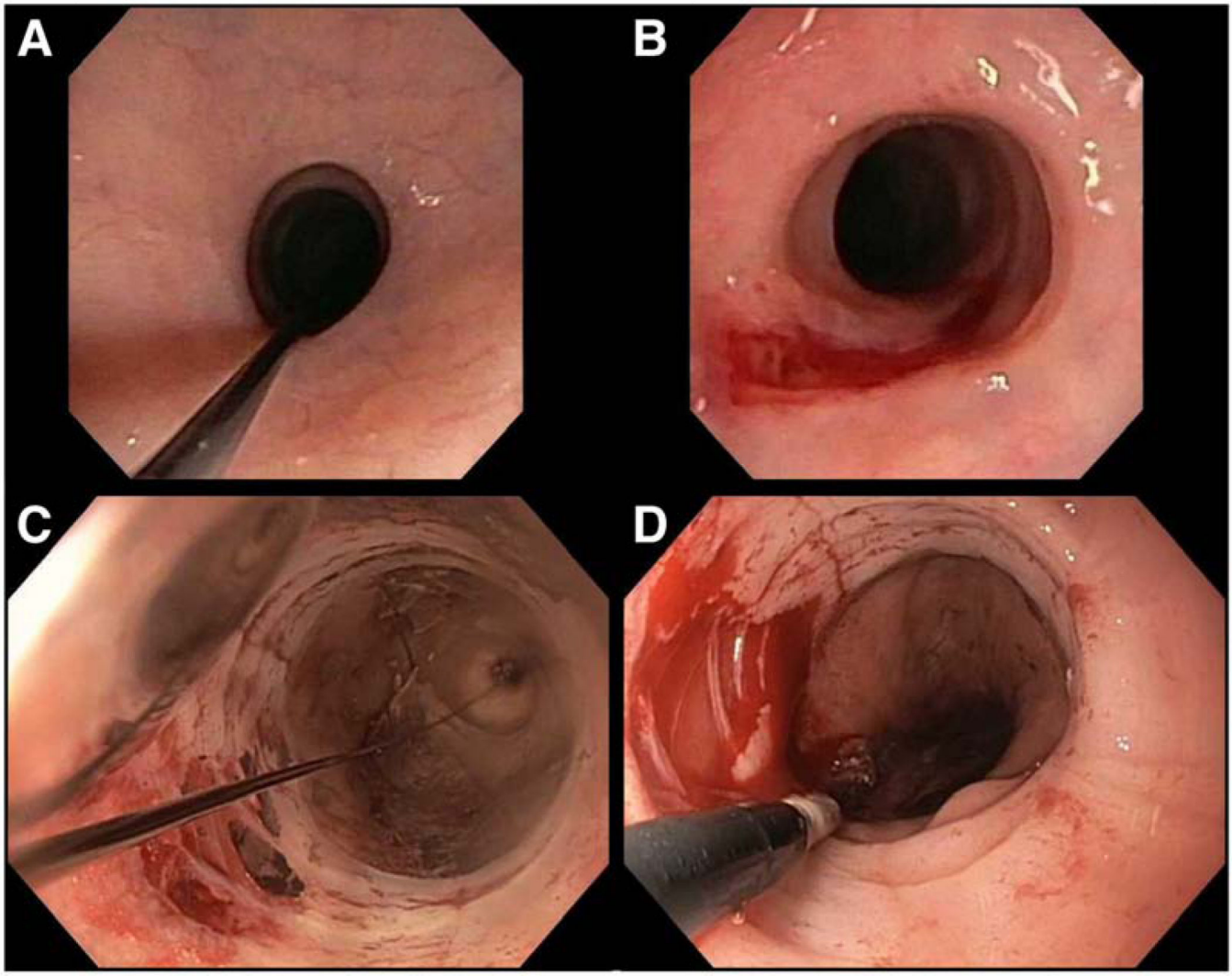

Figure 5.

Examples of esophageal dilation to treat EoE. **(A)** A guidewire, which was placed with the neonatal scope, is seen coursing through a very tight proximal esophageal stricture prior to passing the wire-guided bougie. **(B)** The desired post-dilation effect with a mucosal tear. **(C)** View through an inflated through-the-scope balloon during a dilation at the gastro-esophageal junction. The developing mucosal tear is seen in the 7–8 o'clock area. **(D)** The desired post-dilation effect with a mucosal tear.

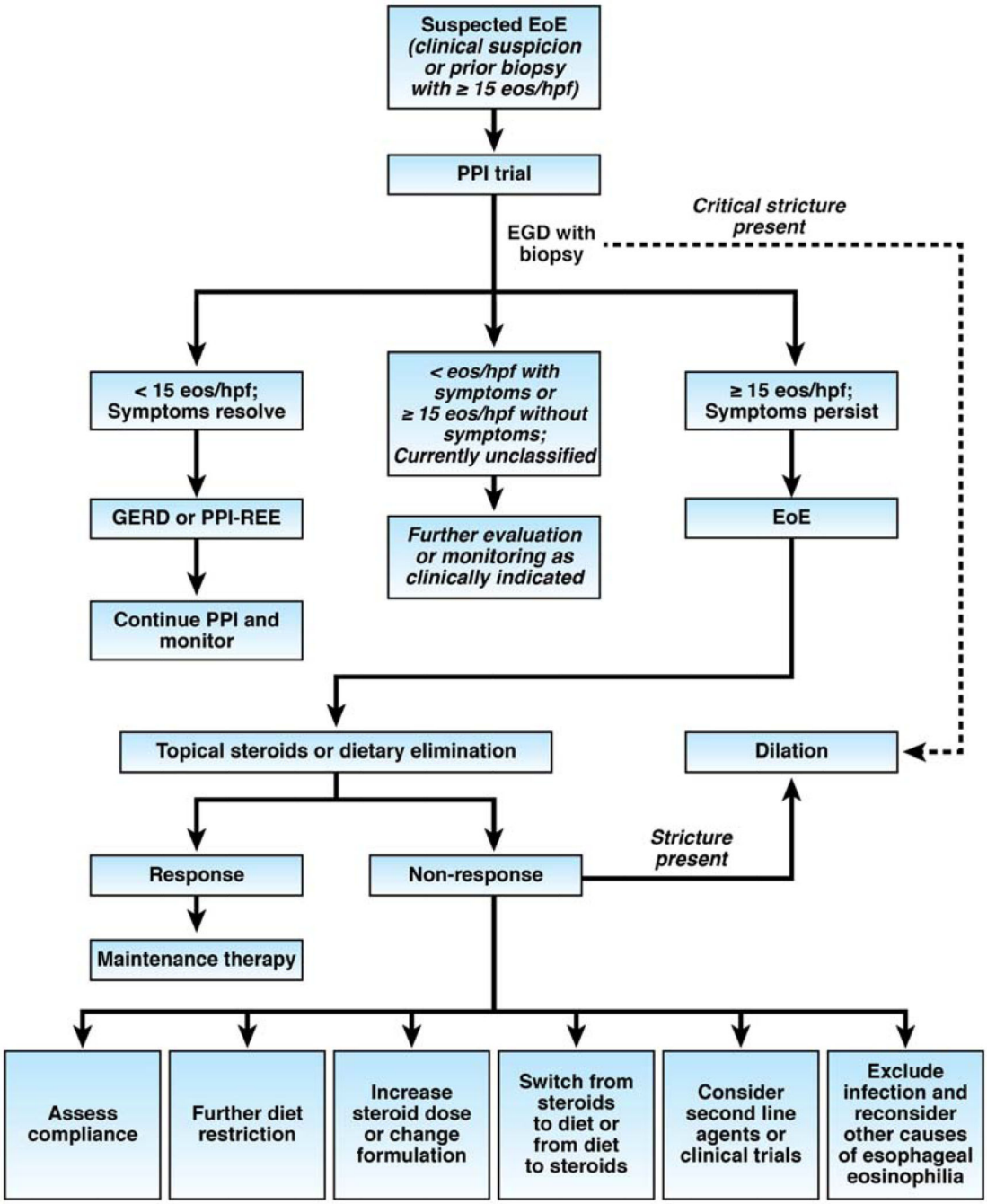

Figure 6.
Algorithm for diagnosis and treatment of EoE.

Table 1

Differential Diagnosis of Esophageal Eosinophilia

- Eosinophilic esophagitis
- Gastroesophageal reflux disease
- PPI-responsive esophageal eosinophilia
- Celiac disease
- Eosinophilic gastroenteritis
- Crohn's disease
- Hypereosinophilic syndrome
- Achalasia
- Vasculitis, pemphigus, connective tissue diseases
- Infections (fungal, viral)
- Graft versus host disease