

Eosinophilic esophagitis: update on management and controversies

Joan W Chen, John Y Kao

Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109-5362, USA

Correspondence to: J W Chen, 3912 Taubman Center, 1500 E. Medical Center Drive, SPC 5362, Ann Arbor, MI 48109-5362, USA
chenjoan@med.umich.edu

Cite this as: *BMJ* 2017;359:j4482
doi: 10.1136/bmj.j4482

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

ABSTRACT

Eosinophilic esophagitis is a chronic allergen driven immune mediated disease that is increasingly recognized as a leading cause of dysphagia and foregut symptoms in children and adults. Much knowledge has been gained in recent years on the genetic and environmental risk factors for this disease, the associated inflammatory milieu, and the long term complications from esophageal remodeling. In this review we will highlight recent progress made in research into this disease, focusing on adults. We will discuss ongoing efforts to develop a minimally invasive technique that may obviate the need for repeated endoscopic assessment of disease activity. Moreover, we will review studies using novel tools such as mucosal impedance and functional lumen imaging as potential surrogate markers for mucosal integrity and esophageal remodeling. With regard to the treatment of eosinophilic inflammation, we will discuss the controversies surrounding responsiveness to proton pump inhibitors in some patients. Therapeutic trials continue to support the use of topical glucocorticoids and empiric food elimination diets as first line treatments. We will discuss ongoing efforts to optimize the elimination diet protocol to decrease the level and duration of food restrictions. Looking ahead, our growing knowledge on the pathogenesis of eosinophilic esophagitis has enabled further advancement of promising targeted biologic therapies.

Introduction

Eosinophilic esophagitis is a chronic immune mediated condition characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophilic predominant inflammation.¹ Although it has not been associated with an increased risk of mortality or cancer, the chronic progressive nature of the disease has a negative impact on patients' quality of life.² Since its recognition as a clinical entity in the 1990s,^{3,4} the disease has evolved from sporadic case reports to become a widely recognized cause of esophageal morbidity.^{5,6} However, despite growing efforts to elucidate its pathogenesis and the increasing number of well designed clinical trials, the practical management of eosinophilic esophagitis is often challenging because of controversies related to therapeutic endpoints and the need for long term treatments. To date, three main consensus recommendations for management have been published.¹⁻⁸ The most recent of these guidelines was published in 2013, and most of the recommendations were "conditional" rather than "strong," because of the relatively low quality of evidence.

We conducted a thorough review of the literature, with an emphasis on studies published since the most recent consensus guideline and focusing on adults with eosinophilic esophagitis. Our review includes recent discoveries on pathogenic mechanisms, genetic and environmental risk

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

To engage patient participation and contribution to this review, we reviewed the "Frequently asked questions" on the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) website (see appendix 2 at end of document) and incorporated answers to these patient oriented questions in our review. In addition, we solicited a list of 10 questions polled from an eosinophilic esophagitis patient support group on social media. These questions were answered and are included in appendix 3. Our review was also critically reviewed by two adult patients with eosinophilic esophagitis before submission.

factors, advances and controversies in the development of a minimally invasive diagnostic biomarker, techniques to quantify fibrostenosis and mucosal integrity in eosinophilic esophagitis, novel treatment options including biologic agents, and optimization of the dietary elimination therapy. Finally, we propose key research questions to be addressed in future translational research and therapeutic trials.

Sources and selection criteria

We searched PubMed up to April 2017 to identify English language articles published in peer reviewed journals using a list of search terms that can be found in the

supplemental material (see appendix at end of document for details). Reference lists from selected manuscripts were also used to identify additional relevant articles. We prioritized recent prospective and randomized controlled trials (RCTs), although laboratory studies, population based and observational studies, meta-analyses, and systematic reviews are included whenever prospective controlled trials were unavailable. The search terms used did not limit the results to adults or children because many studies included both age groups. However, the review focuses on adults because pediatric specific data are limited. Data on pediatric specific eosinophilic esophagitis, when included, will be specified.

Incidence and prevalence

The incidence and prevalence of eosinophilic esophagitis have risen over the past two decades.¹⁻¹⁰ In a report from Olmstead County, Minnesota, USA, no cases were documented before 1990, and the incidence rose from 0.35 cases/100 000 people to 9.5 cases/100 000 people over a 15 year period.⁶ Increased incidence has also been reported in Switzerland,⁵ the Netherlands,¹¹ and Denmark.¹² The reasons for this increase are poorly understood, and increased recognition is probably not the only cause.^{5,6}

Using a large scale administrative claims database from the United States, a recent study reported about 152 000 cases of eosinophilic esophagitis in the US, with a prevalence of 39/100 000 to 153/100 000, depending on the case definition used.¹³ Pooled data from a systematic review showed that the sample size weighted average was 0.03% in two population based studies and 2.8% in seven studies evaluating symptomatic patients.¹⁴ There are also regional differences in prevalence; for example, prevalence in Western countries, including the US and Europe, is estimated at 0.4-1%,¹⁵⁻¹⁷ whereas in Japan it is estimated to be much lower (0.01%).^{18,19} Three to four times more males are affected than females, and the disease is more common in white people than in other ethnic groups.²⁰⁻²² A recent meta-analysis that extracted adult only or pediatric only prevalence data reported a higher prevalence in adults than in children (43.4/100 000 (95% confidence interval 22.5 to 71.2) v 29.5/100 000 (17.5 to 44.7)).¹⁵

Disease pathogenesis

Animal and human studies have shown that an allergen mediated inflammatory process is the key mechanism of pathogenesis. Between 50% and 80% of patients have concurrent allergic diseases including food allergies, allergic rhinitis or sinusitis, atopic dermatitis, and asthma.¹⁰⁻²⁷ However, unlike asthma or other common immune mediated diseases, eosinophilic esophagitis does not seem to be a classic IgE mediated immune response. Rather, it is a T helper type 2 cell (Th2) predominant inflammatory process triggered by allergens.²⁸⁻³⁰ In an experimental animal model, eosinophilic esophagitis can be induced directly by delivering cytokines produced by Th2 cells.³¹ In mice, deletion of central downstream mediators in the Th2 allergic cascade, such as interleukin 4 (IL-4), IL-5, and IL-13, protects against the develop-

ment of eosinophilic esophagitis,^{31,32} and overexpression of IL-5 leads to an eosinophilic esophagitis phenotype.³³

The Th2 inflammatory cascade

Figure 1 illustrates a proposed molecular pathogenic pathway of eosinophilic esophagitis. An increase in thymic stromal lymphopoietin (TSLP) is thought to induce Th2-type immune mediated inflammation. Genetic gain-of-function mutations of genes encoding TSLP and the TSLP receptor have been shown to favor the development of eosinophilic esophagitis, and TSLP expression is significantly higher in patients with active disease.³⁴⁻³⁶ Th2 lymphocytes subsequently produce a combination of type 2 cytokines, including IL-4, IL-5, and IL-13.³⁷ IL-4 promotes the differentiation of T cells into Th2 cells and has been linked to other atopic diseases.³⁸ IL-5 is essential for the proliferation and maturation of eosinophils,³⁹ and IL-13 promotes eosinophilic infiltration by stimulating esophageal epithelial cells to produce eotaxin-3, a potent chemokine that recruits and activates eosinophils.⁴⁰ In addition, IL-13 has been associated with dysfunction of the epithelial barrier.²⁹

Eosinophils, a hallmark cell type found in eosinophilic esophagitis, are recruited to the esophagus by eotaxin-3 and chemoattractant proteins such as CCR2 (prostaglandin D2 receptor 2).⁴¹⁻⁴³ Once eosinophils are recruited to the esophagus, they are activated to release granules containing major basic protein, eosinophil derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase,^{44,45} in addition to several cytokines. Together, they facilitate inflammation,⁴⁴⁻⁴⁸ increase smooth muscle activation,^{49,50} and trigger degranulation of mast cells and basophils.⁵¹ Mast cells have also been implicated; their numbers are increased in patients with eosinophilic esophagitis compared with controls and those with gastroesophageal reflux disease (GERD).⁵²⁻⁵⁹ Mast cells may promote inflammation and fibrosis in eosinophilic esophagitis by secreting transforming growth factor β (TGF- β),⁵⁰ which results in epithelial proliferation, epithelial-mesenchymal transition, deposition of collagen, and fibrosis of the esophagus.⁶⁰⁻⁶³ Recently, basophils and invariant natural killer (iNK) cells have also been linked to the disease,^{64,65} but their roles are not well understood.

Additional insights from genetic studies

Recent genetic studies have helped gain additional insights into the molecular pathogenesis of eosinophilic esophagitis. Genome-wide RNA profiling of esophageal biopsies found that *CCL-26*, which encodes eotaxin-3, a potent chemoattractant of eosinophils stimulated by IL-13, was overexpressed about 50-fold in patients with eosinophilic esophagitis compared with normal controls or those with GERD.⁶⁶ Another gene of interest, the gene encoding filaggrin, is crucial in skin barrier function.^{29,37} It is downregulated by IL-13, leading to the disruption of esophageal wall integrity and an increase in antigen exposure.³⁷ Other genes that are potentially important in the pathogenesis of eosinophilic esophagitis have been identified through recent genome-wide array studies (GWAS),^{34,67} but further studies are needed to improve our understanding of their functional importance.

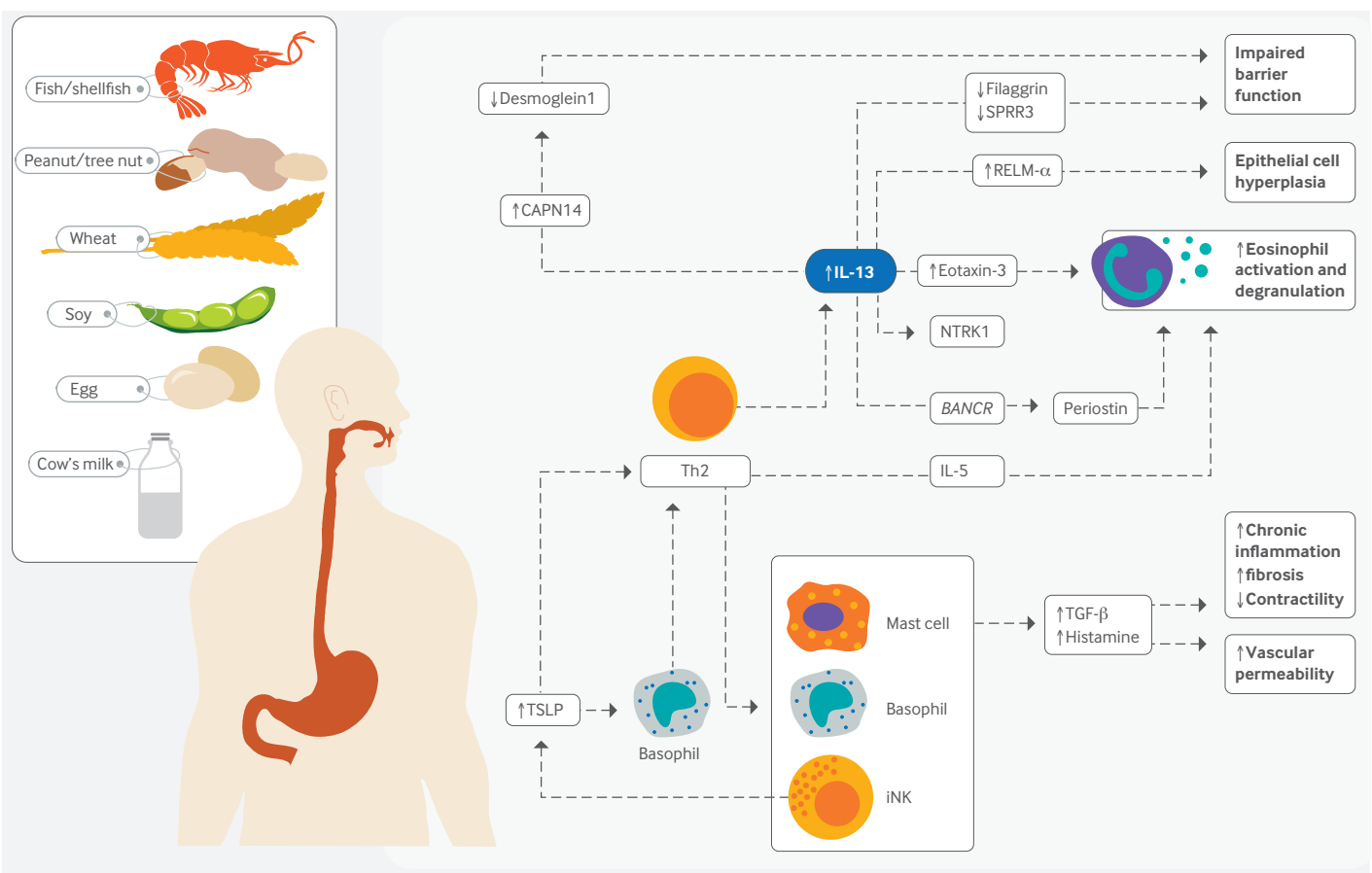


Fig 1 | Proposed molecular pathogenic pathway of eosinophilic esophagitis. Food allergens induce Th2 cells to produce IL-13, which causes the overexpression of eotaxin-3 and periostin and downregulation of filaggrin and desmoglein 1. Eotaxin-3 is an eosinophil chemoattractant responsible for the accumulation of eosinophils in eosinophilic esophagitis. Downregulation of filaggrin and desmoglein 1 contribute to an impaired barrier function. Activated Th2 cells also produce IL-5, which is responsible for the proliferation and maturation of eosinophils. In addition to eosinophils, mast cells, basophils, and iNK cells have been shown to contribute to the pathogenesis of eosinophilic esophagitis. Mast cells promote inflammation and fibrosis through the production of histamine and TGF- β . CAPN14=calpain 14; IL-13/5=interleukin 13/5; iNK=invariant natural killer cell; NTRK1=neurotrophic tyrosine kinase receptor type 1; RELM- α =resistin-like molecule α , TGF- β =transforming growth factor β ; Th2=T helper 2 cell; TSLP=thymic stromal lymphopoietin; SPRR3=small proline-rich repeat protein.

Risk factors

Accumulative evidence now shows that the pathogenesis of eosinophilic esophagitis is multifactorial, and that it probably arises from an allergic response to environmental factors in genetically susceptible individuals.⁷

Genetic risks

Genetic epidemiologic studies of families suggest that genetics plays a role in susceptibility, although the disease does not follow the classic Mendelian inheritance pattern.^{9,68} Monozygotic twin studies show a high concordance for the trait, estimated at 41%⁶⁹; 21% of people with an affected dizygotic twin developed the disease, whereas this figure was only 2.4% in the nuclear family cohort. This supports the additional contribution of environmental factors to phenotypic variance. In another study, the sibling risk ratio—the ratio of risk in people with an affected sibling compared with the disease prevalence in the general population—was 60.⁶⁹ Recurrence risk ratios ranged from 10 to 64, depending on the family relationship—it was highest in brothers, followed by fathers, and lower in sisters and mothers.⁶⁹

Recent GWAS have suggested that eosinophilic esophagitis, atopic diseases, and autoimmune conditions

have a shared genetic etiology.³⁴⁻⁶⁷ The Utah Population Database (covering >85% of Utah's population) was used to determine associations between specific autoimmune diseases in probands diagnosed with eosinophilic esophagitis and their extended family members.⁷⁰ First degree relatives of people with eosinophilic esophagitis had an increased risk of several autoimmune conditions including celiac disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, IgA deficiency, common variable immune deficiency, multiple sclerosis, and Hashimoto's thyroiditis. In addition, probands and their families with ulcerative colitis, systemic sclerosis, and multiple sclerosis had an increased risk of having eosinophilic esophagitis.

Early life risks factors

Several early life perturbations increase the risk of developing eosinophilic esophagitis. One study found an association between early use of antibiotics and the development of esophageal eosinophilia (odds ratio 6.1, 1.7 to 20.8).⁷¹ Another study found a link between the development of esophageal eosinophilia and cesarean delivery and antibiotic use (3.2, 1.2 to 8.6 and 3.6, 1.3 to 10.1 respectively).⁷² Finally, an inverse association has

been reported between exposure to smoking in the first year of life and esophageal eosinophilia (0.48, 0.23 to 1.02).⁷³ A causal association between these early life risk factors and esophageal eosinophilia has not been proved, but one theory is that early exposure can lead to altered gut microbiota (dysbiosis), which may have an effect on normal immune development.⁷⁴

Gut microbiome

The human microbiome has been the subject of intense research interest in recent years; however, there is still a paucity of data on the microbiome of the esophagus. The composition of the intestinal microflora and the resulting immunologic response are important for the induction of tolerance. In dysbiosis, the metabolic profile shifts towards a more favorable environment for pathogenic constituents, disrupting immune regulatory systems and leading to a state of immune intolerance.⁷⁵ In esophageal eosinophilia, the absence of beneficial bacteria may lead to a decrease in the induction of regulatory T cells that suppress proinflammatory effector cells (such as eosinophils), as well as disruption of the gastrointestinal barrier function. There is some evidence to suggest that the alteration in gut microbiota in early life (for example, from the use of antibiotics) might trigger an abnormal immune response that persists throughout life. Two recent studies have shown a difference in the load and composition of esophageal microbiota in patients with esophageal eosinophilia compared with controls.^{76,77} With advances in high throughput DNA sequencing technologies and bioinformatics tools, disease associated esophageal microbiota signatures may emerge that will enable the development of microbiota biomarkers that can help define clinical phenotypes.

Helicobacter pylori

Helicobacter pylori has been inversely associated with allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, and inflammatory bowel disease.⁷⁸⁻⁸⁰ The specific mechanism leading to a protective role for *H pylori* in allergic diseases is unknown but is probably related to systemic immunomodulation induced by the infection.

The inverse association between *H pylori* and esophageal eosinophilia was first observed in a population based study from Sweden,¹⁷ in which the infection was found to be an independent negative predictor for esophageal eosinophilia (odds ratio 0.41, 0.19 to 0.92). In a cross sectional study using a pathology database of 165 000 patients with both esophageal and gastric biopsies, the presence of esophageal eosinophilia was inversely associated with *H pylori* infection (0.77, 95% CI 0.69 to 0.87).⁸¹ The odds appear to reduce further as levels of esophageal eosinophilia increase. Two case-control studies have also supported the inverse association between *H pylori* and eosinophilic esophagitis.^{82,83} Because the prevalence of esophageal eosinophilia and *H pylori* infection both vary widely by patient ethnicity,⁸³ *H pylori* may be partly responsible for the observed ethnic distribution of the disease.

Currently, there are two hypotheses for the potential protective effect of *H pylori* on esophageal eosinophilia. The first is the hygiene hypothesis, which attributes the

rise in allergic diseases to improved sanitation and reductions in childhood infections, including *H pylori* infection. The other involves the observation that *H pylori* may drive a Th1 mediated allergic response, shifting the Th1–Th2 balance, and thus “protecting” from an allergic Th2 response in patients with eosinophilic esophagitis.

Presentation and diagnosis

Clinical presentation

Adults and children with eosinophilic esophagitis have different clinical presentations.⁸⁴⁻⁸⁷ Children commonly present with difficulty feeding, vomiting, abdominal pain, or failure to thrive, whereas adults typically have symptoms of dysphagia, heartburn, chest pain, and food impactions.²⁰⁻⁸⁸ This difference is thought to be, at least in part, related to gradual esophageal tissue remodeling arising from unabated inflammation.⁸⁹⁻⁹² An inflammatory phenotype—endoscopic features including white exudates, linear furrows, and edema—is thought to eventually evolve as a result of longstanding inflammation into a fibrostenotic phenotype, with fibrotic features on endoscopy such as rings, strictures, and a narrow caliber esophagus.⁸⁹⁻⁹⁴

Monitoring of disease activity and treatment endpoint

Potential treatment endpoints in eosinophilic esophagitis include improvements in clinical symptoms, esophageal eosinophilic inflammation, and severity of endoscopic features. The use of treatment endpoints varies considerably in the literature, and this variability has hindered the interpretability and comparability of clinical trials.⁹⁵ Owing to the relative ease in identifying and interpreting esophageal eosinophilia, most studies have relied on histology to assess therapeutic response. However, the specific threshold for a reduction in eosinophilia to define treatment efficacy remains uncertain, and <20, <15, <10, <5 eosinophils/high power field (HPF) have all been used in the literature. Both mean eosinophil and peak eosinophil densities have also been used. The absence of subepithelial tissue in routine biopsies for assessment of esophageal remodeling further hampers the utility of histologic examination.⁹⁶ Recent validation of patient reported outcome (PRO) instruments—which combine an endoscopic grading system, histologic scoring system, and surrogate measurements of esophageal remodeling and tissue integrity—have led the way in establishing more consistent and meaningful treatment endpoints.

Clinical assessment: PRO instruments

Symptom assessment can be challenging because most patients have chronic progressive symptoms and may have developed adaptive behaviors such as avoidance of specific food textures, excessive mastication, or increased meal times to avoid dysphagia and food impaction. In addition, dysphagia and food impaction may occur as sporadic events in many patients and may not be captured in therapeutic studies of short duration. PRO instruments have recently been developed and validated in adults, including the eosinophilic esophagitis activity index (EEsAI) and dysphagia symptom questionnaire

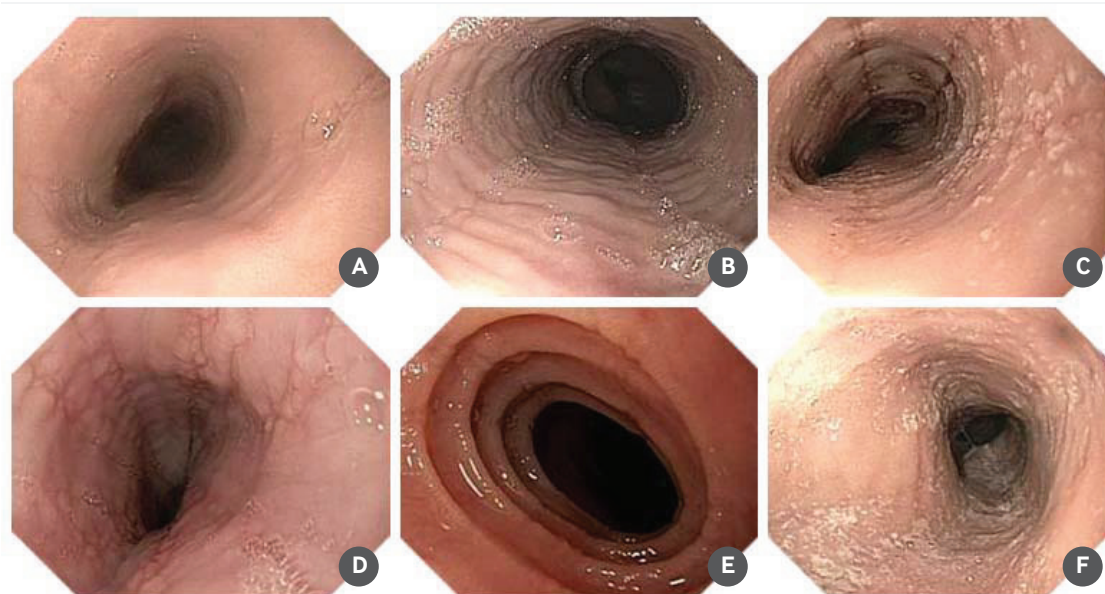


Fig 2 | Examples of endoscopic features (using the endoscopic reference score) of eosinophilic esophagitis. A: Loss of vascular markings/edema (grade 1) and subtle rings (grade 1). B: Moderate rings (grade 2) and furrows (grade 1). C: Subtle rings (grade 1), furrows (grade 1), and exudates (grade 1). D: Furrows (grade 1). E: Severe rings (grade 3). F: Mild rings (grade 1) and severe exudates (grade 2)

(DSQ).⁹⁷ The EEsAI is composed of seven PRO items that assess esophageal symptoms over a seven day recall period. The instrument accounts for behavioral adaptations such as avoidance of specific food textures and meal time length in adults with eosinophilic esophagitis.⁹⁸ However, in a prospective, observational study of 269 adults with eosinophilic esophagitis, the EEsAI score alone was inadequate in the detection of patients with endoscopic, histologic, and combined remission (area under the curve values of 0.67, 0.60, and 0.67, respectively).⁹⁹ The authors cautioned that assessment of disease activity on the basis of symptoms alone is probably inadequate.

Endoscopic assessment

The presence of endoscopic features is not required for the diagnosis of eosinophilic esophagitis, but the endoscopic presence of edema, rings, exudates, or strictures increases the clinical likelihood of histologic esophageal eosinophilia. Prospective studies have identified endoscopic features in 93% of patients with eosinophilic esophagitis according to a meta-analysis that pooled data from 15 prospective studies (N=378 patients).¹⁰⁰ A classification and grading system to assess the endoscopic findings in the disease—the endoscopic reference score (EREFS)—was proposed in 2013 in an effort to standardize endoscopic assessment (figs 2 and 3).¹⁰¹ Interobserver agreement was moderate for rings, white exudates, furrows, and strictures, and intraobserver agreement was moderate to substantial for rings, furrows, white exudates, and strictures in a study that enrolled four experts and four trainee endoscopists to assess the endoscopic images of 30 eosinophilic esophagitis patients.¹⁰²

The diagnostic utility of the EREFS system was investigated in a recent prospective study that compared EREF scores between 67 patients with eosinophilic esophagitis

and 144 controls¹⁰³; the mean total EREF score was 3.88 in patients and 0.42 in controls ($P<0.001$, area under the curve (AUC) 0.934). After treatment, the mean EREF score in patients decreased from 3.88 to 2.01 ($P<0.001$). This change was more prominent in patients with a histologic response than in non-responders. The study suggests that endoscopic EREFS evaluation can be used to identify those with eosinophilic esophagitis and to monitor treatment response. However, another recent retrospective study of 69 patients with eosinophilic esophagitis found that EREF scores correlated only weakly to moderately with peak eosinophil count.¹⁰⁴ Therefore the system's predictive value of disease activity may be insufficient for clinical use, and biopsies remain indispensable for the assessment of disease activity.

Histologic assessment

Eosinophilic esophagitis is associated with characteristic esophageal histopathology, including increased intraepithelial eosinophils, eosinophil abscesses, basal cell hyperplasia, and lamina propria fibrosis.^{105 106} Besides increased eosinophil density (≥ 15 eosinophils/HPF), the pathologic changes are characteristic but not pathognomonic. A recent study found that even pathology trainees can accurately diagnose eosinophilic esophagitis by histologic examination.¹⁰⁷ A histologic scoring system for esophageal biopsies that incorporates evaluation and scoring based on eight features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intracellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis has recently been proposed.¹⁰⁸ This method objectively assesses histologic changes in the esophagus beyond numbers of eosinophils, but the clinical utility of this scoring system has not been validated.

Features	Grade	Description
Edema	0	Distinct vascular markings
	1	Loss of vascular markings
Rings	0	None
	1	Mild-subtle circumferential ridges
	2	Moderate rings, do not impair standard scope passage
	3	Severe rings that do not permit standard scope passage
Exudates	0	None
	1	Mild, involving <10% of surface area
	2	Severe, involving >10% of surface area
Furrows	0	Absent
	1	Vertical lines present
Stricture	0	Absent
	1	Present

Fig 3 | Endoscopic reference score (EREFS) system is a classification system for the endoscopic assessment of esophageal signs of eosinophilic esophagitis. Endoscopic features, including edema, rings, exudates, furrows, and stricture, are graded according to the descriptions

Non-invasive biomarkers

The quest for a non-invasive biomarker for diagnosis and monitoring of disease activity is an ongoing effort of high priority. Biomarkers investigated either involved immunohistochemistry on esophageal biopsy samples⁵⁸⁻¹¹¹ or clinical immunology techniques on serum samples.¹¹²⁻¹¹⁴ To date, no single marker in blood or esophageal tissue has proved reliable for diagnosis.¹¹⁵⁻¹¹⁶ Recently, the focus has shifted to the development of a panel of biomarkers. A molecular diagnostic test that used a 94 gene quantitative polymerase chain reaction (PCR) array and a scoring system was highly sensitive and specific in identifying active eosinophilic esophagitis. It also distinguished between patients with eosinophilic esophagitis who were in remission and controls, as well as those exposed to swallowed glucocorticoids.¹¹⁷ Another study that investigated the diagnostic value of a 94 gene expression score using PCR of prospectively collected esophageal tissue in adults found that the score had high diagnostic utility for distinguishing between patients with and without eosinophilic esophagitis, with an AUC of 0.927.¹¹⁸ These techniques would not eliminate the need for endoscopy with esophageal tissue collection but could be useful for patients with diagnostic uncertainty on the basis of conventional testing.

Office based testing

Office based testing of disease activity for diagnosis or assessment of treatment response has been of great interest. The esophageal string test⁴⁴ and cytosponge¹¹⁹ are

examples of minimally invasive clinical devices that have been tested in small prospective trials to collect esophageal samples. Multicenter studies involving these two tests are currently under way.

Measurement of luminal distensibility

The dominant symptoms in adults—dysphagia and food impaction—are often more relevant to tissue remodeling and fibrosis rather than active eosinophilic inflammation. Fibrosis of the subepithelial space has been demonstrated in both pediatric and adult cohorts⁹⁰⁻¹²⁰; however, in standard esophageal biopsies, only the superficial epithelial layer of the esophagus is examined. The introduction of high resolution impedance planimetry has enabled the assessment of tissue remodeling and its effect on mechanical properties of the esophagus. The functional luminal imaging probe (FLIP) uses high resolution impedance planimetry to render a three dimensional approximation of intraluminal esophageal anatomy during volumetric distention. One study prospectively analyzed the pressure geometric properties of the esophagus in 33 patients with eosinophilic esophagitis and 15 controls using FLIP. It showed that distensibility, defined by the change in the narrowest measurable cross sectional area within the distal esophagus versus intraluminal pressure, was significantly reduced in patients compared with controls independent of mucosal eosinophil count.¹²¹ In a follow-up study, 70 patients with eosinophilic esophagitis and previous food impactions showed significantly reduced esophageal distensibility as measured by FLIP. In addition, reduced esophageal distensibility predicted risk of food impaction and the need for esophageal dilatation during the prospective follow-up period.¹²² Another cross sectional study of 72 adults with eosinophilic esophagitis showed an inverse association between endoscopic ring severity and esophageal distensibility as measured by FLIP.¹²³ No association between distensibility and inflammation was seen, highlighting the dissociation between the fibrostenotic and inflammatory features of eosinophilic esophagitis. Figure 4 shows sample FLIP images and distensibility according to ring severity (grades 0-3). As such, FLIP may be a useful tool for measuring esophageal remodeling and stratifying the risk of food impaction in patients with eosinophilic esophagitis.

Measurement of mucosal integrity

Mucosal integrity in eosinophilic esophagitis has been measured using mucosal impedance in 11 patients with eosinophilic esophagitis and 11 healthy controls using 24 hour pH impedance monitoring in a cross sectional study.¹²⁴ A decreased baseline impedance value was found throughout the esophagus in patients but not in the controls. A follow-up prospective study by the same group that used electrical tissue impedance spectroscopy to compare esophageal mucosa integrity between 16 patients with eosinophilic esophagitis and 11 controls showed that electrical tissue impedance and transepithelial electrical resistance were reduced in patients.¹²⁵ This suggests that esophageal mucosal integrity is impaired in eosinophilic esophagitis, potentially leading to antigen exposure.

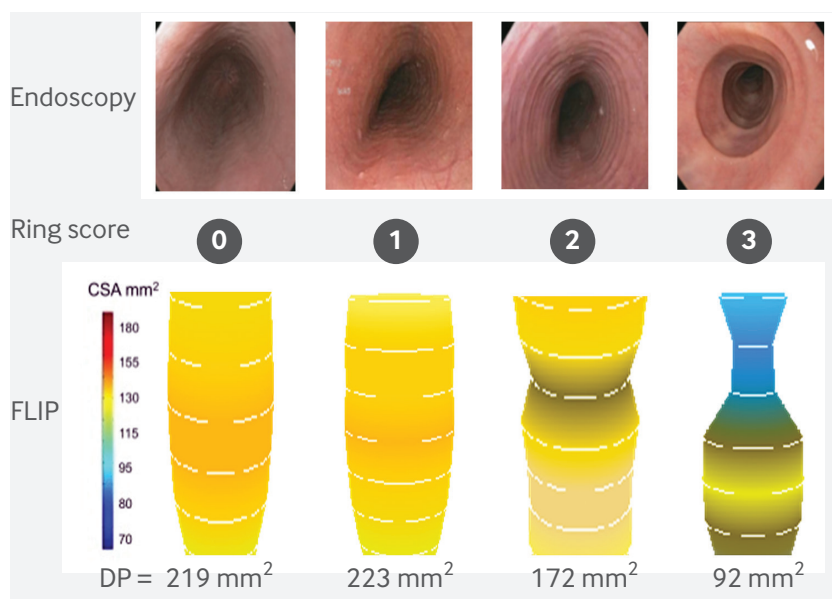


Fig 4 | Functional luminal imaging probe (FLIP) images and distensibility parameter (distensibility plateau (DP)) according to endoscopic ring severity (ring scores 0-3). An inverse association is seen between severity of endoscopic rings and esophageal distensibility. CSA=cross sectional area

Mucosal impedance was measured at 2 cm, 5 cm, and 10 cm above the squamocolumnar junction in a cross sectional study that enrolled 61 patients with erosive esophagitis, 81 with non-erosive reflux disease, 18 with achalasia, 15 with eosinophilic esophagitis, and 93 controls. Mucosal impedance was significantly lower ($P<0.001$) in patients with GERD or eosinophilic esophagitis than in patients without GERD or patients with achalasia. Furthermore, patients with GERD had lower mucosal impedance closer to the squamocolumnar junction that increased proximally (median of 1427 Ω , 2013 Ω , 3236 Ω at 2 cm, 5 cm, and 10 cm above the squamocolumnar junction, respectively), whereas patients with eosinophilic esophagitis had low mucosal impedance along the length of the esophagus (median 123 Ω , 1259 Ω , 1365 Ω at 2 cm, 5 cm, and 10 cm, respectively).¹²⁶ Finally, in a prospective study, 15 patients with eosinophilic esophagitis underwent esophagogastroduodenoscopy before and after an eight week course of twice daily swallowed fluticasone and esophageal mucosal impedance was measured by esophageal electrical tissue impedance in vivo during endoscopy and transepithelial electrical resistance and molecular flux in Ussing chambers using biopsy specimens. This study found that mucosal impedance increased substantially ($P<0.01$ for electrical tissue impedance and transepithelial electrical resistance, and $P<0.05$ for transepithelial molecular flux) after treatment, indicating a restoration of mucosal integrity with topical corticosteroids.¹²⁷

Treatment

Proton pump inhibitors (PPIs)

According to recent practice guidelines, a trial of acid suppression is required to fulfill the diagnostic criteria of eosinophilic esophagitis.¹⁷ Patients with significant improvement of symptoms and esophageal eosinophilia after an eight week course of at least a moderate PPI dose

have either GERD or PPI responsive esophageal eosinophilia (PPI-REE).¹²⁸⁻¹²⁹ PPI-REE was first described in 2006.¹³⁰ Since that time, multiple prospective and retrospective adult and pediatric studies have shown that at least a third of patients with esophageal eosinophilia will respond to PPI monotherapy,⁷⁻¹³⁶ and that the response to PPIs is not reliably predicted by pH monitoring, indicating a therapeutic mechanism separate from acid suppression in PPI-REE.¹³⁴

The mechanism behind PPI responsiveness in PPI-REE is not fully understood. However, it has been postulated that PPI may have anti-inflammatory properties in eosinophilic esophagitis,¹³⁷ because in vitro and in vivo models have demonstrated antioxidant and anti-inflammatory effects of PPIs.¹³⁸ Another proposed mechanism involves repair of a leaky mucosa. In patients with PPI-REE and not eosinophilic esophagitis, PPIs partially restored mucosal integrity, thus preventing the influx of food allergens through the mucosa.¹²⁵ A third potential mechanism involves blockage of Th2 cytokine stimulated esophageal secretion of eotaxin-3 by PPIs.³⁸⁻¹³⁹

Whether PPI-REE represents GERD, eosinophilic esophagitis, or neither remains an area of controversy, although recent studies indicate that PPI-REE and eosinophilic esophagitis have important similarities. Separate studies using immunohistochemistry to quantify esophageal tissue eosinophil associated molecular markers showed that PPI-REE and eosinophilic esophagitis have similar alterations in tissue molecular markers.⁵⁷⁻¹⁴⁰ PPI-REE and eosinophilic esophagitis have also been shown to share similar genetic alterations based on transcriptome analysis using the 94 gene eosinophilic esophagitis diagnostic panel or a whole genome approach.¹³⁷⁻¹⁴¹ PPI therapy reverses both molecular and genetic alterations in PPI-REE, similar to the effect of topical steroids in eosinophilic esophagitis, and early studies have shown that patients with PPI-REE respond to diet and topical steroid therapy in a similar way to those with eosinophilic esophagitis.¹⁴²⁻¹⁴³ These pieces of evidence support the notion that PPI-REE probably shares the pathogenic allergic mechanisms that underlie eosinophilic esophagitis.

Sustained efficacy of maintenance PPI therapy in PPI-REE has been shown in a prospective study that included 40 patients with PPI-REE; over 80% of patients with PPI-REE remained in histologic remission on reduced dose daily maintenance PPIs.¹⁴⁴ Adverse events from the short term use of PPIs were mild, including hypertransaminasemia and esophageal candidiasis in two patients on high dose PPIs. Although long term data are unavailable, in light of recent concerns regarding complications from chronic use of PPIs, maintenance therapy at the lowest effective dose to maintain disease remission is currently recommended.

Diet modifications

Diet modifications have steadily become accepted as first line treatment for patients with eosinophilic esophagitis because of their high efficacy, low cost, and safety profile. Various dietary treatment modalities have been proposed and can be separated into three main categories: the elemental diet, empiric elimination diets, and elimination diet guided by allergy testing.

Table 1 | Trials of food elimination diets in eosinophilic esophagitis*

Ref	Age group	N	Study type	Diet type	Histologic endpoint	Clinical response	Histologic response	Food triggers identified
Kagalwalla 2006 ¹⁴⁹	Children	35	Cohort	SFED	≤10 eos/HPF	N/A	74%	Milk 74%Wheat 26%Egg 17%
Kagawalla 2007 ¹⁵¹	Children	1	Case report	SFED	≤10 eos/HPF	100%	100%	Milk 100%
Henderson 2012 ¹⁵²	Children	26	Cohort	SFED	≤15 eos/HPF	N/A	81%	Milk 65%Egg 40%Soy 38%Wheat 37%
Gonsalves 2012 ¹⁵³	Adults	50	Prospective non-randomized	SFED	≤10 eos/HPF ≤15 eos/HPF	94%	70%74%	Wheat 60%Milk 50%
Lucendo 2013 ¹⁵⁴	Adults	67	Prospective non-randomized	SFED	<15 eos/HPF	N/A	73.1%	Milk 62%Wheat 29%Egg 26%Legumes 24%
Wolf 2014 ¹⁵⁵	Adults	9	Cohort	SFED	<15 eos/HPF	78%	56%	Milk 44%Egg 44%Wheat 22%
Philpott 2016 ¹⁵⁶	Adults	56	Prospective non-randomized	SFED	<5 eos/HPF	N/A	52%	Milk 43%Wheat 43%Egg 34%
Colson 2014 ¹⁵⁷	Children	59	Cohort	SFED+ AT directed	<5 eos/HPF <15 eos/HPF	98.3%	59.3%69.3%	N/A
Rodriguez-Sanchez 2014 ¹⁵⁸	Adults	17	Prospective non-randomized	SFED	<15 eos/HPF	Improved clinical index (P<0.001)	53%	Milk 64%Wheat 28%Egg 21%Legumes 7%
Molina-Infante 2014 ¹⁵⁹	Adults	52	Prospective non-randomized	FFED+ rescue SFED	<15 eos/HPF	N/A	54%72% (after rescue SFED)	Milk 50%Egg 36%Wheat 31%
Kagalwalla 2015 ¹⁶⁰	Children	55	Prospective non-randomized	FFED	<15 eos/HPF	82% improved in histologic responders	71%	Milk 68%Egg 26%Soy 21%Wheat 16%
Molina-Infante 2016 ¹⁶¹	Adults and children	93	Prospective non-randomized	TFEDFFEDSFED	<15 eos/HPF	N/A	TFED 40%FFED 52%SFED 65%	Milk 60%Milk and wheat 15%Wheat 25%

*FFED=four food elimination diet; eos/HPF=eosinophils per high power field; N/A=not available; SFED=six food elimination diet; TFED=two food elimination diet.

Elemental diet

The elemental formula, which consists of free amino acids devoid of proteins or potential dietary antigens, has been tested in eosinophilic esophagitis. The efficacy of this diet in achieving clinical and histologic remission of disease was first shown in 1995. In this study, normalization of esophageal histology and complete clinical remission was seen in eight of 10 children with eosinophilic esophagitis after six weeks of the diet; near normalization was seen in the remaining two children.¹⁴⁵ The elemental diet has since been shown to induce clinical and histologic improvement in a large (N=51) prospective pediatric trial (median esophageal eosinophils per high power field decreased from 33.7 to 1.0; P<0.001) and histologic remission in an adult prospective trial (N=18, esophageal eosinophilia decreased from 54 to 10 per high power field; P=0.0006).^{146 147} Overall, effectiveness was 90.8% (84.7% to 95.5%, $I^2=52.3\%$) in both children and adults in a recent meta-analysis that included 13 retrospective studies, prospective studies, and case reports and a total of 429 patients with eosinophilic esophagitis (411 children and 18 adults).¹⁴⁸ However, this treatment method is generally unsustainable because of its poor palatability, the negative impact on quality of life related to the avoidance of all table foods, and the high cost of the formula.

Six food elimination diet

With the clinical unfeasibility of the elemental diet, an empiric six food elimination diet (SFED) was first tested in children with eosinophilic esophagitis in 2006.¹⁴⁹ The SFED consists of the elimination of the top six food groups most commonly associated with food allergy (cow's milk, wheat, egg, soy, peanut/tree nut, and fish/seafood) and subsequent sequential reintroduction with histologic examination to monitor response.¹⁵⁰ The SFED led to clinical and histologic remission in 74% of children. Similar results were seen in all age groups.¹⁴⁸ A recent

meta-analysis showed a homogeneous ($I^2=0\%$) histologic remission rate of 72% (66% to 78%) in both children and adult patients (75 children and 122 adults).¹⁴⁸ No adverse events were reported from the SFED; however, the high level of dietary restriction and number of endoscopies during the reintroduction phase often result in patient refusal or low compliance with this diet.

Four food elimination diet

The fact that only one or two foods have been identified as triggers for eosinophilic esophagitis in most children and adults indicates that the level of dietary restriction in SFED may be unnecessary in many cases. The top four causative foods identified are cow's milk, wheat, egg, and soy/legumes. Consequently, an elimination diet including the top four foods—the four food elimination diet (FFED)—was proposed. A prospective multicenter trial in 52 adult patients showed a 54% remission rate with the FFED.¹⁵ A large proportion of non-responders to the FFED (31%) achieved remission after broadening to the SFED, resulting in a 72% overall efficacy, similar to that expected for empiric SFED. The benefits of FFED include a less restrictive diet, better acceptance by patients, and potentially a shorter study time with fewer endoscopies needed to identify food triggers. Table 1 summarizes studies of six and four food elimination diets.

Step-up elimination diet

A step-up approach, eliminating first the top two foods (milk and wheat), then top four, then top six in non-responders has recently been proposed in an abstract.¹⁶¹ A two food elimination diet achieved remission in 40% of patients, and remission rates increased to previously known rates with subsequent FFED and SFED in non-responders. Compared to starting with an SFED, this step-up strategy enabled diagnostic time to be reduced by 35%, prevented unnecessary dietary restriction, and reduced endoscopic procedures by 25%.

Table 2 | Randomized controlled trials using topical corticosteroids in eosinophilic esophagitis*

Ref	Age group	N	Study type	Drug dose	Histologic endpoint	Clinical response	Histological response	Endo response
Konikoff 2006 ¹⁶³	Children	36	Double blind RCT	Fluticasone 880 µg BID v placebo	Peak eos ≤1/HPF	Resolution of vomiting (P=0.04)	50% v 9% (P=0.047)	Improvement
Peterson 2010 ¹⁶⁴	Adults	30	Prospective RCT	Fluticasone 440 µg BID v esomeprazole 40 mg QD x 8 weeks	Partial (≤15 eos/HPF) or complete (≤5 eos/HPF)	No difference in improvement in dysphagia scores	No difference between PPI or fluticasone groups	N/A
Dohil 2010 ¹⁶⁵	Children	24	Double blind RCT	OVB 1 mg or 2 mg daily v placebo	<20 eos/HPF	Improvement	86.7% responded	Improved
Straumann 2010 ¹⁶⁶	Adults	36	Double blind RCT	OBS 1 mg BID x 15 days v placebo	Decrease in mean number of eos	Improvement in dysphagia scores	Improvement in mean eos/HPF (P<0.0001) in OBS group	Improvement in white exudates and red furrows
Dellon 2012 ¹⁶⁷	Adults	22	Prospective open label RCT	NEB v OVB 1 mg BID x 8 weeks	Improved mean and maximum eos count	Improvement in dysphagia symptom scores in both groups	Improvement in eos counts in OVB but not NEB group	Higher rate of improvement in OVB group
Alexander 2012 ¹⁶⁸	Adults	42	Double blind RCT	Fluticasone 880 µg BID v placebo x 6 weeks	>90% decrease in mean eos	Dysphagia reduced in 57% v 33% (P=0.22)	62% in fluticasone group and 0% in placebo	N/A
Moawad 2013 ¹⁶⁹	Adults	42	Single blind RCT	Fluticasone 440 µg BID v esomeprazole 40 mg QD x 8 weeks	<7 eos/HPF	MDQ score improved after PPI but not steroid	No difference between steroid and PPI groups	N/A
Butz 2014 ¹⁷⁰	Children and adults	42	Double blind RCT	Fluticasone 880 µg BID v placebo x 3 months	≤1 eos/HPF	No significant differences	65% in fluticasone group, 0% in placebo	N/A
Gupta 2015 ¹⁷¹	Children	71	Double blind RCT	OBS v placebo x 12 weeks	≤6 eos/HPF	No difference in ≥50% reduction in symptom score	Significant improvement seen in medium-high dose OBS (~50%)	N/A
Miehlke 2015 ¹⁷²	Adults	76	Double blind RCT	Budesonide effervescent tablet v viscous suspension v placebo x 14 days	<16 eos/HPF	Persistent improvement in dysphagia in budesonide groups	94.7-100% improvement in budesonide groups v 0% in placebo	Improvement in total endoscopic intensity score in budesonide groups
Dellon 2017 ¹⁷³	Children and adults	93	Double blind RCT	OBS 2 mg v placebo BID x 12w	≤6 eos/HPF	Significant improvement in DSQ score	39% histologic response v 3% in placebo group	Improvement in endoscopic severity score (P<0.0001)

*BID=twice daily; eos/HPF=eosinophils per high power field; DSQ=Dysphagia Symptom Questionnaire; MDQ=Mayo Dysphagia Questionnaire; NEB=nebulized; OBS=oral budesonide suspension; OVB=oral viscous budesonide; PPI=proton pump inhibitor; RCT=randomized controlled trial; QD=once a day.

Once a food trigger that is responsible for inducing esophageal eosinophilia in an individual patient is identified, long term avoidance is advisable to maintain drug-free disease remission. Studies evaluating the short term efficacy of a maintenance avoidance diet have shown that patients who strictly avoided food(s) known to trigger disease remained in clinical and histologic remission for three years.¹⁵³⁻¹⁵⁹

Allergy testing directed elimination diet

Although elimination diets are successful, the need for multiple endoscopies after each food is reintroduced makes this management option untenable to many. A non-invasive, rapid investigation that can accurately predict food triggers is needed. However, several recent studies have shown that the skin prick test, patch test, and serum food antigen-specific IgE testing are not useful in identifying food triggers. The reasons for this are not fully understood but may be partly due to the involvement of a delayed type, non-IgE-mediated hypersensitivity reaction.

Skin prick tests involve the application of a droplet of commercially prepared antigen to the patient's skin and the use of a hand held lancet to puncture the epidermis and cause subcutaneous exposure. Patients are observed for a specified time interval and characteristic changes on the skin are assessed. A study found that only one in 20 patients with eosinophilic esophagitis had food triggers correctly identified by this test,¹⁶² and another also showed that the test performed poorly, with a positive predictive value of 13% for the identification of eosinophilic esophagitis food triggers.¹⁵³ A further study found that positive skin prick test results were not concordant

with confirmed food triggers and that patients who test positive or negative for a given food antigen are equally likely to relapse on food reintroduction.¹⁵⁴ On the basis of these studies, an allergy testing directed elimination diet is not currently recommended.

Drug treatments

Topical corticosteroids have been shown to be effective in children and adults and are considered the other first line treatment option. Table 2 summarizes RCTs that have investigated the efficacy of topical corticosteroids, including topical fluticasone and budesonide, in eosinophilic esophagitis. Oral viscous budesonide has been shown to have a greater mucosal contact time than the nebulized solution.¹⁶⁷

A recent systematic review and meta-analysis of placebo controlled RCTs determining the efficacy of topical steroids¹⁷⁴ included five RCTs that looked at 85 adults and 89 children in total.¹⁶³⁻¹⁷⁰ Overall, topical steroids, as compared with placebo, were effective in inducing complete histologic remission (odds ratio 20.81, 7.03 to 61.63). Complete or partial histologic response with topical steroids was 57.8-82.1%. Topical steroids were not associated with a statistically significant improvement in clinical symptoms (2.72, 0.9 to 8.23), probably in part because of the high placebo response rates. Topical steroids were well tolerated among patients in all studies. Esophageal candidiasis was consistently noted in the treatment arm, ranging from 4% to 26% of treated patients. However, this responded well to oral nystatin treatment. No significant adrenal suppression was reported.

Table 3 | Trials of biologic agents for eosinophilic esophagitis*

Reference	Age group	N	Study type	Drug dose	Clinical response	Histologic/serologic response	Adverse events
<i>Anti-IL-5</i>							
Stein 2006 ¹⁸⁰	Adults	4	Open label phase I/II trial	Mepolizumab IV 750 mg, weeks 8, 12, 16	Improved SF-36 QOL scores	Decreased peripheral eos, decreased mean/max esophageal eos	Mild, headache and URI symptoms most common
Stein 2008 ¹⁸¹	Adults	6	Open label phase I/II trial	Mepolizumab 10 mg/kg, weeks 8, 12, 16	N/A	Decreased peripheral eos	Mild, most commonly headache
Straumann 2010 ¹⁸²	Adults	11	Randomized double blind placebo controlled	Mepolizumab (n=5) 750 mg v placebo (n=6) IV weekly ×2 doses	Limited improvement of symptoms seen	Decreased peripheral eos, decreased peak/mean esophageal eos (not meeting endpoint of >5 eos/HPF)	Mild fatigue, URI symptom
Assa'ad 2011 ¹⁸³	Children	59	Randomized double blind parallel group study	Mepolizumab 0.55, 2.5, or 10 mg/kg every 4 weeks ×3 doses	No clinical improvement	Decreased peak and mean esophageal eos; 5 of 57 (8.8%) reached remission (peak eos <5 /HPF)	86.4% reported adverse events, most often vomiting, diarrhea, and abdominal pain
Spergel 2012 ¹⁸⁴	Children	226	Randomized double blind placebo controlled	Reslizumab 1, 2, or 3 mg/kg v placebo	No clinical improvement compared with placebo	Decreased peak esophageal eos	Most commonly headache, cough, nasal congestion, and URI
<i>Anti-IL-13</i>							
Rothenberg 2015 ¹⁸⁵	Adults	23	Randomized placebo controlled	QAX576 6 mg/kg (n=15) v placebo (n=8) every 4 weeks ×3 doses	Trend towards improvement in MDQ score	40% achieved >75% reduction in peak esophageal eos; normalized eosinophilic esophagitis related gene expression	Mild; cough and reflux symptoms most common
Dellon 2016 ¹⁸⁶	Adults	90	Randomized placebo controlled	RPC4046 at 180 or 360 mg v placebo IV then subcutaneous weekly	Improvement in daily symptom diary	Significantly reduced mean esophageal eos at both doses	Headache (up to 20.6%), URI (14.7%), arthralgia (5.9%)
<i>Anti-IgE</i>							
Clayton 2014 ¹⁸⁷	Adults	30	Randomized double blind placebo controlled	Omalizumab (n=16) or placebo every 2-4 weeks for 16 weeks	No improvement in symptoms	No improvement in esophageal eos compared with placebo	N/A
Loizou 2015 ¹⁸⁸	Children and adults	15	Open label single arm	Omalizumab every 4 weeks for 12 weeks	Improvement in 7 of 15 subjects	Decrease in esophageal eos and mast cells, but remission (<15 eos/HPF) was seen in only 5 (33%)	No serious adverse events
<i>CRTH2 antagonist</i>							
Straumann 2013 ¹⁷⁸	Adults	26	Double blind placebo controlled trial	OC000459 100 mg (n=14) or placebo (n=12) BID ×8 weeks	PRO improved in both groups	Reduced esophageal eos by 36.2%	Well tolerated; no serious drug related adverse events

*CRTH2= prostaglandin D2 receptor 2 gene; eos=eosinophils; IV=intravenous; MDQ=Mayo Dysphagia Questionnaire; N/A=not available; PRO=patient reported outcome; URI=upper respiratory infection.

Although corticosteroids are considered the first line drug treatment for patients diagnosed with eosinophilic esophagitis, currently none are approved for this purpose by the Food and Drug Administration. A phase II multicenter trial using budesonide oral suspension in 93 patients showed that this treatment significantly improved symptomatic, endoscopic, and histologic parameters compared with placebo.¹⁷⁵ A multicenter phase III trial is currently under way.

Emerging treatments Drugs

Although most patients respond with histologic improvement of eosinophilia to topical corticosteroids or dietary elimination, a subset of patients will be refractory to standard treatment. Alternative drugs have been explored, including a leukotriene receptor antagonist (montelukast), mast cell stabilizer (cromolyn sodium), and antihistamine, but benefits have been limited.¹⁷⁶⁻¹⁷⁷ A CRTH2 antagonist (OC000459) showed only modest improvement in esophageal eosinophilia and symptoms in adults with refractory disease.¹⁷⁸ Azathioprine and 6-mercaptopurine were effective in case series of patients with steroid dependent eosinophilic esophagitis,¹⁷⁹ but potential side effects make these drugs experimental treatments at this time.

Biologic drugs

Biologic drugs targeting IL-5, IL-13, and IgE have been investigated as potential treatments for refractory eosino-

philic esophagitis (table 3). Although antibodies against IL-5, including mepolizumab and reslizumab, have been shown to decrease the esophageal eosinophil count they did not lead to histologic remission or clinical improvement.¹⁸⁰⁻¹⁸⁴ A recent RCT comparing two dose levels of RPC4046, an IL-13 blocker, and placebo showed that RPC4046 significantly reduced esophageal mean eosinophil count and improved endoscopic features at both doses.¹⁸⁵ Several trials have investigated the use of an anti-IgE antibody, omalizumab, but no clinical or histologic disease remission was seen, probably because eosinophilic esophagitis is not primarily an IgE-mediated disease.¹⁸⁷⁻¹⁸⁸ Further research is needed, but a combination of drugs that inhibit mast cells and eosinophils might be effective for refractory disease.

Esophageal dilatation

Eosinophils and mast cells produce TGF- β , which in turn recruits fibroblasts, promotes epithelial-mesenchymal transition, and increases smooth muscle contractility—all of which contribute to esophageal remodeling in eosinophilic esophagitis (fig 2).⁵⁰⁻⁶³ Ongoing fibrotic changes result in the phenotype of strictures, rings, and narrow caliber esophagus seen in adult patients.²⁰⁻¹⁹¹ Although some anti-inflammatory agents may improve fibrosis at the microscopic level, in most patients esophageal dilatation is key to providing immediate and long lasting relief of dysphagia.

Case reports and series have described a deep esophageal tear associated with pain, need for hospital admis-

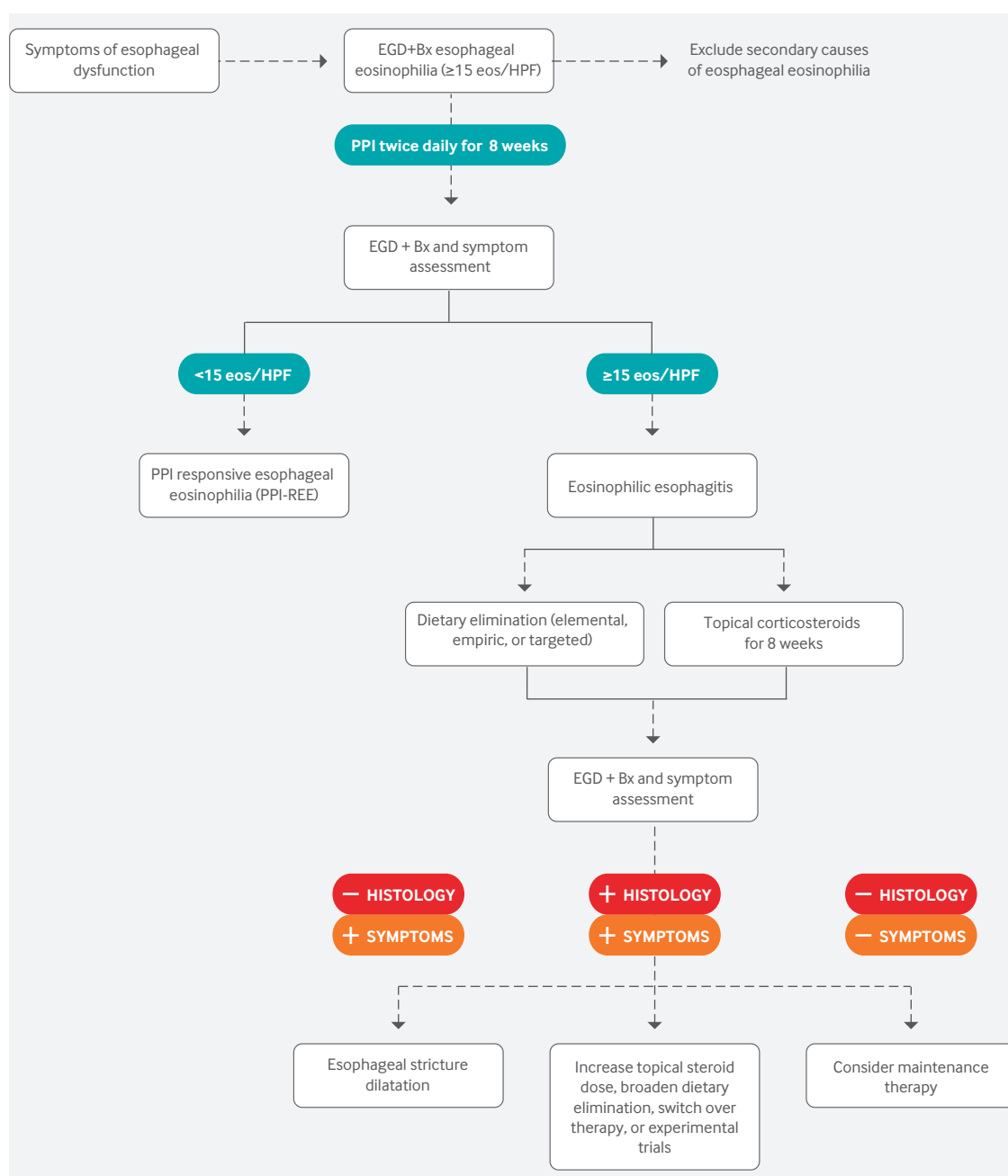


Fig 5 | Eosinophilic esophagitis management algorithm according to available consensus guidelines and expert recommendations. EGD=esophagogastroduodenoscopy; PPI=proton pump inhibitor; Bx=biopsy

sion, and perforation in patients with eosinophilic esophagitis after esophageal dilatation. This resulted in an early consensus recommendation that whenever possible medical or dietary therapy for eosinophilic esophagitis should be attempted before performing esophageal dilatation.⁸ However, multiple large scale studies have reported low rates (<1%) of severe complications from esophageal dilatation in eosinophilic esophagitis,¹⁹²⁻¹⁹⁹ prompting the inclusion of esophageal dilatation as a potential treatment in symptomatic patients in recent guidelines.¹ A systematic review of studies involving esophageal dilatation in eosinophilic esophagitis found an overall perforation rate of 0.6%,²⁰⁰ similar to that of dilatations done for other indications. Esophageal dilatation has been shown to be highly effective although

often associated with post-procedural retrosternal pain (74%). However, this was rarely severe and all patients were agreeable to repeating dilatation if needed.¹⁹³

Guidelines

The latest practice guideline was published in 2013.⁷ Similar to previous guidelines, eosinophilic esophagitis is defined as peak eosinophil density of ≥ 15 cells and exclusion of secondary causes of esophageal eosinophilia (box). The 2013 guideline emphasizes the exclusion of PPI-REE with a two month course of PPI followed by endoscopy with biopsies. Recommendations on treatment endpoints continue to be “conditional” owing to the lack of supporting data, but symptom assessment was again discouraged as the sole parameter to moni-

Secondary causes of esophageal eosinophilia

Proton pump inhibitor responsive esophageal eosinophilia
 Gastroesophageal reflux disease
 Eosinophilic gastrointestinal diseases
 Crohn's disease
 Achalasia
 Celiac disease
 Infection
 Drug hypersensitivity
 Vasculitis
 Pemphigus
 Connective tissue disease
 Graft versus host disease

tor treatment response. Either topical steroids or dietary elimination is recommended as first line treatment for the management of esophageal eosinophilic inflammation. Both treatments have similar efficacies, so the choice is usually based on patient preference and resources, and esophageal dilatation is recommended in symptomatic patients with evidence of strictures. Owing to the propensity for progressive fibrosis, maintenance treatment is recommended, particularly in those with severe symptoms and a history of high grade strictures, to prevent complications. Figure 5 shows a treatment algorithm based on currently available guidelines. Most recommendations are “conditional” or based on relatively low quality of evidence and will probably change with the emergence of higher quality data.

Conclusion

In the past two decades, eosinophilic esophagitis has evolved from a relatively unknown and underdiagnosed entity to a well defined disease now known to be a major cause of foregut symptoms in children and adults. Estimated annual healthcare costs are up to \$1.4bn (£1.04bn; €1.18bn) in the US.²⁰¹ In addition, with the increasing recognition of eosinophilic esophagitis as a global health concern, research to expand our understanding of its pathogenesis and treatment has increased in recent years.

In vitro and in vivo studies, animal models, drug trials, and genetic analyses have led to a considerable breakthrough in the understanding of the pathophysiology of eosinophilic esophagitis. We have also made strides in the understanding of the genetic and environmental risk factors that affect the phenotypic expression of the disease. The lack of a clear endpoint in the assessment of disease activity and treatment response has been a limiting factor in clinical trials. Recent advances in patient reported outcome assessment and a standardized method to evaluate endoscopic features will improve the interpretability of future clinical trials. Disease prognostication and risk stratification may be possible with novel technology such as FLIP and mucosal impedance. From a management standpoint, phase III drug trials are under way for eosinophilic esophagitis specific drugs, and effort is being made to optimize dietary elimination protocols to reduce upfront restriction of diet and decrease the number of endoscopies. Novel treatment options, such as biologic

QUESTIONS FOR FUTURE RESEARCH

- What risk factors (such as a Western diet or dysbiosis) can predict a rapid progressive or fibrostenotic eosinophilic esophagitis phenotype?
- Are there any non-invasive biomarkers or testing strategies that could be used to assess disease activity?
- Could combination therapy be useful in the treatment of patients with refractory disease?
- Could treatments that target barrier function and dysbiosis be useful as primary or adjunctive therapy in eosinophilic esophagitis?
- What is the long term prognosis of eosinophilic esophagitis and proton pump inhibitor responsive esophageal eosinophilia? Do maintenance therapies change the clinical outcome?

drugs, are being investigated for treatment of refractory disease. Many areas of controversy remain in the management of eosinophilic esophagitis, and guidelines will probably be updated in the coming years as a result of fast evolving data on non-invasive diagnostic strategies, new treatment modalities, and the long term prognosis of eosinophilic esophagitis.

Contributors: JWC was responsible for the initial outline, literature search, drafting of the initial and revised manuscript; she is also the guarantor. JYK was responsible for the initial concept and outline of the work and offered critical revisions and final approval of the manuscript.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Provenance and peer review: Commissioned; externally peer reviewed.

- 1 Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3-20.e6, quiz 21-2. doi:10.1016/j.jaci.2011.02.040 pmid:21477849.
- 2 Safroneeva E, Coslovsky M, Kuehni CE, et al. International EEA Study Group. Eosinophilic oesophagitis: relationship of quality of life with clinical, endoscopic and histological activity. *Aliment Pharmacol Ther* 2015;42:1000-10. doi:10.1111/apt.13370 pmid:26271642.
- 3 Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109-16. doi:10.1007/BF01296781 pmid:8420741.
- 4 Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vögtlin J. [Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings]. *Schweiz Med Wochenschr* 1994;124:1419-29. pmid:7939509.
- 5 Hruz P, Straumann A, Bussmann C, et al. Swiss EoE study group. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J Allergy Clin Immunol* 2011;128:1349-1350.e5. doi:10.1016/j.jaci.2011.09.013 pmid:22019091.
- 6 Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2009;7:1055-61. doi:10.1016/j.cgh.2009.06.023 pmid:19577011.
- 7 Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. American College of Gastroenterology. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013;108:679-92, quiz 693. doi:10.1038/ajg.2013.71 pmid:23567357.
- 8 Furuta GT, Liacouras CA, Collins MH, et al. First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342-63. doi:10.1053/j.gastro.2007.08.017 pmid:17919504.
- 9 Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940-1. doi:10.1056/NEJM200408263510924 pmid:15329438.
- 10 Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005;115:418-9. doi:10.1016/j.jaci.2004.11.006 pmid:15696105.
- 11 van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil* 2013;25:47-52.e5. doi:10.1111/nmo.12009 pmid:22963642.

- 12 Dellon ES, Erichsen R, Baron JA, et al. The increasing incidence and prevalence of eosinophilic oesophagitis outpaces changes in endoscopic and biopsy practice: national population-based estimates from Denmark. *Aliment Pharmacol Ther* 2015;41:662-70. doi:10.1111/apt.13129 pmid:25684441.
- 13 Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. *Clin Gastroenterol Hepatol* 2014;12:589-96.e1. doi:10.1016/j.cgh.2013.09.008 pmid:24035773.
- 14 Sealock RJ, Rendon G, El-Serag HB. Systematic review: the epidemiology of eosinophilic oesophagitis in adults. *Aliment Pharmacol Ther* 2010;32:712-9. doi:10.1111/j.1365-2036.2010.04411.x pmid:20662785.
- 15 Arias Á, Pérez-Martínez I, Tenías JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment Pharmacol Ther* 2016;43:3-15. doi:10.1111/apt.13441 pmid:26510832.
- 16 Kapel RC, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology* 2008;134:1316-21. doi:10.1053/j.gastro.2008.02.016 pmid:18471509.
- 17 Ronkainen J, Talley NJ, Aro P, et al. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 2007;56:615-20. doi:10.1136/gut.2006.107714 pmid:17135307.
- 18 Fujishiro H, Amano Y, Kushiya Y, Ishihara S, Kinoshita Y. Eosinophilic esophagitis investigated by upper gastrointestinal endoscopy in Japanese patients. *J Gastroenterol* 2011;46:1142-4. doi:10.1007/s00535-011-0435-5 pmid:21750884.
- 19 Fujiwara Y, Sugawa T, Tanaka F, et al. A multicenter study on the prevalence of eosinophilic esophagitis and PPI-responsive esophageal eosinophilic infiltration. *Intern Med* 2012;51:3235-9. doi:10.2169/intermalmedicine.51.8670 pmid:23207117.
- 20 Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;125:1660-9. doi:10.1053/j.gastro.2003.09.024 pmid:14724818.
- 21 Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009;48:30-6. doi:10.1097/MPG.0b013e3181788282 pmid:19172120.
- 22 Sperry SL, Woosley JT, Shaheen NJ, Dellon ES. Influence of race and gender on the presentation of eosinophilic esophagitis. *Am J Gastroenterol* 2012;107:215-21. doi:10.1038/ajg.2011.342 pmid:21971538.
- 23 Veerappan GR, Perry JL, Duncan TJ, et al. Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study. *Clin Gastroenterol Hepatol* 2009;7:420-6, 426.e1-2. doi:10.1016/j.cgh.2008.10.009 pmid:19162236.
- 24 Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005;115:1090-2. doi:10.1016/j.jaci.2005.01.017 pmid:15867873.
- 25 Iyonouchi S, Brown-Whitehorn TA, Spergel JM. Association of eosinophilic gastrointestinal disorders with other atopic disorders. *Immunol Allergy Clin North Am* 2009;29:85-97, x. doi:10.1016/j.iac.2008.09.008 pmid:19141344.
- 26 Assa'ad A. Eosinophilic esophagitis: association with allergic disorders. *Gastrointest Endosc Clin N Am* 2008;18:119-32, x. doi:10.1016/j.giec.2007.09.001 pmid:18061106.
- 27 Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2008;6:531-5. doi:10.1016/j.cgh.2007.12.045 pmid:18304887.
- 28 Aceves SS. Eosinophilic esophagitis. *Immunol Allergy Clin North Am* 2015;35:145-59. doi:10.1016/j.iac.2014.09.007 pmid:25459582.
- 29 Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology* 2009;137:1238-49. doi:10.1053/j.gastro.2009.07.007 pmid:19596009.
- 30 Dellon ES. The pathogenesis of eosinophilic esophagitis: beyond the eosinophil. *Dig Dis Sci* 2013;58:1445-8. doi:10.1007/s10620-013-2679-9 pmid:23625288.
- 31 Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* 2003;125:1419-27. doi:10.1016/j.gastro.2003.07.007 pmid:14598258.
- 32 Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002;168:2464-9. doi:10.4049/jimmunol.168.5.2464 pmid:11859139.
- 33 Masterson JC, McNamee EN, Hosford L, et al. Local hypersensitivity reaction in transgenic mice with squamous epithelial IL-5 overexpression provides a novel model of eosinophilic oesophagitis. *Gut* 2014;63:43-53. doi:10.1136/gutjnl-2012-303631 pmid:23161496.
- 34 Sleiman PM, Wang ML, Cianferoni A, et al. GWAS identifies four novel eosinophilic esophagitis loci. *Nat Commun* 2014;5:5593. doi:10.1038/ncomms6593 pmid:25407941.
- 35 Rothenberg ME, Spergel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010;42:289-91. doi:10.1038/ng.547 pmid:20208534.
- 36 Sherrill JD, Kc K, Wu D, et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. *Mucosal Immunol* 2014;7:18-29. doi:10.1038/mi.2013.90 pmid:24220297.
- 37 Zhang Z, Sferri TJ, Eroglu Y. T cell co-stimulatory molecules: a co-conspirator in the pathogenesis of eosinophilic esophagitis? *Dig Dis Sci* 2013;58:1497-506. doi:10.1007/s10620-013-2599-8 pmid:23456499.
- 38 Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut* 2013;62:824-32. doi:10.1136/gutjnl-2012-302250 pmid:22580413.
- 39 Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160:1001-8. doi:10.1164/ajrccm.160.3.9812110 pmid:10471631.
- 40 Blanchard C, Mingle MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;120:1292-300. doi:10.1016/j.jaci.2007.10.024 pmid:18073124.
- 41 Johnsson M, Bove M, Bergquist H, et al. Distinctive blood eosinophilic phenotypes and cytokine patterns in eosinophilic esophagitis, inflammatory bowel disease and airway allergy. *J Innate Immun* 2011;3:594-604. doi:10.1159/000331326 pmid:21921589.
- 42 Lingblom C, Bergquist H, Johnsson M, et al. Topical corticosteroids do not revert the activated phenotype of eosinophils in eosinophilic esophagitis but decrease surface levels of CD18 resulting in diminished adherence to ICAM-1, ICAM-2, and endothelial cells. *Inflammation* 2014;37:1932-44. doi:10.1007/s10753-014-9926-x pmid:24870064.
- 43 Bullock JZ, Villanueva JM, Blanchard C, et al. Interplay of adaptive th2 immunity with eotaxin-3/C-C chemokine receptor 3 in eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007;45:22-31. doi:10.1097/MPG.0b013e318043c097 pmid:17592361.
- 44 Furuta GT, Kagalwalla AF, Lee JJ, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut* 2013;62:1395-405. doi:10.1136/gutjnl-2012-303171 pmid:22895393.
- 45 Saffari H, Hoffman LH, Peterson KA, et al. Electron microscopy elucidates eosinophil degranulation patterns in patients with eosinophilic esophagitis. *J Allergy Clin Immunol* 2014;133:1728-34.e1. doi:10.1016/j.jaci.2013.11.024 pmid:24439077.
- 46 Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006;24:147-74. doi:10.1146/annurev.immunol.24.021605.090720 pmid:16551246.
- 47 Moqbel R, Ying S, Barkans J, et al. Identification of messenger RNA for IL-4 in human eosinophils with granule localization and release of the translated product. *J Immunol* 1995;155:4939-47. pmid:7594499.
- 48 Möller GM, de Jong TA, van der Kwast TH, et al. Immunolocalization of interleukin-4 in eosinophils in the bronchial mucosa of atopic asthmatics. *Am J Respir Cell Mol Biol* 1996;14:439-43. doi:10.1165/ajrcmb.14.5.8624248 pmid:8624248.
- 49 Jacoby DB, Gleich GJ, Fryer AD. Human eosinophil major basic protein is an endogenous allosteric antagonist at the inhibitory muscarinic M2 receptor. *J Clin Invest* 1993;91:1314-8. doi:10.1172/JCI116331 pmid:8473484.
- 50 Aceves SS, Chen D, Newbury RO, Dohil R, Bastian JF, Broide DH. Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF-β1, and increase esophageal smooth muscle contraction. *J Allergy Clin Immunol* 2010;126:1198-204.e4. doi:10.1016/j.jaci.2010.08.050 pmid:21047675.
- 51 O'Donnell MC, Ackerman SJ, Gleich GJ, Thomas LL. Activation of basophil and mast cell histamine release by eosinophil granule major basic protein. *J Exp Med* 1983;157:1981-91. doi:10.1084/jem.157.6.1981 pmid:6854212.
- 52 Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954-61. doi:10.1067/mai.2001.119917 pmid:11742273.
- 53 Lucendo AJ, Navarro M, Comas C, et al. Immunophenotypic characterization and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the cellular mechanisms of the disease and the immunologic capacity of the esophagus. *Am J Surg Pathol* 2007;31:598-606. doi:10.1097/JOP.0b0000000000000000 pmid:17414108.
- 54 Gupta SK, Fitzgerald JF, Kondratyuk T, HogenEsch H. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2006;42:22-6. doi:10.1097/01.mpg.0000188740.38757.d2 pmid:16385249.
- 55 Kirsch R, Bokhary R, Marcon MA, Cutz E. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2007;44:20-6. doi:10.1097/MPG.0b013e31802c0d06 pmid:17204948.
- 56 Mueller S, Neureiter D, Aigner T, Stolt M. Comparison of histological parameters for the diagnosis of eosinophilic oesophagitis versus gastro-oesophageal reflux disease on oesophageal biopsy material. *Histopathology* 2008;53:676-84. doi:10.1111/j.1365-2559.2008.01387.x pmid:19076684.

- 57 Dellon ES, Speck O, Woodward K, et al. Markers of eosinophilic inflammation for diagnosis of eosinophilic esophagitis and proton pump inhibitor-responsive esophageal eosinophilia: a prospective study. *Clin Gastroenterol Hepatol* 2014;12:2015-22. doi:10.1016/j.cgh.2014.06.019 pmid:24993367.
- 58 Dellon ES, Chen X, Miller CR, et al. Tryptase staining of mast cells may differentiate eosinophilic esophagitis from gastroesophageal reflux disease. *Am J Gastroenterol* 2011;106:264-71. doi:10.1038/ajg.2010.412 pmid:20978486.
- 59 Abonia JP, Blanchard C, Butz BB, et al. Involvement of mast cells in eosinophilic esophagitis. *J Allergy Clin Immunol* 2010;126:140-9. doi:10.1016/j.jaci.2010.04.009 pmid:20538331.
- 60 Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:206-12. doi:10.1016/j.jaci.2006.10.016 pmid:17208603.
- 61 Kagalwalla AF, Akhtar N, Woodruff SA, et al. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. *J Allergy Clin Immunol* 2012;129:1387-1396.e7. doi:10.1016/j.jaci.2012.03.005 pmid:22465212.
- 62 Lucendo AJ, Arias A, De Rezende LC, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. *J Allergy Clin Immunol* 2011;128:1037-46. doi:10.1016/j.jaci.2011.08.007 pmid:21880354.
- 63 Cheng E, Souza RF, Spechler SJ. Tissue remodeling in eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2012;303:G1175-87. doi:10.1152/ajpgi.00313.2012 pmid:23019192.
- 64 Noti M, Wojno ED, Kim BS, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med* 2013;19:1005-13. doi:10.1038/nm.3281 pmid:23872715.
- 65 Lexmond WS, Neves JF, Nurko S, et al. Involvement of the iNKT cell pathway is associated with early-onset eosinophilic esophagitis and response to allergen avoidance therapy. *Am J Gastroenterol* 2014;109:646-57. doi:10.1038/ajg.2014.12 pmid:24513807.
- 66 Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116:536-47. doi:10.1172/JCI26679 pmid:16453027.
- 67 Kottyan LC, Davis BP, Sherrill JD, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet* 2014;46:895-900. doi:10.1038/ng.3033 pmid:25017104.
- 68 Sleiman PMA, March M, Hakonarson H. The genetic basis of eosinophilic esophagitis. *Best Pract Res Clin Gastroenterol* 2015;29:701-7. doi:10.1016/j.bpg.2015.09.003 pmid:26552769.
- 69 Alexander ES, Martin LJ, Collins MH, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. *J Allergy Clin Immunol* 2014;134:1084-1092.e1. doi:10.1016/j.jaci.2014.07.021 pmid:25258143.
- 70 Peterson K, Firszt R, Fang J, Wong J, Smith KR, Brady KA. Risk of autoimmunity in eoe and families: a population-based cohort study. *Am J Gastroenterol* 2016;111:926-32. doi:10.1038/ajg.2016.185 pmid:27215923.
- 71 Jensen ET, Kappelman MD, Kim HP, Ringel-Kulka T, Dellon ES. Early life exposures as risk factors for pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2013;57:67-71. doi:10.1097/MPG.0b013e318290d15a pmid:23518485.
- 72 Radano MC, Yuan Q, Katz A, Fleming JT, Kubala S, Shreffler W, et al. Cesarean section and antibiotic use found to be associated with eosinophilic esophagitis. *J Allergy Clin Immunol In Practice* 2014;2:475-7.e1.
- 73 Slae M, Persad R, Leung AJ, Gabr R, Brocks D, Huynh HQ. Role of environmental factors in the development of pediatric eosinophilic esophagitis. *Dig Dis Sci* 2015;60:3364-72. doi:10.1007/s10620-015-3740-7 pmid:26062820.
- 74 Jensen ET, Bertelsen RJ. Assessing early life factors for eosinophilic esophagitis: lessons from other allergic diseases. *Curr Treat Options Gastroenterol* 2016;14:39-50. doi:10.1007/s11938-016-0083-1 pmid:26801504.
- 75 McKenzie C, Tan J, Macia L, Mackay CR. The nutrition-gut microbiome-physiology axis and allergic diseases. *Immunol Rev* 2017;278:277-95. doi:10.1111/immr.12556 pmid:28658542.
- 76 Benitez AJ, Hoffmann C, Muir AB, et al. Inflammation-associated microbiota in pediatric eosinophilic esophagitis. *Microbiome* 2015;3:23. doi:10.1186/s40168-015-0085-6 pmid:26034601.
- 77 Harris JK, Fang R, Wagner BD, et al. Esophageal microbiome in eosinophilic esophagitis. *PLoS One* 2015;10:e0128346. doi:10.1371/journal.pone.0128346 pmid:26020633.
- 78 Chen Y, Blaser MJ. Inverse associations of *Helicobacter pylori* with asthma and allergy. *Arch Intern Med* 2007;167:821-7. doi:10.1001/archinte.167.8.821 pmid:17452546.
- 79 Reibman J, Marmor M, Filner J, et al. Asthma is inversely associated with *Helicobacter pylori* status in an urban population. *PLoS One* 2008;3:e4060. doi:10.1371/journal.pone.0004060 pmid:19112508.
- 80 D'Elia MM, Codolo G, Amedei A, et al. *Helicobacter pylori*, asthma and allergy. *FEMS Immunol Med Microbiol* 2009;56:1-8. doi:10.1111/j.1574-695X.2009.00537.x pmid:19220467.
- 81 Dellon ES, Peery AF, Shaheen NJ, et al. Inverse association of esophageal eosinophilia with *Helicobacter pylori* based on analysis of a US pathology database. *Gastroenterology* 2011;141:1586-92. doi:10.1053/j.gastro.2011.06.081 pmid:21762663.
- 82 von Arnim U, Wex T, Link A, et al. *Helicobacter pylori* infection is associated with a reduced risk of developing eosinophilic esophagitis. *Aliment Pharmacol Ther* 2016;43:825-30. doi:10.1111/apt.13560 pmid:26898731.
- 83 Sonnenberg A, Dellon ES, Turner KO, Genta RM. The influence of *Helicobacter pylori* on the ethnic distribution of esophageal eosinophilia. *Helicobacter* 2017;22. doi:10.1111/hel.12370 pmid:28029200.
- 84 Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198-206. doi:10.1016/S1542-3565(05)00885-2 pmid:16361045.
- 85 Gonsalves N. Distinct features in the clinical presentations of eosinophilic esophagitis in children and adults: is this the same disease? *Dig Dis* 2014;32:89-92. doi:10.1159/000357078 pmid:24603387.
- 86 Straumann A, Aceves SS, Blanchard C, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;67:477-90. doi:10.1111/j.1398-9995.2012.02787.x pmid:22313241.
- 87 Lucendo AJ, Sánchez-Cazalilla M. Adult versus pediatric eosinophilic esophagitis: important differences and similarities for the clinician to understand. *Expert Rev Clin Immunol* 2012;8:733-45. doi:10.1586/eci.12.68 pmid:23167685.
- 88 Baxi S, Gupta SK, Swigonski N, Fitzgerald JF. Clinical presentation of patients with eosinophilic inflammation of the esophagus. *Gastrointest Endosc* 2006;64:473-8. doi:10.1016/j.gie.2006.03.931 pmid:16996334.
- 89 Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc* 2014;79:577-85.e4. doi:10.1016/j.gie.2013.10.027 pmid:24275329.
- 90 Aceves SS, Ackerman SJ. Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. *Immunol Allergy Clin North Am* 2009;29:197-211, xiii-xiv. doi:10.1016/j.jaci.2008.10.003 pmid:19141355.
- 91 Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. *Gastroenterol Clin North Am* 2014;43:297-316. doi:10.1016/j.gtc.2014.02.015 pmid:24813517.
- 92 Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013;145:1230-6.e1, 2. doi:10.1053/j.gastro.2013.08.015 pmid:23954315.
- 93 Straumann A. The natural history and complications of eosinophilic esophagitis. *Thorac Surg Clin* 2011;21:575-87. doi:10.1016/j.thorsurg.2011.09.004 pmid:22040638.
- 94 Menard-Katcher P, Marks KL, Liacouras CA, Spergel JM, Yang YX, Falk GW. The natural history of eosinophilic esophagitis in the transition from childhood to adulthood. *Aliment Pharmacol Ther* 2013;37:114-21. doi:10.1111/apt.12119 pmid:23121227.
- 95 Sodikoff J, Hirano I. Therapeutic strategies in eosinophilic esophagitis: Induction, maintenance and refractory disease. *Best Pract Res Clin Gastroenterol* 2015;29:829-39. doi:10.1016/j.bpg.2015.09.002 pmid:26552781.
- 96 Gonsalves N, Policarpio-Nicolas M, Zhang Q, Rao MS, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006;64:313-9. doi:10.1016/j.gie.2006.04.037 pmid:16923475.
- 97 Dellon ES, Irani AM, Hill MR, Hirano I. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. *Aliment Pharmacol Ther* 2013;38:634-42. doi:10.1111/apt.12413 pmid:23837796.
- 98 Schoepfer AM, Straumann A, Panczak R, et al. International Eosinophilic Esophagitis Activity Index Study Group. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology* 2014;147:1255-66.e21. doi:10.1053/j.gastro.2014.08.028 pmid:25160980.
- 99 Safroneeva E, Straumann A, Coslovsky M, et al. International Eosinophilic Esophagitis Activity Index Study Group. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. *Gastroenterology* 2016;150:581-590.e4. doi:10.1053/j.gastro.2015.11.004 pmid:26584601.
- 100 Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:988-96.e5. doi:10.1016/j.cgh.2012.04.019 pmid:22610003.
- 101 Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the esophageal features of eosinophilic esophagitis: validation of a novel classification and grading system. *Gut* 2013;62:489-95. doi:10.1136/gutjnl-2011-301817 pmid:22619364.
- 102 van Rhijn BD, Warners MJ, Curvers WL, et al. Evaluating the endoscopic reference score for eosinophilic esophagitis: moderate to substantial intra- and interobserver reliability. *Endoscopy* 2014;46:1049-55. doi:10.1055/s-0034-1377781 pmid:25208033.

- 103 Dellon ES, Cotton CC, Gebhart JH, et al. Accuracy of the eosinophilic esophagitis endoscopic reference score in diagnosis and determining response to treatment. *Clin Gastroenterol Hepatol* 2016;14:31-9. doi:10.1016/j.cgh.2015.08.040 pmid:26404868.
- 104 van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. The Endoscopic Reference Score shows modest accuracy to predict histologic remission in adult patients with eosinophilic esophagitis. *Neurogastroenterol Motil* 2016;28:1714-22. doi:10.1111/nmo.12872 pmid:27254480.
- 105 Whitney-Miller CL, Katzka D, Furth EE. Eosinophilic esophagitis: a retrospective review of esophageal biopsy specimens from 1992 to 2004 at an adult academic medical center. *Am J Clin Pathol* 2009;131:788-92. doi:10.1309/AJCPOMPXJFP7EB4P pmid:19461084.
- 106 Collins MH. Histopathology of eosinophilic esophagitis. *Dig Dis* 2014;32:68-73. doi:10.1159/000357012 pmid:24603383.
- 107 Rusin S, Covey S, Perjar I, et al. Determination of esophageal eosinophil counts and other histologic features of eosinophilic esophagitis by pathology trainees is highly accurate. *Hum Pathol* 2017;62:50-5. doi:10.1016/j.humpath.2016.12.017 pmid:28041975.
- 108 Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis Esophagus* 2017;30:1-8. doi:10.1111/dote.12470 pmid:26857345.
- 109 Dellon ES, Chen X, Miller CR, Woosley JT, Shaheen NJ. Diagnostic utility of major basic protein, eotaxin-3, and leukotriene enzyme staining in eosinophilic esophagitis. *Am J Gastroenterol* 2012;107:1503-11. doi:10.1038/ajg.2012.202 pmid:22777338.
- 110 Bhattacharya B, Carlsen J, Sabo E, et al. Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease. *Hum Pathol* 2007;38:1744-53. doi:10.1016/j.humpath.2007.05.008 pmid:17900656.
- 111 Lucendo AJ, De Rezende L, Comas C, Caballero T, Bellón T. Treatment with topical steroids downregulates IL-5, eotaxin-1/CCL11, and eotaxin-3/CCL26 gene expression in eosinophilic esophagitis. *Am J Gastroenterol* 2008;103:2184-93. doi:10.1111/j.1572-0241.2008.01937.x pmid:18844613.
- 112 Dellon ES, Rusin S, Gebhart JH, et al. Utility of a noninvasive serum biomarker panel for diagnosis and monitoring of eosinophilic esophagitis: a prospective study. *Am J Gastroenterol* 2015;110:821-7. doi:10.1038/ajg.2015.57 pmid:25781367.
- 113 Subbarao G, Rosenman MB, Ohnuki L, et al. Exploring potential noninvasive biomarkers in eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr* 2011;53:651-8. pmid:21694637.
- 114 Dellon ES, Higgins LL, Beitia R, et al. Prospective assessment of serum periostin as a biomarker for diagnosis and monitoring of eosinophilic esophagitis. *Aliment Pharmacol Ther* 2016;44:189-97. doi:10.1111/apt.13672 pmid:27193351.
- 115 Blanchard C. Molecular pathogenesis of eosinophilic esophagitis. *Curr Opin Gastroenterol* 2015;31:321-7. doi:10.1097/MOG.0000000000000186 pmid:26039724.
- 116 Lepe M, O'Connell D, Lombardo KA, et al. The inflammatory milieu of eosinophilic esophagitis: a contemporary review with emphasis in putative immunohistochemistry and serologic markers. *Appl Immunohistochem Mol Morphol* 2016. doi:10.1097/PAI.0000000000000450 pmid:27801733.
- 117 Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterology* 2013;145:1289-99. doi:10.1053/j.gastro.2013.08.046 pmid:23978633.
- 118 Dellon ES, Veerappan R, Selitsky SR, et al. A gene expression panel is accurate for diagnosis and monitoring treatment of eosinophilic esophagitis in adults. *Clin Transl Gastroenterol* 2017;8:e74. doi:10.1038/ctg.2017.2 pmid:28181994.
- 119 Katzka DA, Geno DM, Ravi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2015;13:77-83. e2. doi:10.1016/j.cgh.2014.06.026 pmid:24997328.
- 120 Aceves SS. Tissue remodeling in patients with eosinophilic esophagitis: what lies beneath the surface? *Allergy Clin Immunol* 2011;128:1047-9. doi:10.1016/j.jaci.2011.09.026 pmid:22036097.
- 121 Kwiatek MA, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011;140:82-90. doi:10.1053/j.gastro.2010.09.037 pmid:20858491.
- 122 Nicodème F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2013;11:1101-1107.e1. doi:10.1016/j.cgh.2013.03.020 pmid:23591279.
- 123 Chen JW, Pandolfino JE, Lin Z, et al. Severity of endoscopically identified esophageal rings correlates with reduced esophageal distensibility in eosinophilic esophagitis. *Endoscopy* 2016;48:794-801. doi:10.1055/s-0042-107340 pmid:27200524.
- 124 van Rhijn BD, Kessing BF, Smout AJ, Bredenoord AJ. Oesophageal baseline impedance values are decreased in patients with eosinophilic oesophagitis. *United European Gastroenterol J* 2013;1:242-8. doi:10.1177/2050640613496411 pmid:24917968.
- 125 van Rhijn BD, Weijenborg PW, Verheij J, et al. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;12:1815-23.e2. doi:10.1016/j.cgh.2014.02.037 pmid:24657840.
- 126 Ates F, Yuksel ES, Higginbotham T, et al. Mucosal impedance discriminates GERD from non-GERD conditions. *Gastroenterology* 2015;148:334-43. doi:10.1053/j.gastro.2014.10.010 pmid:25448923.
- 127 van Rhijn BD, Verheij J, van den Bergh Weerman MA, et al. Histological response to fluticasone propionate in patients with eosinophilic esophagitis is associated with improved functional esophageal mucosal integrity. *Am J Gastroenterol* 2015;110:1289-97. doi:10.1038/ajg.2015.247 pmid:26303134.
- 128 Dellon ES, Gibbs WB, Fritchie KJ, et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2009;7:1305-13, quiz 1261. doi:10.1016/j.cgh.2009.08.030 pmid:19733260.
- 129 Sayej WN, Patel R, Baker RD, Tron E, Baker SS. Treatment with high-dose proton pump inhibitors helps distinguish eosinophilic esophagitis from noneosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2009;49:393-9. doi:10.1097/MPG.0b013e31819c4b3e pmid:19633574.
- 130 Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus--peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006;101:1666-70. doi:10.1111/j.1572-0241.2006.00562.x pmid:16863575.
- 131 Dranove JE, Horn DS, Davis MA, Kernek KM, Gupta SK. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *J Pediatr* 2009;154:96-100. doi:10.1016/j.jpeds.2008.07.042 pmid:18783791.
- 132 Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig Dis Sci* 2010;55:1313-9. doi:10.1007/s10620-009-0859-4 pmid:19533356.
- 133 Molina-Infante J, Ferrando-Lamana L, Ripoll C, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011;9:110-7. doi:10.1016/j.cgh.2010.09.019 pmid:20920599.
- 134 Francis DL, Fox-Orenstein A, Arora AS, et al. Results of ambulatory pH monitoring do not reliably predict response to therapy in patients with eosinophilic esophagitis. *Aliment Pharmacol Ther* 2012;35:300-7. doi:10.1111/j.1365-2036.2011.04922.x pmid:22111863.
- 135 Schroeder S, Robinson ZD, Masterson JC, et al. Esophageal human β -defensin expression in eosinophilic esophagitis. *Pediatr Res* 2013;73:647-54. doi:10.1038/pr.2013.23 pmid:23385963.
- 136 Vazquez-Elizondo G, Ngamruengphong S, Khrisna M, Devault KR, Talley NJ, Achem SR. The outcome of patients with esophageal eosinophilic infiltration after an eight-week trial of a proton pump inhibitor. *Aliment Pharmacol Ther* 2013;38:1312-9. doi:10.1111/apt.12513 pmid:24117619.
- 137 Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;135:187-97. doi:10.1016/j.jaci.2014.08.043 pmid:25441638.
- 138 Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig Dis Sci* 2009;54:2312-7. doi:10.1007/s10620-009-0951-9 pmid:19714466.
- 139 Zhang X, Cheng E, Huo X, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PLoS One* 2012;7:e50037. doi:10.1371/journal.pone.0050037 pmid:23185525.
- 140 Moawad FJ. Letter: distinguishing PPI-responsive oesophageal eosinophilia from eosinophilic esophagitis - still a long way to go; authors' reply. *Aliment Pharmacol Ther* 2014;39:1249-50. doi:10.1111/apt.12725 pmid:24735151.
- 141 Shoda T, Matsuda A, Nomura I, et al. Eosinophilic esophagitis versus proton pump inhibitor-responsive esophageal eosinophilia: Transcriptome analysis. *J Allergy Clin Immunol* 2017;139:2010-2013.e4. doi:10.1016/j.jaci.2016.11.028 pmid:28063872.
- 142 Sodikoff J, Hirano I. Proton pump inhibitor-responsive esophageal eosinophilia does not preclude food-responsive eosinophilic esophagitis. *J Allergy Clin Immunol* 2016;137:631-3. doi:10.1016/j.jaci.2015.07.008 pmid:26318073.
- 143 Lucendo AJ, Arias A, Gonzalez-Cervera J, Olalla JM, Molina-Infante J. Dual response to dietary/topical steroid and proton pump inhibitor therapy in adult patients with eosinophilic esophagitis. *J Allergy Clin Immunol* 2016;137:931-4.e2.
- 144 Gómez-Torrijos E, García-Rodríguez R, Castro-Jiménez A, Rodríguez-Sánchez J, Méndez Díaz Y, Molina-Infante J. The efficacy of step-down therapy in adult patients with proton pump inhibitor-responsive oesophageal eosinophilia. *Aliment Pharmacol Ther* 2016;43:534-40. doi:10.1111/apt.13496 pmid:26662868.
- 145 Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503-12. doi:10.1016/0016-5085(95)90637-1 pmid:7557132.

- 146 Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol* 2003;98:777-82. doi:10.1111/j.1572-0241.2003.07390.x pmid:12738455.
- 147 Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol* 2013;108:759-66. doi:10.1038/ajg.2012.468 pmid:23381017.
- 148 Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014;146:1639-48. doi:10.1053/j.gastro.2014.02.006 pmid:24534634.
- 149 Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097-102. doi:10.1016/j.cgh.2006.05.026 pmid:16860614.
- 150 Kagalwalla AF, Shah A, Li BU, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011;53:145-9. doi:10.1097/MPG.0b013e31821cf503 pmid:21788754.
- 151 Kagalwalla AF, Shah A, Ritz S, Melin-Aldana H, Li BU. Cow's milk protein-induced eosinophilic esophagitis in a child with gluten-sensitive enteropathy. *J Pediatr Gastroenterol Nutr* 2007;44:386-8. doi:10.1097/01.mpg.0000243430.32087.5c pmid:17325563.
- 152 Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2012;129:1570-8. doi:10.1016/j.jaci.2012.03.023 pmid:22541246.
- 153 Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012;142:1451-9.e1, quiz e14-5. doi:10.1053/j.gastro.2012.03.001 pmid:22391333.
- 154 Lucendo AJ, Arias A, González-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013;131:797-804. doi:10.1016/j.jaci.2012.12.664 pmid:23375693.
- 155 Wolf WA, Jerath MR, Sperry SL, Shaheen NJ, Dellon ES. Dietary elimination therapy is an effective option for adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;12:1272-9. doi:10.1016/j.cgh.2013.12.034 pmid:24440337.
- 156 Philpott H, Nandurkar S, Royce SG, Thien F, Gibson PR. A prospective open clinical trial of a proton pump inhibitor, elimination diet and/or budesonide for eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2016;43:985-93. doi:10.1111/apt.13576 pmid:26939578.
- 157 Colson D, Kalach N, Soulaïnes P, et al. The impact of dietary therapy on clinical and biologic parameters of pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol Pract* 2014;2:587-93. doi:10.1016/j.jaip.2014.05.012 pmid:25213053.
- 158 Rodríguez-Sánchez J, Gómez Torrijos E, López Viedma B, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. *Allergy* 2014;69:936-42. doi:10.1111/all.12420 pmid:24816218.
- 159 Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. *J Allergy Clin Immunol* 2014;134:1093-9.e1. doi:10.1016/j.jaci.2014.07.023 pmid:25174868.
- 160 Kagalwalla AAK, Amsden K, Makhija M, et al. A multicenter study assessing the clinical, endoscopic, and histologic response to four food elimination diet for the treatment of eosinophilic esophagitis. *Gastroenterology* 2015;148(Suppl 1):S-30doi:10.1016/S0016-5085(15)30103-7.
- 161 Molina-Infante J, Gonzalez-Cordero PL, Casabona-Frances S, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 study. *Gastroenterology* 2017;152(Suppl 1):S207doi:10.1016/S0016-5085(17)30998-8.
- 162 Philpott H, Nandurkar S, Royce SG, Thien F, Gibson PR. Allergy tests do not predict food triggers in adult patients with eosinophilic oesophagitis. A comprehensive prospective study using five modalities. *Aliment Pharmacol Ther* 2016;44:223-33. doi:10.1111/apt.13676 pmid:27247257.
- 163 Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381-91. doi:10.1053/j.gastro.2006.08.033 pmid:17101314.
- 164 Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig Dis Sci* 2010;55:1313-9. doi:10.1007/s10620-009-0859-4. pmid:19533356.
- 165 Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 2010;139:418-29. doi:10.1053/j.gastro.2010.05.001 pmid:20457157.
- 166 Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526-37, 1537.e1. doi:10.1053/j.gastro.2010.07.048 pmid:20682320.
- 167 Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology* 2012;143:321-4.e1. doi:10.1053/j.gastro.2012.04.049 pmid:22561055.
- 168 Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012;10:742-749.e1. doi:10.1016/j.cgh.2012.03.018 pmid:22475741.
- 169 Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol* 2013;108:366-72. doi:10.1038/ajg.2012.443. pmid:23399553.
- 170 Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. *Gastroenterology* 2014;147:324-33.e5. doi:10.1053/j.gastro.2014.04.019 pmid:24768678.
- 171 Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2015;13:66-76.e3. doi:10.1016/j.cgh.2014.05.021. pmid:24907502.
- 172 Miehke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. *Gut* 2016;65:390-9. doi:10.1136/gutjnl-2014-308815. pmid:25792708.
- 173 Dellon ES, Katza DA, Collins MH, Hamdani M, Gupta SK, Hirano I. MP-101-06 Investigators. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. *Gastroenterology* 2017;152:776-786.e5. doi:10.1053/j.gastro.2016.11.021. pmid:27889574.
- 174 Murali AR, Gupta A, Attar BM, Ravi V, Koduru P. Topical steroids in eosinophilic esophagitis: Systematic review and meta-analysis of placebo-controlled randomized clinical trials. *J Gastroenterol Hepatol* 2016;31:1111-9. doi:10.1111/jgh.13281. pmid:26699695.
- 175 Dellon ES, Katza DA, Collins MH, Hamdani M, Gupta SK, Hirano I. MP-101-06 Investigators. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. *Gastroenterology* 2017;152:776-786.e5. doi:10.1053/j.gastro.2016.11.021 pmid:27889574.
- 176 Attwood SE, Lewis CJ, Brondor CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003;52:181-5. doi:10.1136/gut.52.2.181 pmid:12524397.
- 177 Lucendo AJ, De Rezende LC, Jiménez-Contreras S, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci* 2011;56:3551-8. doi:10.1007/s10620-011-1775-y pmid:21674173.
- 178 Straumann A, Hoelsi S, Bussmann Ch, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy* 2013;68:375-85. doi:10.1111/all.12096 pmid:23379537.
- 179 Netzer P, Gschossman JM, Straumann A, Sendensky A, Weimann R, Schoepfer AM. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol* 2007;19:865-9. doi:10.1097/MEG.0b013e32825a6ab4 pmid:17873610.
- 180 Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;118:1312-9. doi:10.1016/j.jaci.2006.09.007 pmid:17157662.
- 181 Stein ML, Villanueva JM, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy reduces eosinophil activation ex vivo and increases IL-5 and IL-5 receptor levels. *J Allergy Clin Immunol* 2008;121:1473-83, 1483.e1-4. doi:10.1016/j.jaci.2008.02.033 pmid:18410960.
- 182 Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010;59:21-30. doi:10.1136/gut.2009.178558 pmid:19828470.
- 183 Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology* 2011;141:1593-604. doi:10.1053/j.gastro.2011.07.044 pmid:21835135.
- 184 Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2012;129:456-63, 463.e1-3. doi:10.1016/j.jaci.2011.11.044 pmid:22206777.
- 185 Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2015;135:500-7. doi:10.1016/j.jaci.2014.07.049 pmid:25226850.
- 186 Dellon ESCM, Assouline-Dayana YA, Evans L, et al. A randomized, double blind, placebo-controlled trial of a novel recombinant, humanized, anti-interleukin-13 monoclonal antibody (RPC4046) in patients with active eosinophilic esophagitis: results of the HEROES study. *Am J Gastroenterol* 2016;111:S186-235. pmid:27685294.
- 187 Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology* 2014;147:602-9. doi:10.1053/j.gastro.2014.05.036 pmid:24907494.

- 188 Loizou D, Enav B, Komlodi-Pasztor E, et al. A pilot study of omalizumab in eosinophilic esophagitis. *PLoS One* 2015;10:e0113483. doi:10.1371/journal.pone.0113483 pmid:25789989.
- 189 Bohm ME, Richter JE. Review article: oesophageal dilation in adults with eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2011;33:748-57. doi:10.1111/j.1365-2036.2011.04593.x pmid:21320137.
- 190 Mishra A, Wang M, Pemmaraju VR, et al. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. *Gastroenterology* 2008;134:204-14. doi:10.1053/j.gastro.2007.10.002 pmid:18166354.
- 191 Rieder F, Nonevski I, Ma J, et al. T-helper 2 cytokines, transforming growth factor β 1, and eosinophil products induce fibrogenesis and alter muscle motility in patients with eosinophilic esophagitis. *Gastroenterology* 2014;146:1266-77.e1, 9. doi:10.1053/j.gastro.2014.01.051 pmid:24486052.
- 192 Dellon ES. Diagnosis and management of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012;10:1066-78. doi:10.1016/j.cgh.2012.06.003 pmid:22728382.
- 193 Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. *Am J Gastroenterol* 2010;105:1062-70. doi:10.1038/ajg.2009.657 pmid:19935783.
- 194 Bohm M, Richter JE, Kelsen S, Thomas R. Esophageal dilation: simple and effective treatment for adults with eosinophilic esophagitis and esophageal rings and narrowing. *Dis Esophagus* 2010;23:377-85. pmid:20353444.
- 195 Dellon ES, Gibbs WB, Rubinas TC, et al. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. *Gastrointest Endosc* 2010;71:706-12. doi:10.1016/j.gie.2009.10.047 pmid:20170913.
- 196 Kaplan M, Mutlu EA, Jakate S, et al. Endoscopy in eosinophilic esophagitis: "feline" esophagus and perforation risk. *Clin Gastroenterol Hepatol* 2003;1:433-7. doi:10.1016/S1542-3565(03)00222-2 pmid:15017642.
- 197 Cohen MS, Kaufman AB, Palazzo JP, Nevin D, Dimarino AJ Jr, Cohen S. An audit of endoscopic complications in adult eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2007;5:1149-53. doi:10.1016/j.cgh.2007.05.017 pmid:17683993.
- 198 Kavitt RT, Penson DF, Vaezi MF. Eosinophilic esophagitis: dilate or medicate? A cost analysis model of the choice of initial therapy. *Dis Esophagus* 2014;27:418-23. doi:10.1111/j.1442-2050.2012.01409.x pmid:22947137.
- 199 Runge TM, Eluri S, Cotton CC, et al. Outcomes of esophageal dilation in eosinophilic esophagitis: safety, efficacy, and persistence of the fibrostenotic phenotype. *Am J Gastroenterol* 2016;111:206-13. doi:10.1038/ajg.2015.399 pmid:26753894.
- 200 Alexander J. Esophageal dilation in eosinophilic esophagitis. *Tech Gastrointest Endosc* 2014;16:16-31 doi:10.1016/j.tgie.2013.08.009.
- 201 Jensen ET, Kappelman MD, Martin CF, Dellon ES. Health-care utilization, costs, and the burden of disease related to eosinophilic esophagitis in the United States. *Am J Gastroenterol* 2015;110:626-32. doi:10.1038/ajg.2014.316 pmid:25267327.

Appendix 1: Search terms

The following search terms were used alone and in combination:

Eosinophilic esophagitis, eosinophilic oesophagitis, oesophageal eosinophilia, prevalence, incidence, epidemiology, pathophysiology, pathogenesis, genetic, natural history, familial, helicobacter, pylori, celiac disease, celiac sprue, connective tissue disease, Ehler-Danlos, microbiota, bacteria, flora, epidemiology, diagnosis, diagnoses, diagnostic, clinical features, presentation, biopsy, biopsies, histology, histologic, treatment, treatments, therapy, therapies, therapeutic, maintenance, dilation, intervention, management, guideline, consensus recommendation, allergy testing, prick test, patch test, food, diet, elemental, proton pump inhibitor, PPI, proton pump inhibitors, omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, dextansoprazole, steroid, steroids, corticosteroid, corticosteroids, prednisone, fluticasone, budesonide, EndoFLIP, impedance planimetry, mucosal impedance, FLIP, PPI-responsive esophageal eosinophilia, PPI-REE, PPIREE, impaction, perforation, narrow-caliber esophagus, EREFS, endoscopic reference, endoscopy, endoscopic score, cytosponge, string, esophageal string test, patient reported outcome, questionnaire, genome, genome-wide, genetic profile, transcriptome, interleukin, mepolizumab, reslizumab, QAX576, RPC4046, omalizumab, OC000459, biologics, biologic, cost, cost effective, outcome, side effect, side effects, fibrosis, complication, complications, remodel, remodeling.

Appendix 2: Relevant “Frequently Asked Questions” on the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) website

Can an allergy cause EGID?

Can an injury cause EGID?

Will EGID (EC, EoE, or EG) ever go away? Will it get worse?

Do all patients experience similar symptoms?

Are treatment plans for all EGIDs the same?

What is dietary management?

What is the risk of EoE developing into Barrett esophagus or cancer of the esophagus?

Does diagnosis and/or treatment of EGID require a specialist?

How effective is allergy testing in identifying food triggers for EGID?

Is there any consensus as to how frequently a child with EGID should undergo an endoscopic procedure? What about an adult?

Are there any other methods to diagnose/monitor EGID other than endoscopy?

Appendix 3: Answers to 10 questions gathered from an online eosinophilic esophagitis (EoE) patient support group:

1. I tested negative for all food allergies but tested positive for environmental allergies. Does this mean that food doesn't cause my EoE?

There are currently no accurate allergy testing methods to accurately determine a patient's EoE trigger. Testing negative for food allergies, unfortunately, does not mean there is not a food trigger for EoE.

2. Do you have to have a high blood EOS count to have EoE? What does a high blood EoS count mean?

In EoE, increased eosinophil is isolated in the esophagus and not in the peripheral blood.

3. Can EoE spread? Aka could my EoE become EG/EGE or EC?

EoE is not known to extend to eosinophilic gastroenteritis or colitis.

4. Why is EoE treated differently in adults vs. children? Is it the same disease? If it's the same disease why don't I get the same options as children?

This is an interesting question that is not completely understood. Pediatric and adult EoE patients can have different clinical presentations, but they are thought to be the same disease entity. In the pediatric population, symptoms are thought to be predominantly inflammation-driven; whereas, in adults, symptoms are often driven by consequences of esophageal remodeling and fibrosis from chronic inflammation.

5. When doing the PPI trial do you just stay on it forever or just the 6-8 weeks? Especially if you feel like the PPI didn't help with symptoms.

The current recommendation for determination of PPI-responsiveness involves an 8-week course of PPI followed by an endoscopy with biopsies to assess response. If esophageal eosinophil count does not respond to a PPI after 8 weeks, the PPI does not need to be continued unless the patient has underlying reflux disease.

6. How long does it take for me to have an Eosinophilic reaction? Some people say they are reacting in minutes is that an Eosinophilic reaction? How long does Eosinophil infiltration actually take? Are delayed reactions days - 1 week common?

EoE is triggered by a delayed hypersensitive reaction in response to specific food antigens. The delayed reaction should not be felt immediately and can take up to a few days or longer for symptom manifestation.

7. How do I take swallowed Budesonide? Do I have to use the Splenda?

Topical steroid in a viscous solution can increase esophageal-medication contact time and maximize its efficacy. To thicken the budesonide solution into a "slurry," previous studies have utilized packs of sugar such as sucralose (Splenda). However, other substitutions can be used including honey, maple or chocolate syrup, etc., in those intolerant to sucralose. In the future, we will likely have an FDA-approved viscous oral budesonide solution available for EoE.

8. Is repeat dilation (several times a year) of the esophagus adequate as the only form of treatment for EOE? And is it safe?

The fear of treating only the fibrosis consequence of EoE and not the active inflammation is that chronic inflammation-related esophageal remodeling is allowed to progress, which may increase the risks of complications such as food impaction or development of a narrow caliber and stiff esophagus.

However, in mild disease with no food impaction history, intermittent dilation alone may be sufficient.

9. How long should pain last after an EGD with/without dilation?

EoE patients are more likely to have pain after dilation than other conditions (up to 75%). Chest pain is usually self-limited within 48-72 hours and can typically be managed with over the counter medications.

10. Do "trace amounts" or potential cross contamination on a food package matter? How do I know what's safe to eat/not safe?.

When undergoing a food elimination diet trial, it is best to adhere strictly to the diet plan. It is not clear the amount of food trigger one has to be exposed to before causing inflammation. Therefore, trace amounts of a potential food trigger should be avoided during the dietary elimination trial. Once a food trigger is identified, it is possible that trace amounts of the trigger food or mild cross contamination infrequently may not cause any clinically significant consequences.