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Alex Straumann, David A. Katzka

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Diagnosis and Treatment of Eosinophilic Esophagitis

Alex Straumann and David A. Katzka

Swiss EoE Clinic, Praxis Römerhof, Olten, Switzerland and Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

Correspondence:

David A. Katzka

Division of Gastroenterology and Hepatology

Mayo Clinic

200 First Ave., S.W.

Rochester, MN 55905

Katzka.david@mayo.edu

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Abstract

Eosinophilic esophagitis (EoE) is a new disease. It is caused by a T-helper 2 cell response to food antigens in contact with the esophageal mucosa. Although no single feature defines EoE, a constellation of compatible demographic, clinical, endoscopic, and histologic findings establish the diagnosis. Children present with symptoms and endoscopic patterns characteristic of inflammation whereas adolescents and adults have manifestations of fibrosis and gross esophageal strictures. Clinical and endoscopic scoring systems have helped to standardize diagnosis. There is controversy in EoE research over the optimal endpoint for treatment. Although the most common endpoint is a reduced number of eosinophils in biopsies, changes in symptoms and endoscopic features are becoming important targets of therapy. We should improve our understanding of EoE progression and the need for maintenance therapy, and continue development of diagnostic tools that avoid endoscopy and biopsy analyses, to more easily monitor disease activity.

Keywords: Eosinophilic esophagitis, esophagitis, esophagus

The first case of eosinophilic esophagitis (EoE) was described in 1978 and misinterpreted as achalasia[1]. In the early 1980s, the importance of esophageal eosinophilia was perceived, and EoE was considered to be a diagnostic criterion for reflux disease[2]. It took more than a decade before EoE was described in 2 case series and recognized as a distinctive disease entity characterized by symptoms of esophageal dysfunction and eosinophil infiltration[3, 4]. Both studies found EoE to be prevalent in younger males with atopic conditions, and endoscopic findings to be discreet and differ from those of gastroesophageal reflux disease (GERD). Meanwhile, EoE has been observed in children and adults, in North and South America, Europe, Asia, and Australia [5].

Initially EoE was regarded as rare, but soon it became evident that its incidence and prevalence were rapidly increasing [6]. Several population-based studies from the United States[7, 8] and from Europe [9, 10] have provided evidence that this is a true increase, rather than the effect of raised awareness. Based on a recently published meta-analysis, the prevalence of EoE in adults is 32.5 and in children 30.9 patients per 100,000 inhabitants. In other words, in Westernized areas, 1 patient with EoE lives in a community of approximately 3000 inhabitants[11]. Although EoE mainly affects persons 20–40 years old, it is seen in all age groups [12]. The incidence and the prevalence of EoE are comparable with the values of Crohn's disease.

Diagnosis

An international panel of experts in pediatric and adult gastroenterology, allergy, immunology, and pathology defined EoE as "an esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant inflammation" [6]. Other causes of esophageal eosinophilia must be ruled out—particularly GERD. Experts had therefore recommended that patients be treated with a double dose of proton pump inhibitors (PPIs) for 2 months; the effects are used differentiate between EoE and GERD[13]. Unexpectedly, in a subset of patients with EoE, symptoms and histologic abnormalities resolved following PPI treatment, even in the documented absence of GERD[14]. This PPI trial brought more confusion than clarification, so a panel of experts recently recommended that PPI response not be used in diagnosis[15]. However, it is not clear how to differentiate reliably between EoE and GERD. Additional, disorders leading to infiltration of the esophagus by eosinophils include eosinophilic gastroenteritis, celiac disease, Crohn's disease, achalasia, and drug hypersensitivity. The diagnosis of EoE is complex, so clinicians should diagnose EoE based on a combination of

symptoms, histologic and endoscopic findings—no single feature is sufficient to establish a definitive diagnosis[16].

Symptoms in children vs adults

The symptoms of EoE follow a hierarchal and pyramidal pattern from early childhood to adulthood (List 1)[7, 17, 18]. This presumably follows decades of diffuse inflammation leading to esophageal fibrosis. Specifically, the symptoms of EoE in early childhood are protean and include failure to thrive, feeding difficulties, nausea, vomiting, and abdominal pain. In older children symptoms become more esophageal, with heartburn, chest pain, and early manifestations of dysphagia such as slow and picky eating. In adolescents and adults, symptoms become specific to esophageal narrowing, with solid food dysphagia and food impaction. On rare occasions, impaction can lead to esophageal perforation (Boerhaave's Syndrome)[19-21].

As the population of patients with EoE increases and they are studied more carefully, it becomes clear that this time line is not firm. For example, recent data show that chest pain may be a prominent symptom in adults, perhaps reflecting an inflammatory component[22]. Similarly, heartburn may occur in adults[12]. Conversely, school-age children may present with dysphagia[18]. It is not clear if these are different symptoms of a similar disease or the degree of esophageal inflammation and fibrosis varies with age.

Symptom scoring systems

As for many chronic diseases, symptoms of EoE may be obvious or arise via compensatory maneuvers to cope with the disease. It is important to document the frequency and chronicity of symptoms, as well as the intensity. Several scoring symptoms have been developed for the comprehensive evaluation of EoE symptoms. These systems serve not only to achieve greater accuracy in grading a patient's symptoms but also function as a standardized objective tool; it can be used to assess the disease over time and evaluate the effects of treatments or agents in clinical trials.

The EoE activity index [16, 23] is a patient-reported outcome instrument; it was developed using symptoms of 183 patients in Switzerland with eosinophilic esophagitis. The system is based on a

conceptual framework to assess symptoms, behavioral adaptations, and biologic activity of adult patients with EoE over periods of 1, 7, and 30 days. The score is an indicator of dysphagia. It is comprehensive, documenting the frequency, intensity, and duration of dysphagia; the duration of dysphagia episodes and occurrence of food impaction; time required to eat a regular meal; frequency of pain with eating. This scoring system also detects accommodating symptoms of EoE, such as slow eating, careful chewing, and food avoidance. The score is validated in a 7-day recall period, which was deemed adequate. Scores have been shown to correlate with global assessment score endoscopic and histologic findings.

The Mayo dysphagia questionnaire is a validated symptom scoring system that has been used for EoE but was originally developed for peptic esophageal strictures or general use with dysphagia. It is a 28-item instrument that takes, on average, 10 minutes to complete[24]. It has been used in several trials of therapeutic agents EoE;[25-27] findings correlate variably with findings from histologic analysis. It is not clear if this variation is due to the inaccuracy of the scoring system for inflammation or differing presentations of peptic and EoE strictures.

Dysphagia scoring systems have also been used to evaluate pediatric patients with EoE. For example, the University of Cincinnati developed the Pediatric EoE Symptom Scoring System;[28] [29] scores correlate with findings from histology. This scoring instrument also assesses quality of life, and can include parental interpretations of symptoms.

Nevertheless, many studies have used their own non-validated indices to evaluate EoE symptoms. One problem with the scoring systems is that although they are well suited for clinical trials, they can be cumbersome in clinical care. Some investigators have developed more patient-friendly scoring systems. For example, the Dysphagia Symptom Questionnaire[30] is a 3-question instrument, administered daily for 30 consecutive days; it was developed and tested in a small group of patients with EoE. The questions are: Since you woke up this morning, did you eat solid food? Since you woke up this morning, has food gone down slowly or been stuck in your throat or chest? And, for the most difficult time you had swallowing food today (during the past 24 hrs), did you have to do anything to make the food go down or to get relief? Patient compliance and acceptance was excellent. Even though many studies use non-validated scoring

systems, more concerning is a general lack of scoring system use to accurately monitoring clinical disease.

Endoscopy

Patients with EoE undergo endoscopy for collection of epithelial biopsies and detection of gross abnormalities. With increasing physician recognition of the characteristic endoscopic findings. normal-appearing esophageal mucosa is found in less than 5% of patients with EoE[31]. Findings vary among children and adults. Like symptoms, in children, endoscopic findings change with level of inflammation. Exudates, linear furrows, and edema are the most common endoscopic features of EoE in children [32, 33]. In adults, endoscopy often detects a combination of inflammation and fibrosis, including rings and strictures. In an effort to standardize endoscopic findings for the purpose of monitoring disease activity and clinical trials, a graded endoscopic grading tool has been developed[31]. The endoscopic reference score is calculated based on findings of edema, rings, exudates, furrows, and strictures (EREFS, see Figure 1). It is easy to calculate and incorporated in some endoscopic imaging platforms.

One of the key questions is whether EREFS score corresponds to histologically defined disease activity. Several studies have addressed this question and produced conflicting results. For example, a recent controlled trial of a topical steroid associated EREFS score with findings of active disease from histology with an area under the curve value of .934 [34]. Other studies have shown weak to modest association between EREFS score and histology findings[35, 36]. This discrepancy might be related, in part, to the variable resolution of endoscopic findings with medical therapy, depending on whether the resolution occurs via reductions in inflammation or fibrosis. Endoscopic findings (and symptoms) might also be an important marker of disease activity, regardless of biopsy eosinophil count. At the very least, the EREFS score provides a common endoscopic language for diagnosis and monitoring of patients with EoE. Finally, the mucosa is commonly fixed with a more forceful pull of the forceps required to obtain a good mucosal sample[37].

Radiology

Barium esophagography is a complementary examination to endoscopy, particularly in adolescents and adults. Although barium esophagography does not accurately detect mucosal abnormalities in patients with EoE, it detects strictures with a significantly higher level of sensitivity than endoscopy. A study that used a radiographic technique to measure esophageal diameter in adults found that endoscopy detects strictures with an esophageal diameter of less than 13 mm with a sensitivity value below 26% [38]. These radiographically identified strictures help determine mechanisms of dysphagia in patients with almost normal findings from endoscopy. A barium esophagram may also detect ring formation. Radiography also helps plan endoscopy and dilation in advance, particularly for narrow proximal strictures or small-caliber esophagus (Figure 2). There is limited use of barium radiography in children, but strictures detected by contrast esophagram were not seen by endoscopy in 50% of 22 children studied[39]

Histology

Six to 8 biopsies from the distal and mid- and/or proximal esophagus, obtained during endoscopy, are needed to identify patients with EoE with a high level of sensitivity [40]. Within these biopsies, an eosinophil count greater than 15 in a high-power field (HPF) is the sine qua non for diagnosis of patients with active EoE [6]. Although an ostensibly firm threshold, several considerations must be understood. The level of 15 eosinophils/HPF is somewhat arbitrary—different cut-off values were used in earlier studies. Also, the lack of a standardized diameter for the HPF on microscopes can lead to variations in determination of eosinophil density[41]. Furthermore, esophageal eosinophilia is patchy in biopsies—even from patients with active disease. There has been debate about how many HPFs of esophageal eosinophilia are sufficient to identify a patient with active disease and begin treatment. Studies to distinguish patients with active vs inactive EoE on the basis of mucosal impedance measurements correlated the histologic threshold of 15 eosinophils/HPF with loss of esophageal mucosal integrity [42, 43].

Another concern with using eosinophil count is that the whole cell has undergone dissolution in the active phase and is therefore not visible with routine histologic staining. Patients can have robust staining for products of eosinophil degranulation (such as eosinophil peroxidase and eosinophil derived neurotoxin) in esophageal biopsies, even though few eosinophils are present[44,

[45]. Nevertheless, in most patients, eosinophil count associates with the presence of eosinophil degradation products.

In addition to esophageal eosinophilia, other histologic factors are associated with EoE. These include spongiosis (dilation of intercellular spaces, DIS), increased numbers of mast cells and lymphocytes, and basal-zone hyperplasia[46, 47]. Little is known about the precise cellular and cytokine mechanisms that lead to these changes, so their relationship with to disease activity is unclear. For example, a preliminary study reported that abnormal basal zone hyperplasia in biopsies from patients may persist after treatment despite resolution of esophageal eosinophilia[48]. Basal zone hyperplasia appears to be induced by interleukin-13 (IL13) and is associated with fibrosis[49] —it might serve as an endpoint of therapy. Similarly, spongiosis has been reported persist in patients with eosinophil reductions to fewer than 15/HPF[50]. It is not clear if persistent DIS is a marker of incomplete or slowly resolving inflammation, or a baseline histologic finding in some patients with EoE. The authors of this study questioned whether EoE disease activity should be further defined, by normalization of all pathology findings.

Similar to the assessment of symptoms and endoscopy, a replicable histologic scoring system has recently been devised[47]. The EoE histologic scoring system evaluates 8 features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis. When applied to treated and untreated patients, the score discriminates well between patients with vs without spongiosis—eosinophil surface layering and eosinophil abscess. Importantly it gives pathologists a common language for assessment of EoE activity and for conduction of therapeutic trials.

Although pathology analysis of esophageal biopsies is essential for diagnosis of EoE, features of the biopsies indicate variable morphologic responses to specific mechanisms of inflammation. Generally, these mechanisms are mediated by genetic, epigenetic, and environmental influences. The concept of diagnosing EoE by molecular methods has great appeal. Using cluster analysis and dimensionality reduction, Wen et al identified an expression pattern of 96 genes in esophageal tissues from patients with EoE, which they called the EoE diagnostic panel (EDP)[51].

This pattern identified patients with EoE with 96% sensitivity and approximately 98% specificity, and distinguished patients with EoE in remission from controls. The EDP also identified patients exposed to swallowed corticosteroids. Formalin-fixed, paraffin-embedded tissues can be used to identify the EDP, which distinguished patients with EoE from those with reflux esophagitis, identified by pH-impedance testing. This test may offer an exciting alternative to routine histologic analysis of endoscopic biopsies.

New Methods of Diagnosis

Although EoE is best diagnosed by endoscopy and esophageal biopsy, the cost and risk of repeated procedures to monitor histologic response to pharmacologic or dietary interventions is burdensome. It is therefore important to identify alternatives that are less expensive and/or less invasive.

Transnasal endoscopy (TNE)

TNE appears to be an excellent alternative to endoscopy; it is office based, does not require sedation, and directly visualizes the esophageal mucosa. In a study of 22 children (8–17 years old) with EoE, most patients and parents favored TNE over standard endoscopy and would repeat the procedure[52]. Biopsy specimens were adequate without difference in surface area compared to standard endoscopy and biopsy. Further studies are needed to determine if this is generally applicable to adult populations and young children.

Esophageal impedance

DIS increases paracellular fluid and electrolyte flow, increasing the electrical conductance of the epithelium. Measurement of mucosal impedance is therefore a tool that might be used to measure activity of EoE. In a study of 20 patients analyzed with an endoscopic impedance probe, point mucosal measurements identified patients with EoE with 90% sensitivity and 91% specificity, when degree of spongiosis and eosinophils/HPF were used as the reference[43]. Mucosal impedance can also be assessed in patients with EoE by a standard pH/impedance catheter, during the night time, when there is an absence of swallowing and fluid in the esophagus[53]. It is not clear whether impedance measurement will obviate the need for esophageal biopsies.

Impedance planimetry

Stricture formation is a hallmark of esophageal disease in adults with EoE, yet visualization of this degree of fibrosis can be difficult. Biopsies collected during endoscopy might not demonstrate esophageal fibrosis due to its patchy distribution or lack of biopsies taken deep enough to find fibrotic change in the lamina propria. Furthermore, endoscopy underestimates stricture presence and extent compared to barium esophagography[54]. Impedance planimetry is used to measure esophageal distensibility, via an orally passed catheter with an infinitely compliant inflatable balloon. Pressure volume characteristics are determined from step-wide inflations of the balloon and converted into a 3-dimensional color plot reflecting the degree of esophageal fibrosis. This technique can be used to easily assess esophageal distensibility, which could become important biomarker of EoE progression [55]. The balloon catheter may be passed during endoscopy. No perforations have been reported.

Cytosponge collection of tissue

The ideal technique to monitor EoE would obviate the need for endoscopy yet adequately sample the esophageal mucosa for analysis. The cytosponge consists of an ingestible gelatin capsule containing a compressed mesh attached to a string. The capsule is swallowed; in the stomach, the gelatin dissolves within 5 minutes to release a 3-cm diameter spherical mesh. The mesh is withdrawn through the mouth by traction of an attached string, and a robust tissue specimen is collected from the sponge that can be analyzed by histology or immunohistochemistry. The cytosponge was invented for analysis of Barrett's esophagus[56]. In a pilot study of 20 patients, the sponge identified 11 of the 13 individuals with active EoE (83%)[57] as well as 3 cases of active EoE not identified by biopsy. The numbers of eosinophils in samples collected by the sponge correlated with those in samples collected by endoscopy. Additionally, the sponge procedure was preferred by all patients compared with endoscopy.

Esophageal string

The esophageal string device[58] consists of a capsule filled with approximately 90 cm of string. Patients swallow the capsule, which dissolves in the stomach or duodenum. After 1–12 hrs (overnight), the string is withdrawn and secretions scraped from the string are analyzed for eosinophil-derived proteins. When performed in 41 children with GERD, controls, or EoE, the

string test significantly distinguished children with active EoE from those with EoE in remission, GERD, or normal esophagus. Furthermore, levels of luminal eosinophil-derived proteins in string samples correlated with peak and mean numbers of esophageal eosinophils/HPF. The test is performed bedside, is well tolerated in children, and does not require anesthesia.

Blood markers

A simple blood test to diagnose and monitor disease activity in patients with EoE would be highly desirable. Although serum levels of C-C motif chemokine ligand 26 (also called eotaxin-3) are increased in patients with EoE, measurements of levels do not identify patients with EoE with sufficient accuracy for clinical use[59]. Other molecules increased in serum of patients with EoE include IL4, IL5, IL6, IL9, IL13, transforming growth factor alpha (TGFA), TGFB, thymic stromal lymphopoietin, proteoglycan 2 pro eosinophil major basic protein, and ribonuclease A family member 2 (also called eosinophil derived neurotoxin). However, levels of these cannot accurately differentiate patients with active vs inactive EoE[60].

Urine markers

Urine levels of 3-bromotyrosine, a chemical marker of eosinophil activation that is used to measure EoE activity[61], were found to be increased 93-fold in patients with EoE compared with non-atopic controls and 13-fold in patients with EoE compared with atopic controls. Cutoff thresholds were selected for 3-bromotyrosine measurement that identified non-atopic controls with 100% specificity and a negative predictive value of 100%, and atopic controls with 79% specificity and a negative predictive value of 90%. Although this test has not been used to accurately differentiate patients with active vs inactive EoE, this urine marker has potential.

Challenges in Diagnosis of EoE

Unfortunately, symptoms in children and in adults unreliably reflect the endoscopic and histological activity of the disease[16, 28] Adequate diagnosis and monitoring of EoE demands endoscopic and pathologic examinations—invasive and expensive measures. The development of reliable non-invasive methods to determine the inflammatory activity is therefore urgently needed.

Central to the diagnosis of EoE is an almost exclusive reliance on the number of eosinophils in the esophageal epithelium[6]. Despite the prominent appearance of these late-phase inflammatory cells, little is understood about their exact role in the pathogenesis of EoE. Three studies investigated whether monoclonal antibodies against IL5, which block eosinophil recruitment, might be effective in treatment of EoE[62]. Although mepolizumab[63] and reslizumab[64] reduced blood and tissue eosinophilia, by approximately 90% and 55%, respectively, symptoms persisted and numbers of other inflammatory cells, such as T cells and mast cells, did not change. In addition, a recently published case series reported on an EoE-like syndrome in members of EoE families with esophageal dysfunction, but without having eosinophils in the esophageal tissue. Interestingly, immunohistochemical and molecular analyses demonstrated tissue infiltration by T cells and mast cells, as well as a gene expression pattern resembling that of EoE [65]. These findings illustrate although that the role of eosinophils is important, other markers of inflammation must be considered in the pathogenesis and diagnosis of EoE.

EoE is caused by allergies to specific foods; identification of culprit foods is therefore an important part of diagnosis, as it opens the way to non-medical treatment options. Unfortunately, almost all established diagnostic tools are based on the detection of IgE-associated sensitization and have only minimal value in the search for causative food allergens[13, 66]. At present, the only way to identify causative food allergens is to start an empirical elimination diet and confirm histologic remission with each food addition or subtraction[67,68]. The development of a reliable diagnostic test to identify causative food is therefore another unmet diagnostic need in EoE.

Treatment

The goal of treatment of EoE is putatively to control esophageal eosinophilia and inflammation. Unfortunately, control of other parameters, such as symptoms and strictures, is also important. Different therapeutic approaches are therefore best at meeting different endpoints. For example, control of esophageal inflammation may not obviate the need for mechanical dilation to reduce dysphagia and prevent food impaction. Consequently, combinations of therapies are often needed to reach some endpoints.

Control of esophageal eosinophilia

The inflammatory and fibrogenic components of EoE are mediated in large part by the injurious effects of eosinophil degranulation, so control of esophageal eosinophilia is an essential endpoint of therapy (reduced to fewer than 15 eosinophils/HPF in biopsies). Although the optimal goal of therapy is to eliminate all eosinophils from the esophageal mucosa, this is achieved in only a few patients. With this caveat in mind, the biologic meaning of less than 5, 10, or 15 eosinophils/HPF is unclear. Although intuitively reducing the eosinophil count to the lowest possible number per HPF makes sense, the realistic goal of pharmacologic or diet therapy is fewer than 15 eosinophils/HPF.

Symptom control

Control of symptoms is another essential endpoint in the treatment of EoE. In children, symptoms are principally due to the inflammation, with relatively less fibrosis, so medical treatment alone is usually sufficient to relieve symptoms. In adults, however, fibrosis may need to be viewed as a distinct treatment endpoint[16]. In medical treatment studies, the correlation of histologic to symptom improvement varies—particularly in patients with critical strictures and/or small-caliber esophagus[25]. Dilation is therefore an important treatment option for adult patients with EoE, to alleviate dysphagia and prevent food impaction.

Should dilation be performed before or after initiation of medical therapy? There is no clear evidence that dilation in the presence of active esophageal eosinophilia increases risk of complications. Nevertheless, in patients with severe dysphagia and/or history of food impaction, dilation should be performed more urgently. For patients with less-severe dysphagia and fewer critical strictures, a decision to perform dilation can be after a course of medical therapy.

Prevention of remodeling and reversal of fibrosis

Although the short-term goal of medical treatment is to reduce or eliminate esophageal eosinophilia, the long-term goal is to prevent and perhaps reverse esophageal fibrosis and stricture formation. Corticosteroids have been shown to reduce esophageal remodeling[69]. For example, in esophageal biopsies taken from 16 pediatric patients with EoE, 3 months of budesonide significantly reduced esophageal remodeling and reduced fibrosis, level of TGFB1, number of cells with phosphorylated SMAD2 or SMAD3, and vascular activation[70].

A follow-up study was conducted of histologic remodeling and TGFB1 expression in esophageal biopsy specimens from 32 children with EoE treated with topical corticosteroids over 10 years. Fewer than 15 eosinophils/HPF at any time correlated with lower fibrosis and endoscopic severity ([71]). A large retrospective study in adults associated longer durations of untreated EoE with increased risk of esophageal stricture [72]. For example, in patients with untreated symptoms of EoE for 20 years, the chance of stricture formation was 85%.

Therapeutic Options: Drugs, Diet, and Dilation

EoE is similar to allergic airway diseases,[73] in that it involves a T-helper (Th)-2 cell-mediated immune response, and to gastroesophageal reflux[74, 75]. Drugs used to treat asthma and acid suppression agents have therefore been tested as treatments for EoE. In the past, these drugs were selected based on findings from small case series or even anecdotal reports. Fortunately, in the last few years, findings from several double-blind controlled clinical trials have aided physicians in optimizing treatment decisions.

Corticosteroids

In 1998 systemic corticosteroids were first shown to be effective treatment for active EoE in children[76]. Only few months later, researchers reported that 4 children with EoE were treated successfully with swallowed topical corticosteroid[77]. However, it took 10 years before a prospective, controlled trial was demonstrated that topical fluticasone was safer than systemic prednisolone, and as effective, in achieving and maintaining histologic and symptomatic remission[78]. Since then, more than 10 controlled clinical trials in adult and pediatric patients with EoE have confirmed that swallowed topical corticosteroids, such as budesonide, fluticasone, and ciclesonide, are highly effective in resolving symptoms and signs of EoE ([27,78-88,87]). One optimal method of delivery appears to be in a viscous form, shown by scintigraphy[26]. Proper dosing of steroids is essential in the treatment of adults with EoE. Budesonide (1 mg) or fluticasone (800 ug) in a viscous solution, given twice daily, is recommended for initial treatment.

These studies evaluated the ability of corticosteroids to bring active EoE into remission. However, EoE is a chronic disease, and symptoms and inflammation generally relapse within

few weeks after cessation of topical corticosteroid treatment[78, 83]. Many patients therefore need a long-term therapy. So far only 1 long-term, placebo-controlled trial has evaluated this aspect; a low-dose maintenance regimen of swallowed budesonide (0.25 mg), given twice daily, maintained complete histologic remission in only 35.7% of patients over 1 year[89].

Anecdotally, many investigators have used once- or twice-daily budesonide (1 mg). The role and method of interval monitoring is unclear. Some patients are evaluated by barium swallow every 2–3 years, to assess esophageal lumen diameter. Long-term management approaches to EoE must require more development, but certain patient groups have been proposed as candidates for this therapeutic approach (List 2).

PPIs

There are at least 2 reasons that PPIs are used to treat patients with EoE. Given the high prevalence of GERD and EoE, some patients have both [18]. These patients can be given PPIs as adjunct therapy. Esophageal exposure to acid causes more pain in patients with EoE than in healthy individuals[90]. Therefore, acid blockade could reduce symptoms of EoE. Some pediatric and adult patients with typical features of EoE and pH-metric excluded GERD have symptoms and inflammation that respond to PPI monotherapy[14]. A panel of experts recently agreed that PPI-responsive esophageal eosinophilia (based on its clinical, endoscopic, histologic, and molecular similarities with conventional EoE) should be regarded as clinical sub-phenotype of EoE and not as a distinct entity[15]. However, it is still unclear where to position the PPIs in the treatment algorithm of EoE.

Leukotriene inhibitors

An open-label study demonstrated that high doses of montelukast reduced symptoms in patients with active EoE, but did not reduce esophageal inflammation[91]. Subsequently, this drug was not found to be significantly superior to placebo in 2 trials that evaluated the efficacy of montelukast in maintaining a steroid-induced remission[92, 93]. Use of leukotriene inhibitors in induction or maintenance therapy for EoE is therefore not currently recommended.

CRTH2 antagonists

EoE has many features of a Th2 cell-mediated immune response[94, 95]. The prostaglandin D2 receptor 2 (PTGDR2, CRTH2) is a chemoattractant receptor expressed by eosinophils and Th2 cells. This receptor mediates chemotaxis and activation of lymphocytes in response to prostaglandin D_2[96]. The small molecule OC000459 is a first-generation selective CRTH2 antagonist that prevents prostaglandin D_2 from recruiting and activating eosinophils and Th2 cells. In a randomized placebo-controlled trial evaluating the efficacy and safety of OC000459 as a monotherapy for EoE[97], OC000459 reduced eosinophil load by 33% in the esophagus, compared with placebo; the agent also produced mild reductions in symptoms, disease activity, and the endoscopic alterations. However, the overall effect was only moderate, and no patients achieved complete remission during the 8-week study period. Nevertheless, the excellent safety profile and the encouraging in vitro data from studies of second-generation CRTH2 antagonists warrant further investigation of these drugs.

Biologic agents

Mepolizumab and reslizumab are highly selective, humanized antibodies against IL5 that could be promising alternatives for the treatment of eosinophilic inflammation [98]. In 3 controlled trials in children and adults with acute EoE [63, 64, 99], each drug reduced numbers of peripheral blood eosinophils by more than 90% and tissue eosinophilia by 55%. The safety profile was favorable. Unfortunately, clinical improvement was minimal and non-eosinophil inflammatory cells persisted in esophageal tissues. Mepolizumab and reslizumab are therefore not recommended for standard treatment of EoE.

Although the squamous epithelium of the inflamed esophagus expresses high amounts of tumor necrosis factor (TNF), the TNF antagonist infliximab was not effective in reducing tissue infiltration by eosinophils or reducing symptoms in patients with EoE, in an open-label study.[100]

IL13 is an inflammatory cytokine secreted by Th2 cells,[101] so antibodies against IL13 have been tested in patients with EoE. In an 8-week trial, 3 infusions of QAX576, a monoclonal antibody against IL13, reduced numbers of esophageal eosinophils by 60%, compared with an increase of 23% in the placebo group. The reduction in esophageal eosinophils was sustained for as long as 6 months, with a trend toward reduced symptoms. An analysis of gene expression profiles of

esophageal specimens from patients receiving QAX576 revealed changes in levels of EoE-associated mRNAs, including those encoding eotaxin-3, periostin, and markers of mast cells and barrier function. A placebo-controlled phase 2 study of RPC4046, another humanized antibody against IL13[102] in adults with active EoE resulted in a significant reduction in numbers of esophageal eosinophils and improved endoscopic features. Furthermore, RPC4046 reduced dysphagia. The efficacy and safety profile of these compounds supports the development of IL13 antagonists for treatment of patients with severe EoE.

Immune modulators

A small pilot study found that treatment with azathioprine and 6-mercaptopurine was effective in inducing and maintaining a remission in 3 patients with steroid-refractory EoE. [103] No further controlled trials with these drugs have been performed.

Elimination Diets

Diet therapy is attractive for several reasons. With adequate nutrition, there are no potential side effects. An elimination diet, as first-line therapy, is less expensive than steroids[104]. A meta-analysis demonstrated that food elimination diet is effective in a similar proportion of patients (67.2%) to corticosteroid therapy (63.3%) [66]. Nevertheless, several factors mitigate against using diet therapy for EoE. These include effects on quality of life and social activities, as patients must avoid ubiquitous food antigens such as gluten and milk. Furthermore, there is no test other than endoscopy to assess response to changes in food antigen exposure.

The 6-food elimination diet was the first elimination diet to be used in treatment of patients with EoE. Although studies in the United States have tested diets that eliminate gluten, milk, soy, egg, nuts, and seafood as, in that order[67], studies from Spain have strongly implicated legumes as a common antigen[105]. In most studies, gluten and milk were found to be most frequent causes of EoE. Whereas diet therapy typically starts with avoidance of the 6 foods, with measured food reintroduction, the difficulty of this diet has forced new strategies. Investigators recently studied the effects of a 4-food elimination diet,[106] and found it to lead to remission in 28/52 patients (54%), based on clinical and histologic features. Most notably, all patients were found to have just 1 or 2 food triggers, with milk as a only trigger for 27% of patients. Step-up rather than step-

down therapy, starting with elimination of milk and/or gluten and then removal of additional foods, as needed, might be the best approach.

Elemental diet

Although expensive and unpalatable, the elemental diet makes the most intuitive sense, because it is devoid of all food antigens that cause eosinophil infiltration and inflammation. In children, an elemental diet produces nearly complete remission of EoE[107]. Although it is not as effective in adults with EoE, the elemental diet led to remission in 80% and 90% of subjects[108, 109]. Unfortunately, the dropout rate is substantial in trials of adults. Furthermore, the influence of GERD (reducing the role of food allergy) is likely more prominent in adults.

Endoscopic therapy

Dilation with bougienage or balloons is the only available endoscopic treatment for EoE. Dilation of esophageal strictures can lead to long-lasting reductions in dysphagia in adults and children with EoE [110-112]. Early studies reported perforations after dilation of EoE-induced strictures, causing this therapy to be considered risky[113]. However, a meta-analysis of data from 468 patients who underwent a total of 671 dilations reported only 1 perforation (0.1 %)[114]. This rate is comparable to that of esophageal dilation for strictures other than those caused by EoE (risk of approximately 0.1% to 0.2%). Patients should therefore be informed accordingly prior to the procedure.

The main drawback of esophageal dilation is the fact that it does not control the chronic inflammation that contributes to esophageal remodeling[115]. Esophageal dilation should therefore not be used as the only first-line therapy. It is generally used for persistent dysphagia after medical treatment, up front in patients were severe dysphagia and/or history of food impactions or as the only treatment for patients who did not respond to anti-inflammatory agents, based on histologic analysis and symptoms [116]. Dilation should be performed gradually, using rules of 3 and often over several sessions, depending on symptoms and the initial esophageal lumen diameter. After dilation, 75% of patients have considerable chest pain that may last several days[115]

Extra-esophageal allergies

Animal models of EoE have been developed, via instillation of Aspergillus to lungs of mice[117]. Different types of studies have linked the activity of extraesophageal allergies with EoE. For example, many patients have an EoE flare during times of the year when levels of aeroallergens are high[118]. Interestingly, as in the mouse model, in which lung inflammation precedes esophageal eosinophilia, many patients with EoE have a history of rhinitis for up to 10 years[119]. Airway exposure to common household allergens, such as dust mites, cockroaches, and mold can also induce esophageal eosinophilia[120]. There are also reports of initiation and exacerbation of EoE with immunotherapy [121]. Some plant aeroallergens have similar antigenic epitopes to common foods, so patients with EoE might have immune cells that cross-react with plant and food allergens; certain plant allergens might cause EoE through direct exposure to the esophageal epithelium[122]. Unfortunately, there is little data that demonstrate that control of extraesophageal allergies modulate EoE activity[123].

Patients with refractory disease

The definition of refractory EoE varies—patients can be considered to have refractory EoE if they have persistent esophageal eosinophilia, symptoms, or both. Lack of histologic response occurs in 5%–40% of patients treated with topical steroids[124, 125]. Some of these patients may respond to longer courses of steroids[126]. Anecdotally, some clinicians give patients a combination of PPIs and steroids. Patients may also be refractory to treatment because they have a critical stricture or small-caliber esophagus. These patients will likely need a series of dilations to achieve an esophageal diameter that allows reasonable oral intake.

Future Directions

EoE is a relatively new disease that was once considered rare but is now commonplace—diagnosis and therapy must progress with prevalence. We need to develop easy and inexpensive tests that can be performed bedside assess EoE activity. It will also be important to learn more the type and length of time esophageal antigen exposure required to induce esophageal eosinophilia, to guide dietary therapies. If we can increase our understanding of the subtypes of EoE, it might be possible to estimate risk of disease progression for specific patients, and identify those that require intensive and/or chronic maintenance therapy. Therapeutic agents are needed that have been developed specifically for patients with EoE, with FDA approval.

Additionally, it is important to better define the long term-side effects of topical steroids in patients with EoE, which is often a chronic relapsing disease. Similarly, we need to continue to follow large cohorts of patients with EoE carefully, as we strive to understand the course of their disease beyond 10–20 years—particularly because many are children and young adults.

Figure 1. Endoscopic Images of EoE.

EREFS: Endoscopy can detect edema, white exudates, and furrows, which are markers of acute inflammation, whereas rings and strictures indicate remodeling.

Figure 2. Barium Esophagram Demonstrating Small-caliber Esophagus

Figure 3. Treatment Algorithm for EoE

The algorithm illustrates the treatment strategy for EoE. Treatment should start with an anti-inflammatory agent (swallowed topical corticosteroids), PPIs or an elimination diet. Treatment selection depends exclusively on the patient's and physician's preference, because no comparative studies have any of these to be superior to the others. Dilation is indicated if symptoms persist despite successful control of inflammation. After each change of treatment strategy, symptoms, endoscopic, and histologic features should be revaluated, because symptoms do not accurately reflect the inflammatory activity of the disease.

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List 1. Symptoms of EoE in Children vs Adults

Children	**Adults**
Failure to thrive	Dysphagia
Feeding difficulties	Eating slowly
Nausea and vomiting	Solid food avoidance
Abdominal pain	Avoidance of social eating
Heartburn	Chest pain
Picky eating	Heartburn

List 2. Candidates for Long-term Maintenance of Pharmacologic Therapy

1. Small caliber esophagus
2. Symptomatic or objective progression of stricture formation
3. Rapid return of symptoms off therapy
4. Recurrent food impactions
5. Co-morbid conditions increasing risk of endoscopy and dilation
6. Prior spontaneous or dilation induced perforation
7. Travel to areas where food impaction causes greater risk