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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Advances in Clinical Management of Eosinophilic Esophagitis

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

[1]Center for Esophageal Diseases and Swallowing and [2]Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina; and [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, Pennsylvania

Eosinophilic esophagitis (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 biopsy specimens, and exclusion of competing causes of esophageal eosinophilia, including proton pump inhibitor–responsive esophageal eosinophilia. We review what we have recently learned about the clinical aspects of EoE, discussing the clinical, endoscopic, and histological 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 proton pump inhibitor–responsive esophageal eosinophilia. It is also important to consider the epidemiology of EoE (with a current incidence of 1 new case per 10,000 per year and prevalence of 0.5 to 1 case per 1000 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 nondirected empiric elimination diets. Endoscopic dilation has also become an important tool for treatment of fibrostenotic complications of EoE. There are a number of unresolved issues in EoE, including phenotypes, optimal treatment end points, 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.

Keywords: Diagnosis; Endoscopy; Treatment; Management Algorithm.

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 believed 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 eosinophils/high-power field (hpf) in esophageal mucosal biopsy specimens; and exclusion of other recognized causes of esophageal eosinophilia, including proton pump inhibitor–responsive esophageal eosinophilia (PPI-REE).[2,3] To fulfill the last criterion, patients must be placed on proton pump inhibitor (PPI) therapy before confirming the diagnosis of EoE; those with esophageal eosinophilia who respond to therapy 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 one 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, refusal of food, 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 nonspecific (eg, 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 EoE have a higher rate of atopy (asthma, eczema, or rhinitis) than children without EoE.[12]

Abbreviations used in this paper: **EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; hpf, high-power field; IL, interleukin; MDI, multidose inhaler; PPI, proton pump inhibitor; PPI-REE, proton pump inhibitor–responsive esophageal eosinophilia; RCT, randomized controlled trial.**

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Approximately 30% to 50% of children with EoE have asthma and 50% to 75% have allergic rhinitis, compared with 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% to 20% of children with EoE have immunoglobulin E–mediated food allergy (urticaria and anaphylaxis) compared with 1% to 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, a diagnosis of EoE is not appropriate when another condition could account for the histological 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 tracheoesophageal 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% to 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 one-fourth of adults with EoE report 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 the patient is 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% to 60% of patients with EoE.[20,21,23] Among adults with PPI-refractory reflux symptoms, EoE is the cause in 1% to 8%.[23,28–30] Noncardiac chest pain has been reported in 8% to 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 comorbidities in adult patients with EoE. Although this strong association has long been recognized in children with EoE, it was reported more recently in 20% to 80% of adults with EoE, with even higher rates of allergen sensitization on testing.[21,23,32–34] Because of this high prevalence of atopic disease, allergists often collaborate with gastroenterologists to identify and manage extraesophageal allergic conditions, food allergies, and dietary changes. Allergy referral is appropriate if these conditions are detected.[2,3]

Endoscopic Features in Children and Adults

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% to 10% of cases[35]; if biopsy specimens are not analyzed, EoE will be missed.

Additionally, there are differences in 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), whereas 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), and 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 is under investigation as an outcome measure in clinical trials.

Histological Features in Children and Adults

The histological 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

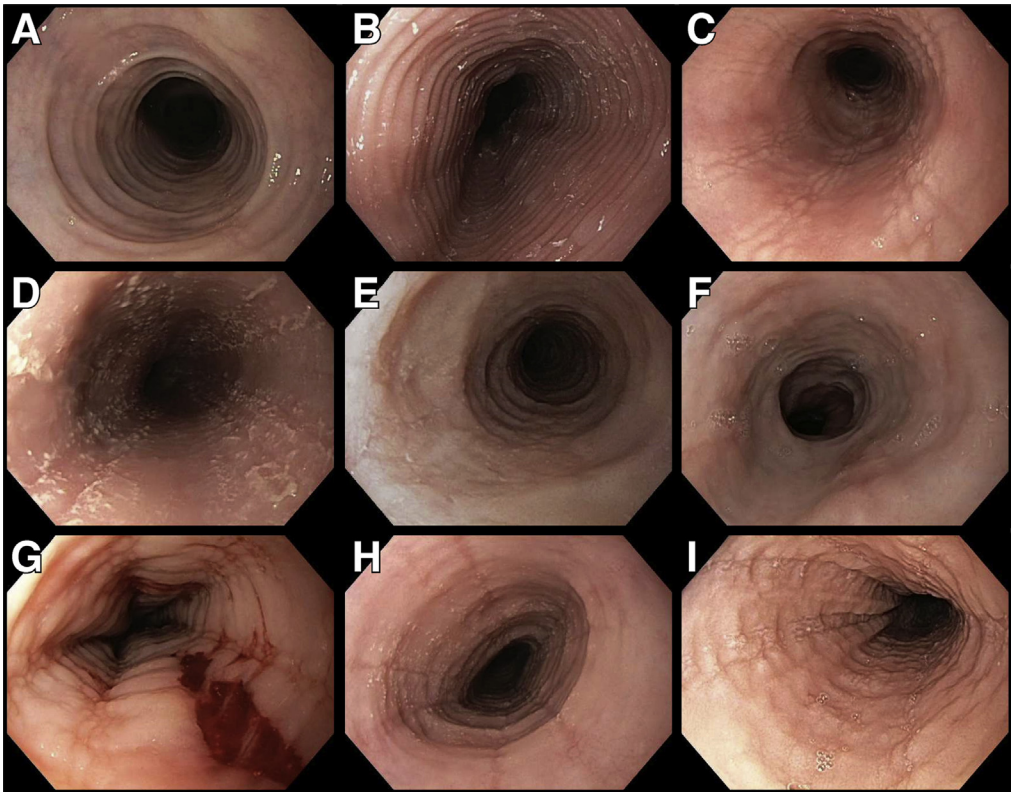

Figure 1. Endoscopic findings in EoE. (*A*) Fixed esophageal rings, previously called trachealization. Rings can vary in severity from subtle ridges to tight fibrotic bands, and full insufflation of the esophagus is required to appreciate their extent. (*B*) Transient esophageal rings, also called felinization. (*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 microabscesses 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 *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 found 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.

standard H&E 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 diagnosis of EoE,[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 microabscesses, basal layer hyperplasia with concomitant elongation of the rete pegs, dilated intracellular spaces or spongiosis, and, if subepithelial tissue is present

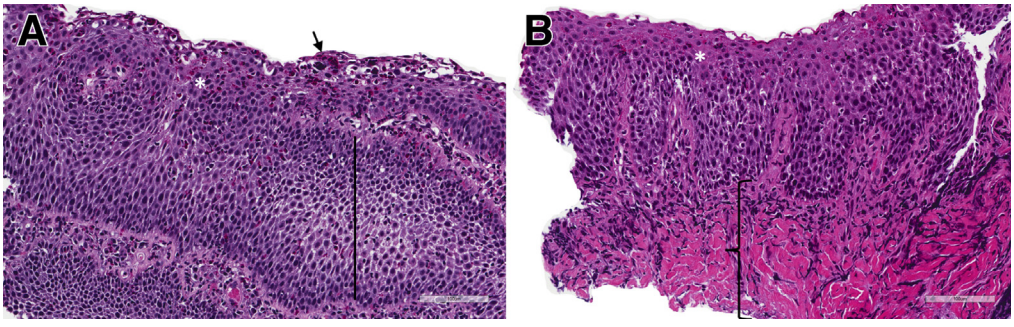

Figure 2. Histological findings in EoE (original magnification 40×). (*A*) Mucosal biopsy specimen of the esophagus showing a marked eosinophilic infiltrate. Additional findings of note include eosinophil degranulation (*white asterisk*), which often indicates eosinophil activation; eosinophil microabscesses, 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 a leaky mucosal barrier (*black bar*). (*B*) In addition to the eosinophilic infiltrate and degranulation (*white asterisk*), this specimen shows lamina propria fibrosis (*black bracket*).

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 biopsy specimens obtained with conventional forceps sample the esophageal epithelium and rarely obtain tissue deeper than the lamina propria, most of the histological 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 ultrasonography 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 biopsy specimens. Hypereosinophilic syndrome is a concern when the peripheral blood eosinophil count is $>1500 \times 10^9$ cells/L. Many other causes of esophageal eosinophilia are relatively uncommon and can be excluded by obtaining a thorough clinical history and performing routine laboratory 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 physiological 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]

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

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 $\geq$15 eosinophils/hpf in esophageal biopsy specimens) undergo clinical and histological resolution after 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% to 74% of patients with esophageal eosinophilia respond to PPIs.[30,44,46,48–50] Clinical, endoscopic, and histological 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 2 cytokine stimulation in EoE cell lines at physiological 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 pathognomonic, biopsy specimens must be obtained; guidelines recommend collecting at least 2 to 4 biopsy specimens 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 specimen from one site.[20,57,59] On histopathologic analysis, the convention is to report the peak, rather than the average, eosinophil counts and also to report the size of the high-power field of the microscope.[2,3,8,38,60]

Emerging Modalities

Development of more efficient and less invasive methods of diagnosis of EoE 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 tomography 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 mechanical 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 is 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 biopsy specimens 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 diagnostic 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 no cases have yet been reported in India or Sub-Saharan Africa.[86] EoE affects patients of any age, although it is more common in children and adults younger than 50 years of age.[2,8,12,87,88] Men are affected more commonly than women, consistently in a ratio of 3 to 4:1; most patients with EoE have been reported to be white, although EoE is found among all races and ethnicities.[2,8,21,23,88–91]

The incidence of EoE is approximately 1 new case per 10,000 per year,[11,89,92,93] although some investigators believe this is an underestimate. The incidence has increased steadily over the past 1 to 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 to 1 case per 1000 per year.[88] This is consistent with other reports of the prevalence of EoE in the general population.[89,93,96–98]

It is intriguing to speculate 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 be 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 of 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 yet sufficient 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 length of symptoms before diagnosis of EoE (a proxy for persistent eosinophilic inflammation without treatment) is strongly associated with increasing development of strictures over time.[18,19,115] These findings not only provide important prognostic information but also 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 T-helper 2 cell–mediated immune response (involving interleukin [IL]-4, IL-5, and IL-13) to food and/or environmental allergens. IL-5 supports eosinophil differentiation and maturation, and IL-5 and IL-13 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 the pathogenesis of EoE, 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 used to treat this disorder are off label. However, there are strong data to support the use of some pharmacological agents.

Corticosteroids

Corticosteroids are the only pharmacological drugs shown to improve the clinical and histological features of

EoE 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 systemic corticosteroid therapy was tapered, symptoms and esophageal eosinophilia recurred rapidly.[123] Most experiences with systemic corticosteroids have been in children. Because of concern about long-term adverse effects, these medications are reserved for patients with severe symptoms or growth failure who require therapy for rapid improvement.

Topical corticosteroids. Because of potential adverse effects from use of systemic corticosteroids, techniques for delivering corticosteroids topically to the esophagus were developed. A case series showed that dispensing fluticasone or beclomethasone from a multidose 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 versus placebo (one in children, one in adults, and one enrolling children and young adults),[106,109,133] one RCT of fluticasone versus prednisone in children,[129] and 2 RCTs of fluticasone versus 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 with the placebo group (Figure 3). Doses of fluticasone typically range from 440 to 880 μg/day in children and 880 to 1760 μg/day in adults. Findings from the 2 most recent trials of fluticasone indicate that an initial dosage of 1760 μg/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 versus placebo in children,[107,111] one RCT of swallowed nebulized budesonide versus placebo in adults,[108] and one RCT of budesonide versus swallowed nebulized budesonide.[131] All have shown great efficacy in decreasing or normalizing eosinophil

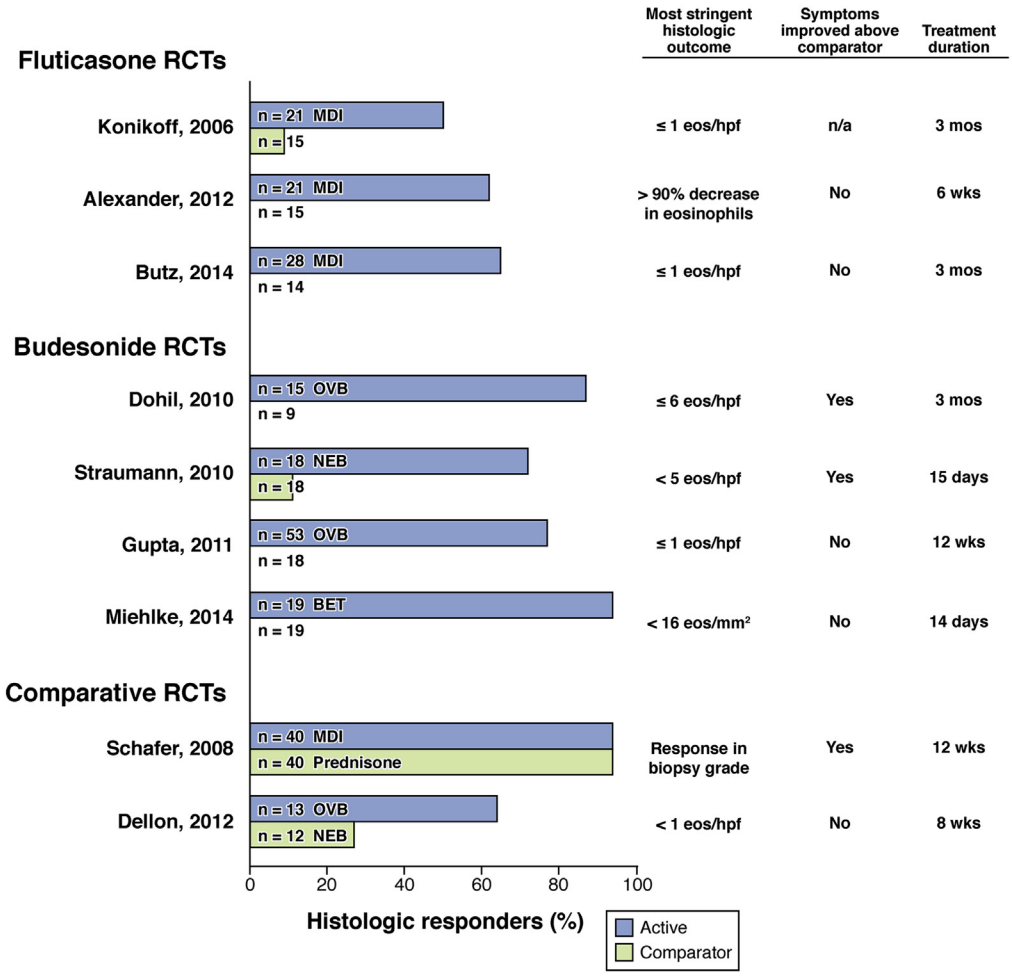

Figure 3. Overview of response rates and treatment outcomes in clinical trials of topical corticosteroids for EoE. The histological response rate for the active (*blue bars*) and comparator (*green bars*) treatments are shown for the most stringent outcome measure reported for each trial. MDI indicates use of an MDI in all 3 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 tablet.[132] The studies listed under the fluticasone RCTs and budesonide RCTs headings are all placebo controlled.

counts (Figure 3). The usual dosage of budesonide ranges from 1 mg/day in children to 2 mg/day in adolescents and adults. When the aqueous solution is used, 3 to 5 g of sucralose is required per 2 mL of aqueous solution to achieve the desired thickened consistency. Preliminary results from an RCT showed that an effervescent budesonide tablet is also effective compared with placebo.[132]

When prescribing these medications, it is important to instruct 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 corticosteroids, administration should be after meals, and patients should not eat or drink anything for 30 to 60 minutes after swallowing the drug.

No study has shown adrenal axis suppression after an 8- to 12-week course of topical corticosteroids,[107,109,111,131] and complications caused by systemic corticosteroids (mood changes, weight gain, and so on) 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% to 20% of patients treated with topical corticosteroids.[106–109,111,129,131,132] Patients who develop candidiasis should be treated with nystatin or fluconazole. Herpes esophagitis has also been reported as a complication of topical corticosteroid treatment of EoE.[138]

Biological Agents

Antibodies against IL-5 (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 histological improvements, the clinical (symptomatic) response was disappointing compared with placebo.[110,112] Because of these mixed results, further studies are in progress.

Omalizumab, an antibody against immunoglobulin E that is used to treat allergic asthma and chronic urticaria, has been examined in one RCT of EoE. There were no differences in outcomes of patients given 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- to 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 6-mercaptopurine 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 treatment. 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 Pharmacological Therapies

Our increased understanding of the pathogenesis of EoE has identified several other therapeutic targets,[116] increasing candidate pharmacological approaches.[147] OCT000459 is an oral agent that blocks the effects of prostaglandin D_2. In a small RCT, its use was associated with a mild but significant decrease in eosinophil count compared with placebo.[148] This agent is available for research purposes only. A number of new biological agents, including monoclonal antibodies against IL-13, IL-4, and eotaxin 3, are under investigation but not yet available for use. Because angiotensin receptor blockers are believed to inhibit transforming growth factor β, an early-phase study is planned to investigate whether this drug is effective against EoE. Finally, new topical corticosteroid 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, the disease returns when they are discontinued. In contrast, when foods that induce symptoms are eliminated from the diet, patients enter 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 nondirected 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, nondirected 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% to 96% of children[9,149,151] and 72% of adults with EoE.[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 histological remission is established, based on a repeat endoscopic evaluation after patients have been on elemental diets for 4 to 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 to 7 days (Figure 4).[154] If symptoms do not recur after reintroduction of food(s) from one group, endoscopy and biopsy are performed 2 to 3 months later to provide histological evidence for remission before the next single food from the next food group is introduced. However, if patients develop symptoms after 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 radioallergosorbent and/or skin prick tests 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 skin prick test in identifying foods that cause symptoms ranged from only 13% to 22%.[155,156] However, when children were evaluated by the skin prick test and atopy patch test 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 atopy patch test and skin prick test. Interestingly, although dairy often produced negative test results, it was the most commonly identified inducer of EoE. Therefore, most allergists restrict dairy from the diet without a test. The atopy patch test has not been

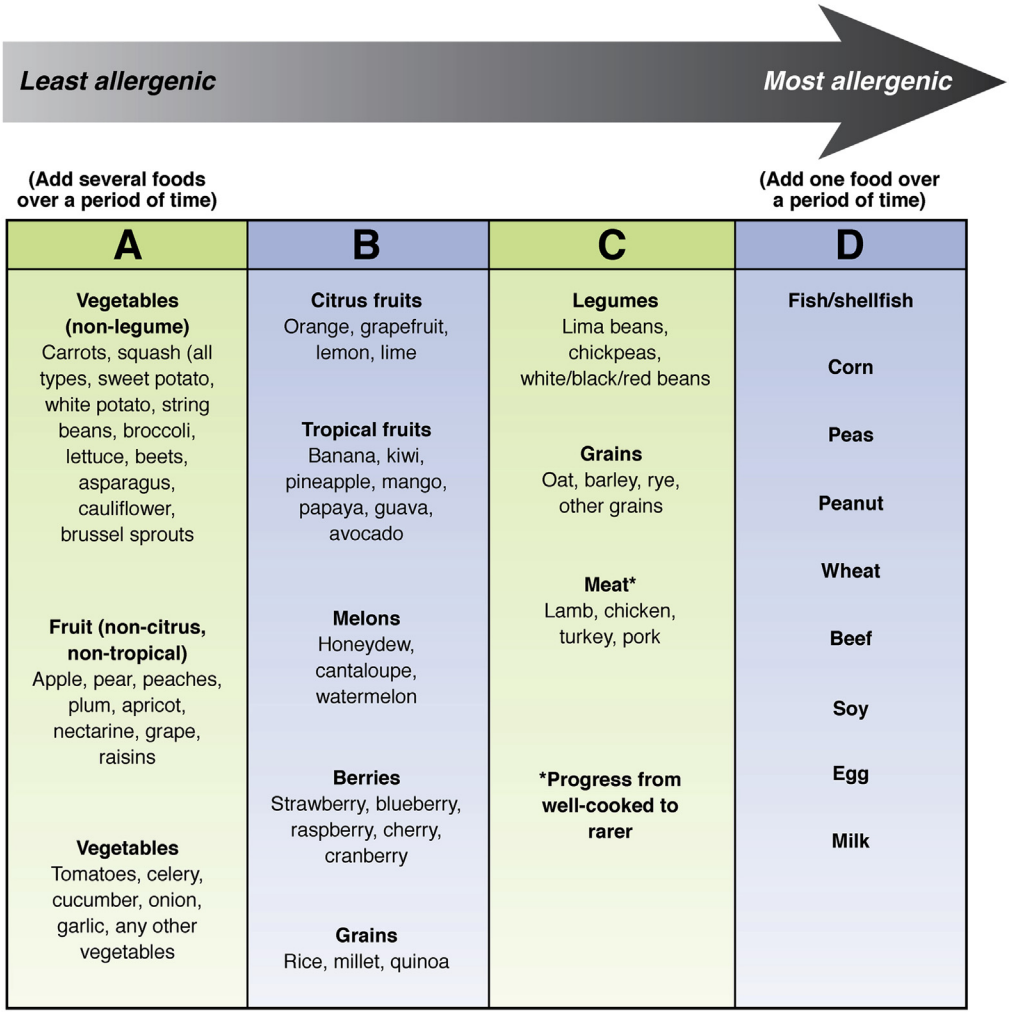

Figure 4. Dietary reintroduction of food allergens. Modified with permission from Spergel and Shuker.[154]

standardized 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.

Nondirected (empiric) elimination diets. The advantage of a nondirected 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, and 74% of subjects had 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] Retrospective studies have provided comparable results.[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 to 6 weeks after each new food is introduced. The next food is reintroduced after the histological 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 in which allergy testing is not easily accessible, and in which 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 reintroduction process, depending on the number of repeat endoscopies needed. As many as 10 endoscopic examinations have been required over a 12- to 18-month period 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 postprocedural 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] which is 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 bougies, 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 the pace of knowledge acquisition has been astounding for a recently recognized disease. The fact that 3 practice guidelines have been published within the past 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 End Points and Symptom-Histology Discordance

The ideal treatment end point 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 histological response (Figure 3).[106–109,111,129–134] The most appropriate treatment outcome is of clinical, research, and regulatory interest, and multiple studies are under way to help define this.

Further complicating the picture is that in some cases of EoE, there is often a dissociation between symptomatic and histological 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

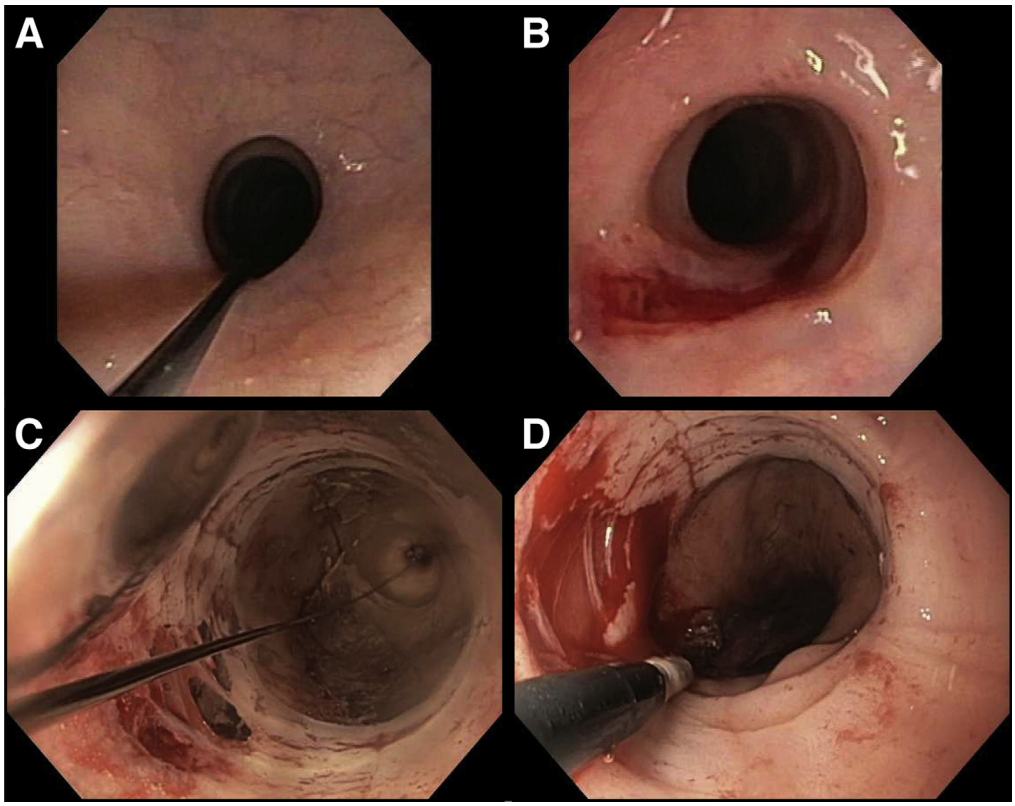

Figure 5. Examples of esophageal dilation to treat EoE. (*A*) A guidewire, which was placed with the neonatal scope, is seen coursing through a very tight proximal esophageal stricture before passing the wire-guided bougie. (*B*) The desired postdilation effect with a mucosal tear. (*C*) View through an inflated through-the-scope balloon during a dilation at the gastroesophageal junction. The developing mucosal tear is seen in the 7 to 8 o'clock area. (*D*) The desired postdilation effect with a mucosal tear.

that is dilated can have a rapid symptom response, but without dietary or pharmacological therapy there will still be marked esophageal eosinophilia. In contrast, a patient with a stricture who is treated with corticosteroids or diet may achieve histological normalization, but symptoms of dysphagia will persist if the stricture does not improve. Modification of eating behavior to avoid foods that induce dysphagia may also have a role. A combination of these factors could explain the results of RCTs of topical corticosteroids or anti–IL-5 agents, in which eosinophil counts significantly decreased in the active group compared with the placebo group but symptoms improved in both groups.[109,111,112]

Maintenance Therapy and Treatment-Refractory Patients

EoE typically recurs when treatment is stopped,[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 corticosteroids should be continued indefinitely, particularly in light of the potential adverse effects and lack of long-term data. An approach in which 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 corticosteroids and findings from studies of selective dietary therapies (not amino acid–based formulas) that between one-fourth and one-half of patients with EoE might not respond.[106,109,155,158]

The first factor 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 corticosteroids to diet, or vice versa, expand an elimination diet or consider elemental formula, increase doses of topical corticosteroids, or consider systemic corticosteroids. If there is a persistent stricture, then dilation is appropriate. Superimposed infection should be excluded. If the esophagus is patent and inflammation has resolved but symptoms persist, other causes should be pursued. There has been limited experience with second- or third-line pharmacological 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.

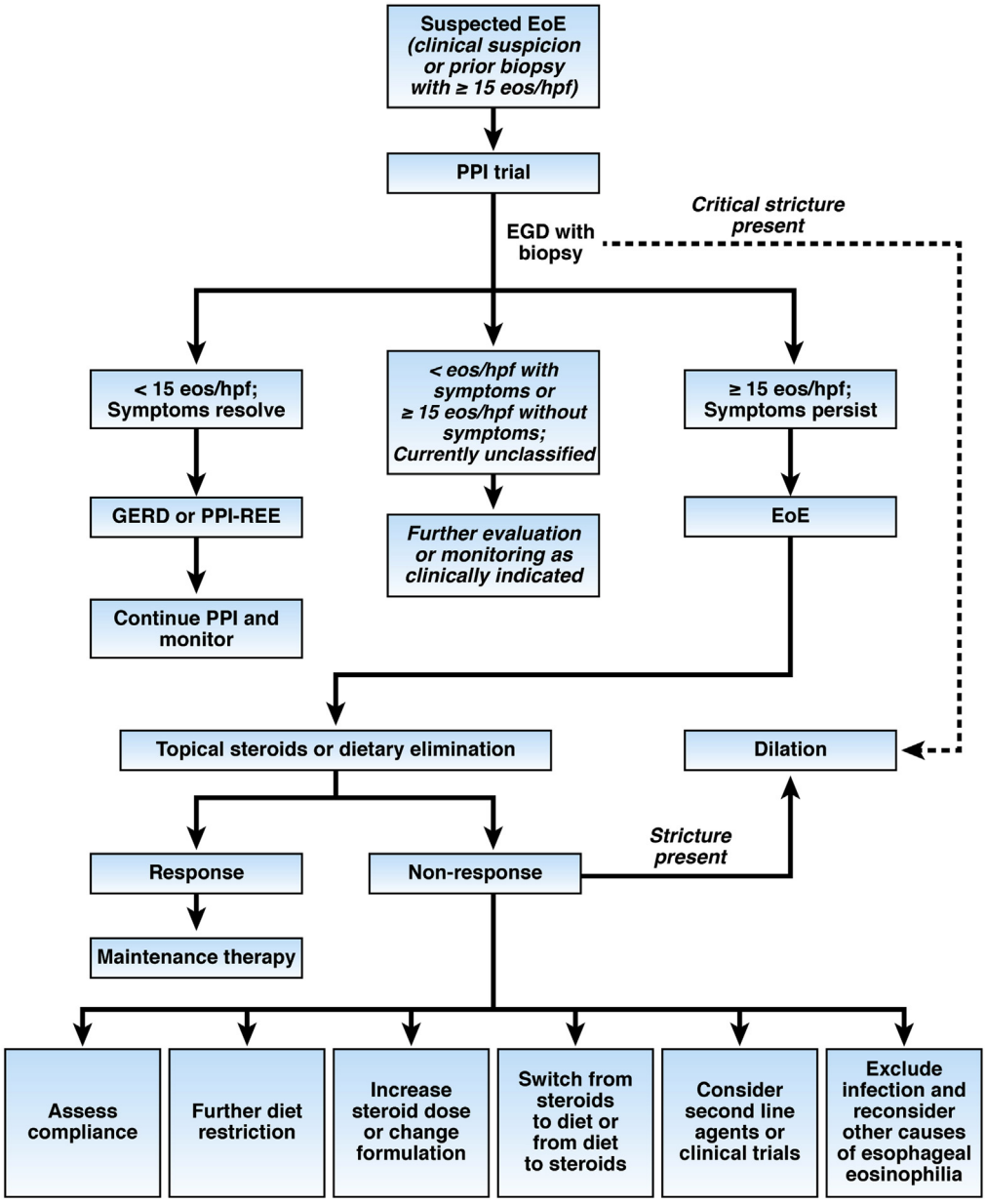

Figure 6. Algorithm for diagnosis and treatment of EoE.

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 biopsy specimens, and exclusion of competing causes of esophageal eosinophilia, including PPI-REE. Esophageal eosinophilia in and of itself does not indicate EoE. The mainstays of treatment of EoE 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 pharmacological agents are prescribed off label, increasing costs and barriers to access for patients. Similarly, dietary treatments and elemental formulas are rarely covered by insurance.

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 of this disease, and ongoing collaborations hold great promise for the future.

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Author names in bold designate shared co-first authorship.

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Reprint requests
Address requests for reprints to: Evan S. Dellon, MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Road, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7080. e-mail: edellon@med.unc.edu; fax: (919) 843-2508.

Conflicts of interest
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