# Management of Eosinophilic Esophagitis Based on Pathophysiological Evidence

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**Abstract:** Over the past decades eosinophilic esophagitis (EoE) has been increasingly diagnosed, and significant progress has been made in our understanding of its pathophysiology. As EoE cannot be cured yet, treatment goals are suppression of disease activity and symptoms as well as the prevention of progression to a more severe disease phenotype. Disease-modifying treatment options can be divided into dietary therapy and immunosuppressive medications, of which topical steroids have been most investigated, yet are still prescribed off-label. In this review, we will summarize recent advances in our understanding of EoE and discuss the mechanisms of action of current treatment options, with emphasis on the role of the esophageal epithelial barrier and the effects of proton-pump inhibitors in the management of patients with EoE.

**Key Words:** eosinophilic esophagitis, epithelial barrier, etiology, PPI-REE, treatment

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Eosinophilic esophagitis (EoE) is a relatively recently discovered chronic immune-mediated esophageal disease, first described as a distinct disease entity in 1993, for which the first consensus guidelines were published only 10 years ago.[1,2] Over the past decades, EoE has been increasingly recognized worldwide, mostly in western countries.[3–11] The diagnosis of EoE is based on the combination of symptoms of esophageal dysfunction and characteristic histologic presence of eosinophilic granulocytes (eosinophils), and requires the exclusion of other diseases.[2] Typical but nonspecific endoscopic findings, observed in the vast majority of patients, are rings, linear furrows, white exudates, edema, and/or narrowing/strictures in the esophagus.[12,13]

As with any "new" disease, the definition of EoE has been subject to debate and has changed over the past years as a result of progressing insights. The hot topic of the lack of response to proton-pump inhibitors (PPIs) in patients with suspected EoE has been one of the stipulations for the diagnosis of EoE in all published guidelines, in order to distinguish EoE from gastroesophageal reflux disease (GERD).[2,14–16] However, the work of several groups has shown that about 50% of patients with esophageal eosinophilia and a phenotype similar to EoE benefit from PPIs; for these patients the term "proton pump inhibitor-responsive esophageal eosinophilia" (PPI-REE) was introduced.[17–19] PPI-REE and EoE have appeared to be clinically, endoscopically, histologically, and pathophysiologically indistinguishable—apart from their response to a PPI.[20] Both entities are now considered part of the same disease spectrum, and it has become generally accepted to offer PPI treatment to every patient with suspected EoE.[16] In this review, we will summarize current concepts on the pathophysiology (Fig. 1) and management (Table 1) of EoE.

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## PATHOPHYSIOLOGY OF EOE

In the past decades it has become evident that EoE results from the interplay between genetic and environmental factors.[48] Allergens, most probably from foods, are thought to induce a T-helper 2 (Th2) cell-mediated immune response characterized by several cytokines, among which are interleukin (IL)-5 and IL-13. These cytokines induce the production of a variety of other cytokines by epithelial cells, leading to esophageal inflammation and symptoms of esophageal dysfunction (heartburn, dysphagia and/or food impaction in adults, failure to thrive, and vomiting in children) and suggestive endoscopic signs of EoE.[12,49] Chronic inflammation may lead to subepithelial remodeling and fibrosis.[50–52] Below, we will discuss different aspects of the pathophysiology of EoE in more detail (Fig. 1).

### Triggers

About 75% of EoE patients have an atopic diathesis, and most of them are sensitized against food and/or inhaled allergens.[14,53–56] Food hypersensitivity is thought to cause EoE, as most EoE patients are sensitized against food and/or aero allergens and generally respond well to removal of (food) allergens from their diet.[14,21,53,54] The relevance of these sensitizations, however, remains unclear, as studies on allergy test–based exclusion of allergens show conflicting effects on disease activity.[21,23,57–59] A possible explanation that was recently hypothesized is that EoE is not immunoglobulin (Ig)E mediated but perhaps IgG4 related.[44,60,61] The role of IgG4 in EoE is still unclear; however, it has been speculated to be a marker of epithelial barrier impairment.[60]

### Potentiating Factors

#### Genetics

EoE has a strong familial association, suggesting a genetic component. A study among 914 EoE probands and 63 monozygotic and dizygotic twins/triplets showed an estimated sibling recurrence risk ratio for EoE of 44, which is high compared with other atopic diseases such as asthma for which it is about 2.[62,63] Genome Wide Association Studies and candidate gene studies have shown associations



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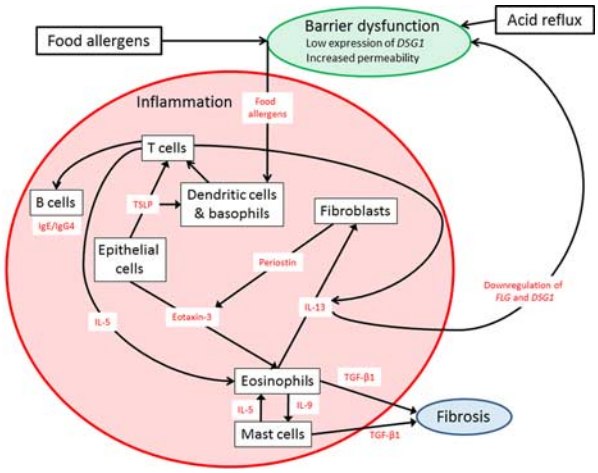


**FIGURE 1.** Overview of eosinophilic esophagitis pathogenesis. Food allergens are thought to trigger inflammation in eosinophilic esophagitis in the presence of esophageal epithelial barrier dysfunction, which may lead to remodeling and fibrosis. Ig indicates immunoglobulin; IL, interleukin; TGF-β1, transforming growth factor-β1. full color online

with the *CCL26* gene (encoding for eotaxin-3) in 14% of EoE patients, and with *TGFB1*, *TSLP*, *FLG*, *CRLF2*, *DSG1*, *CAPN14*, *LRRC32*, and *PTEN* in smaller percentages of patients.[64–68] Previously, genetic variants of *thymic stromal lymphopoietin* (*TSLP*) (and its dysregulated expression)[69] and *filaggrin* (*FLG*)[70] have been linked to other atopic diseases as well. Remarkably, about 75% of EoE patients are male individuals. This could be partially explained by a gene-coding variant located on the X or Y chromosomes, which only in male individuals shows a sex-specific association with the risk for EoE. This variant in the cytokine receptor–like factor 2 (*CRLF2*) gene encodes the receptor for TSLP.[71] An EoE diagnostic gene panel was found to have 96% sensitivity and 98% specificity to distinguish patients with EoE in remission from healthy controls.[72]

## Atopy

About 75% of EoE patients have atopic comorbidities.[14,53,73] In other atopic diseases such as asthma and atopic dermatitis, epithelial barrier dysfunction is thought to contribute to disease pathogenesis.[74] As in asthma and atopic dermatitis, *FLG* is also a susceptibility gene in EoE, which led to the hypothesis that a disrupted epithelial barrier could also play a fundamental role in EoE.[65,70,75]

## Impaired Barrier Function

In patients with GERD, (increased) acid exposure causes an impaired esophageal mucosal barrier function, increased transepithelial permeability to small molecules, and heartburn.[76–79] Similar to GERD, EoE is also characterized by symptoms of dysphagia, heartburn, and acid hypersensitivity.[77,80] These findings led to the hypothesis that similar to its role in GERD, acid reflux might also be (pathologically) present and could disrupt the mucosal barrier in EoE. In theory, exposure to acid reflux could promote the development of EoE by damaging the esophageal epithelium and increasing transepithelial permeability for allergens in the esophagus, or by inducing mast cell degranulation, or by increasing the endothelial expression

**TABLE 1.** Therapeutic Targets and Proven Effects of Available Treatment Modalities for EoE

| Treatment | Target | Relevant Effects in EoE |
|---|---|---|
| Dietary therapies | | |
| Empiric six/four food elimination diet | Empirical food allergen removal | Histologic response relatively good (about 72%)[21,22] |
| Allergy test–based elimination diet | Selective food allergen removal | Histologic response low (about 46%)[21,23] |
| Amino acid diet | Complete food allergen removal | Histologic response high (about 91%), significant decrease of symptoms[21,24] |
| | | Partial restoration of esophageal epithelial barrier defects[25] |
| Medical therapies | | |
| Proton pump inhibitors | Healing esophagitis and restoring mucosal barrier integrity by blocking acid reflux | Histologic response correlates to partial restoration of esophageal epithelial barrier defects[18] |
| | Blocking esophageal epithelial eotaxin-3 release | Histologic response 51%, decrease in symptoms in 61%.[20] |
| Topical corticosteroids | Esophageal inflammation | Histologic response 50%-75%[26–29] |
| Swallowed fluticasone propionate aerosol | Esophageal inflammation | 98% of EoE transcriptome genes normalized when reaching remission |
| | | Histologic response correlates to partial restoration of esophageal epithelial barrier defects[30–33] |
| Oral viscous budesonide | Esophageal inflammation | Significant better effect on eosinophil count than nebulized budesonide due to increased contact time[34] |
| Systemic corticosteroids | Systemic inflammation | Complete histologic remission after 4 wks in 81% of pediatric EoE patients[35] |
| | | More (chance of) side effects than topical corticosteroids[35] |
| Thiopurines (azathioprine, 6-mercaptopurine) | Systemic inflammation (steroid sparing) | Long-term histologic remission in small case series[36] |
| Infliximab | TNF-α (steroid sparing) | No effect on eosinophil count or symptoms[37] |
| Montelukast | Leukotriene receptor on inflammatory cells: eosinophils, mast cells, basophils (steroid sparing) | No maintenance of steroid-induced disease remission[38,39] |


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**TABLE 1.** (*continued*)

| Treatment | Target | Relevant Effects in EoE |
|---|---|---|
| Anti IL-5 (Mepolizumab, Reslizumab) | IL-5 | Significant reduction of eosinophil count but not symptoms[40,41] |
| Anti IL-13 | IL-13 | Improvement of eosinophil count, trend toward decrease of symptoms[42] |
| Anti CRTH2 | CRTH2 on Th2 cells, eosinophils, basophils | Modest improvement of eosinophil count and symptoms[43] |
| Anti IgE (Omalizumab) | IgE | No effect on eosinophil count and symptoms[44] |
| Mechanical therapies | | |
| Esophageal dilation | Esophageal stricture or diffuse narrowing | Relieves dysphagia; no effect on underlying inflammation[45–47] |

CRTH2 indicates chemoattractant receptor-homologous molecule expressed on Th2 cells; EoE, eosinophilic esophagitis; IgE, immunoglobulin E; IL-5, interleukin-5; IL-13, interleukin-13.

of adhesion molecules that are recognized by eosinophils.[81–83] In a study using 24-hour pH impedance monitoring, the amount of gastroesophageal reflux was within normal values in most EoE patients; however, decreased baseline impedance values were found throughout the esophagus of EoE patients, suggesting impairments of the esophageal epithelial barrier.[84]

Shortly thereafter, several studies by different research groups using different techniques found evidence for esophageal epithelial barrier defects in EoE. In children with active EoE, the expression of the intercellular tight junction proteins E-cadherin and claudin-1 was found to be reduced.[85] Sherrill et al[30] demonstrated that downregulation of desmoglein-1 (*DSG1*) by IL-13 impairs the esophageal mucosal barrier integrity and increases inflammation. Desmoglein-1 is an important component of desmosomes, which play a crucial role in maintaining epithelial barrier integrity. Desmoglein-1 downregulation and/or dysfunction has a central role in the pathophysiology of several skin diseases.[86,87] In 2014, 2 studies supporting the hypothesis of a disrupted mucosal barrier in EoE were simultaneously published.[18,31] Using immunohistochemical stainings, Katzka et al[31] showed that in 10 patients with quiescent EoE after treatment with fluticasone propionate, FLG expression—on a protein level—was higher than in 10 untreated patients with active disease. Genetic studies in atopic dermatitis strongly suggest that decreased *FLG* expression impairs skin barrier function.[88] Using several techniques, our group demonstrated that the esophageal mucosal barrier integrity is functionally and structurally impaired in patients with active EoE as well as in patients with active PPI-REE compared with healthy controls.[10] Following treatment with double dose PPI, a decrease in esophageal eosinophilic inflammation in patients with PPI-REE was associated with an increase of *FLG* mRNA expression and partial restoration of the esophageal mucosal integrity, whereas in EoE patients (who did not respond to PPIs) *FLG* mRNA expression was not affected by PPIs, and the mucosal integrity remained impaired.[10] In a subsequent study, topical fluticasone treatment also led to partial restoration of the esophageal mucosal barrier integrity in EoE patients.[32] Interestingly, it has been shown that 2% of the 574 abnormally expressed EoE transcriptome genes are not normalized with adequate therapy, one of them being *DSG1*.[33] Taken all together, these data show that the esophageal mucosal barrier integrity is significantly impaired in patients with active EoE, but also remains slightly impaired in disease remission, suggesting that an underlying barrier defect may propagate the development of EoE. The recent finding of an increased presence of intraepithelial food antigens in the esophagus of active versus inactive EoE as well as healthy controls, further suggests that epithelial barrier dysfunction plays a central role in the pathophysiology of EoE.[89]

## Inflammatory Infiltrate

Eosinophils are pathologically present in the esophagus of patients with EoE, with a threshold of 15 eosinophils per microscopic high-power field as a key criterion for the diagnosis of EoE.[16] Besides eosinophils, other innate immune cells such as mast cells and antigen-presenting cells (dendritic cells and basophils), and adaptive immune cells such as B cells and T cells play a role in the inflammatory response in EoE.[90–97] Interestingly, also, the esophageal epithelial cells themselves may contribute to the inflammatory reaction by acting as nonprofessional antigen-presenting cells or by regulating TSLP expression.[98,99]

### Eosinophils

In western countries, eosinophils mainly have a role in atopic inflammation. Eosinophils express receptors for IgE, complement cytokines and chemokines, and their development is regulated by IL-5.[100] In EoE, they are recruited from the blood into the esophagus by the chemoattractant eotaxin-3.[100] Several studies have shown an increase of esophageal and serum eotaxin-3 levels in EoE, which correlate with esophageal eosinophil and mast cell counts.[18,32,64,101] Eosinophils act via several mechanisms in EoE. They contain the cytotoxic granule proteins' major basic protein, eosinophil peroxidase, and eosinophil cationic protein that are released upon activation and cause damage to the esophageal epithelium.[90] In vitro, major basic protein causes esophageal epithelial cells to secrete fibroblast growth factor 9, leading to basal cell hyperplasia.[102] Eosinophils may also activate mast cells via the production of IL-9.[103] In addition, eosinophils express transforming growth factor-β1 (TGF-β1), which induces fibrosis, a feature more frequently observed with long-standing disease activity.[67,104,105] The severity of epithelial esophageal eosinophilia correlates with epithelial remodeling and fibrosis.[52] Furthermore, eosinophils are thought to be capable of acting as antigen-presenting cells in EoE via the secretion of inflammatory cytokines inducing T cell proliferation, and via the expression of major histocompatibility complex class II proteins.[106]

### Mast Cells

Although the finding of eosinophils in the esophageal mucosa is abnormal, mast cells are physiologically present and located at the basement membrane and the lamina propria. However, in EoE their number is increased, they

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invade the epithelium, and mast cell and eosinophil numbers often correlate.[32,91,96,103,107] Like eosinophils, mast cells express the high affinity IgE receptor (FcεRI). After activation of the FcεRI, mast cells release several cytokines and other mediators, including histamine and TGF-β1, thereby activating eosinophils and inducing fibrosis.[52,96,108] Mast cell numbers are also increased in the esophageal smooth muscle layer, in which they modulate the esophageal contractility.[96] A specific mast cell gene upregulation has been observed in both adult and pediatric EoE, which can be restored with treatment.[91,109]

### T Cells

Mouse studies have established an essential role for T cells in the pathophysiology of EoE.[110] EoE is characterized by a Th2-type inflammatory reaction, and typical Th2 cytokines such as IL-4, IL-5, and IL-13 are increased in EoE.[94] IL-4 causes naive T-helper cells to differentiate into Th2 cells and activates B cell class switching to produce IgE.[111] IL-5 is produced by eosinophils, mast cells, and Th2 cells and promotes eosinophil expansion and survival.[112] Interestingly, IL-5-deficient mice do not develop experimental EoE.[113] In a small randomized trial in adults with EoE, treatment with the anti-IL-5 antibody mepolizumab significantly reduced esophageal eosinophilia and *TGF-β1* expression, although the effects on symptoms were disappointing.[40] IL-13 is overproduced by activated eosinophils and Th2 cells in the esophagus of EoE patients and seems critical for the development of EoE.[33,65,94] IL-13-deficient mice have reduced levels of allergen-induced experimental EoE.[114] IL-13 induces upregulation of *CCL26* (encoding eotaxin-3), which attracts eosinophils, and IL-13 promotes the production of periostin by fibroblasts, leading to increased eosinophil recruitment and remodeling.[50,115] IL-13 also affects the esophageal epithelial barrier integrity as it downregulates the expression of *DSG1*, *FLG*, and *involucrin*, which all play a role in maintaining barrier integrity.[18,30,32] In experimental (mouse) and human EoE, anti-IL-13 treatment caused a significant decrease in esophageal eosinophil numbers, and it restores the expression of *CCL26*, *periostin*, and *DSG1*.[42,116]

### B Cells

The role of B cells in EoE is unclear. However, B cells are thought to produce IgE in EoE, and many EoE patients have abnormal allergen-specific serum IgE.[23] Nevertheless, anti-IgE treatment using omalizumab, indeed, caused IgE depletion but did not affect disease activity in EoE patients.[44]

## Esophageal Motility in EoE

As described above, TGF-β1 production by eosinophils and mast cells causes esophageal remodeling and fibrosis.[96,108] Mast cell numbers are also increased in the esophageal smooth muscle layer and modulate esophageal contractility.[96] It is assumed that symptoms of dysphagia and food impaction in EoE patients are a result of fibrosis and/or disturbed esophageal contractility. Several high-resolution manometry (HRM) studies performed by different research groups have, indeed, shown impaired esophageal motility patterns in a significant proportion of EoE patients (varying between 37% and 76%), mostly weak peristalsis and panesophageal pressurization.[105,117–121] Unfortunately, the HRM abnormalities observed in EoE are nonspecific as they are described to a similar extent in patients with GERD and even healthy controls.[105,117] So far, no clear correlation between HRM abnormalities and the severity of dysphagia or endoscopic signs has been described, and results are contradictory.[118–121] Consequently, HRM studies currently have no role in the diagnosis or follow-up of EoE.

A more promising technique may be the use of a functional lumen-imaging probe to approximate the intraluminal esophageal anatomy during volumetric distention. The functional lumen-imaging probe probe can detect esophageal narrowing and localized strictures in patients with EoE.[122] It has been shown that the esophageal distensibility is significantly reduced in EoE patients.[122] Later, it was shown that a reduced esophageal distensibility predicts the severity of esophageal endoscopic rings as well as the risk for food impaction in patients with EoE.[123,124]

# TREATMENT MODALITIES BASED ON DISEASE PATHOPHYSIOLOGY

## Removing the Trigger: Dietary Therapy

Food allergen elimination is perhaps the most logical treatment option, as EoE is a food allergen-driven disease. Dietary therapies are generally very effective and can be divided into 3 different types of approaches (Table 1). First, elemental diets with an amino acid–based formula show good results with regard to histologic remission in both children[125,126] and adults,[24,127] but have the problem of low palatability. Second, empirical 6 or 4 food elimination diets, in which the most common food triggers are removed, are also reasonably effective in achieving histologic remission and have been shown to decrease mast cells as well.[22,107,128–130] Third, allergy test–based elimination diets have shown disappointing results, perhaps because observed sensitizations are not relevant for EoE and/or because the causative food triggers are not identified by these tests.[23,58,131] In a meta-analysis investigating dietary therapies in patients with EoE, the efficacy rates of elemental diets, empirical elimination diets, and test-based elimination diets for inducing histologic remission were estimated at 91%, 72%, and 46%, respectively.[21] Dietary therapy can also reverse epithelial barrier integrity defects[25] and esophageal subepithelial fibrosis.[132,133]

## Medical Therapies

### PPIs

Until relatively recently, PPI treatment in patients with suspected EoE was used to distinguish patients with GERD (responding to a PPI) from those with EoE (not responding), as the effects of PPIs in GERD were long assumed to result from blocking gastric acid secretion only.[2,14] Indeed, PPIs are effective in healing esophagitis and thereby restoring the epithelial barrier integrity in patients with GERD, and perhaps this is also the mechanism by which disease activity is reduced in patients with EoE.[18,134,135] However, in vitro and clinical studies have shown that omeprazole also exhibits acid-independent anti-inflammatory effects in patients with GERD as well as patients with EoE.[136–140] PPIs can reduce the esophageal expression of eotaxin-3 and Th2-cytokines in patients with suspected EoE.[18,139–141] PPIs are also capable of restoring the esophageal epithelial barrier integrity and improving the expression of *DSG1* and *FLG*.[18,139] All of these findings could explain the observations of several research groups


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that PPIs induce disease remission in patients with suspected EoE.[17,18,142–144] These patients responding to PPI have since been classified as having PPI-REE, although they have appeared to be clinically, histologically, and immunologically indistinguishable from patients with EoE.[140,145–148] In 2 randomized controlled trials comparing PPI treatment with topical steroids in patients with suspected EoE, PPIs had a similar efficacy (33%) as topical steroids.[143,144] According to a recent systematic review and meta-analysis pooling data from 619 patients in 33 studies, PPIs result in histologic remission (< 15 eosinophils per microscopic high-power field) in 51% and a decrease in symptoms in 61% of patients with suspected EoE.[20] In a multicenter follow-up study, a sustained histologic response to PPI treatment after 1 year was found in 55 of 75 (73%) patients with initial response to a PPI.[149] As a result of increasing evidence of their efficacy, PPIs were recently recommended as a first step in the treatment of all patients with suspected EoE.[16,19]

### Topical Corticosteroids

Topical corticosteroids are the best documented treatment for EoE, and their efficacy in reducing esophageal eosinophil counts has been shown in several randomized trials[34,150–155] and meta-analyses.[26–29] However, as none of these drugs is formally approved for EoE treatment by the European Medicines Agency or Food & Drug Administration, these preparations are still prescribed off-label for EoE. The suboptimal histologic response rates of 50% to 75% in randomized clinical trials might be partly explained by the fact that these medications are actually asthma medications and developed as topical treatments in the smaller airways, and not designed for esophageal deposition. The significance of optimizing esophageal deposition was emphasized by a randomized trial comparing oral viscous budesonide and swallowed nebulized budesonide, in which increased esophageal contact time was associated with improved histologic response.[34] In both pediatric and adult EoE, a decrease in epithelial eosinophil counts after topical budesonide treatment has been shown to correlate with reduced esophageal remodeling and fibrosis.[67,152,156] Topical corticosteroids may be less effective than oral prednisone, however, with a lower risk of developing potentially severe side effects.[35]

### Other Therapies

For patients with a more severe disease phenotype, the use of systemic steroids and eventually steroid-sparing therapies such as thiopurines and anti-TNF-α could be considered, although data supporting these therapies are limited.[35–37] Montelukast, a leukotriene inhibitor, has been evaluated as a long-term steroid-sparing therapy after steroid-induced remission, but most patients had a relapse during therapy.[38,39]

## Dilation

In EoE patients with severe esophageal stenosis, endoscopic esophageal dilation can be a useful and relatively safe means to relieve troublesome dysphagia and prevent food bolus impaction by increasing the esophageal diameter.[45–47] The main disadvantages are that dilation has no effect in patients with mild stenosis and that it does not treat the underlying inflammation.[157]

### Targeted Therapies

Over the past decade, the evolving insights into the genetic profiles and the cytokines driving EoE have led to the development of targeted therapies.

In 2 randomized trials, anti-IL-5 treatment (mepolizumab in adults and reslizumab in children and adolescents) significantly reduced esophageal eosinophil counts but not symptoms and mast cell numbers.[41,46] In contrast, in a retrospective study in pediatric EoE, response to IL-5 therapy was associated with a decline in epithelial mast cell numbers.[103]

In moderate-to-severe asthma, anti-IL-13 treatment (using Lebrikizumab) reduces exacerbations and improves lung function.[158] IL-13 has also been targeted in a mouse model of EoE. In mice treated with anti-IL-13, the esophageal eosinophil count decreased significantly.[116] In human EoE, a small double-blind, randomized trial showed improvement of esophageal eosinophil counts and a trend for improved symptoms following treatment with an anti-IL-13 antibody.[42]

Th2 cells (but also other inflammatory cells) express the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), which is an attractive treatment target in allergic disorders.[159,160] In asthma patients, the expression of CRTH2 on blood T cells was demonstrated to be significantly increased on a subgroup of IL-4/IL-13-positive T cells compared with interferon-γ-positive T cells.[161] Given the Th2-nature of EoE, it was hypothesized that anti-CRTH2 could reduce eosinophil counts in EoE. In a small randomized trial among 26 patients with steroid-dependent or steroid-resistent EoE, anti-CRTH2 treatment resulted in a significant, although modest, decrease of eosinophilic inflammation and symptoms.[43]

Given the increased presence of specific IgE against food and inhaled allergens in EoE, IgE seems an obvious therapeutic target.[53–55] However, in a randomized, double-blind, placebo-controlled trial in adults with EoE, an anti-IgE antibody (Omalizumab) did not reduce esophageal eosinophil counts and symptoms compared with placebo.[44]

### Future Therapies?

In a mouse model of EoE, the development of eosinophilic inflammation was dependent upon TSLP. In these mice, the development of EoE could be prevented by TSLP-blockade, using monoclonal antibodies.[93] Anti-TSLP antibodies have not been studied in human EoE yet. Sucralfate is used in acid-peptic diseases in order to heal esophageal mucosal ulceration. The effect of sucralfate on disease activity and various markers of the esophageal epithelial barrier is currently studied in EoE (NCT02353078, www.clinicaltrials.gov). The efficacy of dupilumab is currently being investigated in a randomized controlled trial in adult patients with EoE (NCT02379052, www.clinicaltrials.gov). Dupilumab is a fully human monoclonal antibody to the IL-4 receptor α subunit that inhibits both IL-4 and IL-13 signaling. In a randomized trial in patients with moderate-to-severe asthma and elevated eosinophil levels, fewer asthma exacerbations, improved lung function, and reduced levels of Th2-inflammatory markers were seen following dupliumab treatment.[162] A mast cell stabilizer, cromolyn sodium, is also being investigated (NCT02371941, www.clinicaltrials.gov). Currently, the histologic and symptomatic efficacy and safety of losartan (an angiotensin II receptor antagonist) is studied in EoE patients (NCT01808196, www.clinicaltrials.gov).

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In other diseases such as hypertension and the Marfan syndrome, Losartan seems capable of reducing TGFβ levels and may thus prevent esophageal remodeling.[163,164]

## SUMMARY

EoE is a food-allergen driven, chronic inflammatory esophageal disease that causes remodeling and fibrosis, which leads to troublesome symptoms and requires long-term therapy. Certain aspects of EoE (genetics, epithelial barrier dysfunction, inflammatory response, sensitization patterns) closely resemble the pathophysiology of other atopic diseases such as atopic dermatitis and asthma. Although insights into the pathophysiology have evolved over the past decade, most treatment options are still not designed for esophageal administration and have suboptimal efficacy. A potentially steroid-sparing approach could be to start treatment with a PPI trial in virtually all patients with suspected EoE with the aim to reduce disease activity and symptoms. For cases not responding to a PPI, the subsequent use of dietary and/or topical steroid therapy may be considered, as these treatments have been best investigated and have proven efficacy. Targeted therapies may become promising treatment options in the (near) future.

## REFERENCES


1. Attwood SEA, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia—a distinct clinicopathologic syndrome. *Dig Dis Sci*. 1993;38:109–116.
2. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology*. 2007;133:1342–1363.
3. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology*. 2003;125:1660–1669.
4. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child*. 2006;91:1000–1004.
5. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol*. 2009;7:1055–1061.
6. DeBrosse CW, Collins MH, Buckmeier Butz BK, et al. Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia, 1982-1999. *J Allergy Clin Immunol*. 2010;126:112–119.
7. Hruz P, Straumann A, Bussmann C, et al. 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.
8. Van Rhijn BD, Verheij J, Smout AJPM, et al. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil*. 2013;25:47–52.
9. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. *Clin Gastroenterol Hepatol*. 2014;12:589–596.
10. 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;41:662–670.
11. Arias Á, Pérez-Martínez I, Tenías JM, et al. 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.
12. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut*. 2013;62:489–495.
13. Van Rhijn BD, Verheij J, Smouta JPM, et al. The endoscopic reference score shows modest accuracy to predict histologic remission in adult patients with eosinophilic esophagitis. *Neurogastroenterol Motil*. 2016;28:1714–1722.
14. 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.
15. Papadopoulou A, Koletzko S, Heuschkel R, et al. Management guidelines of eosinophilic esophagitis in childhood. *J Pediatr Gastroenterol Nutr*. 2014;58:107–118.
16. Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J*. 2017;5:335–358.
17. 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;9:110–117.
18. 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;12:1815–1823.
19. Molina-Infante J, Bredenoord AJ, Cheng E, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut*. 2016;65:521–531.
20. Lucendo AJ, Arias Á, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14:13–22.
21. Arias Á, González-Cervera J, Tenias JM, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146:1639–1648.
22. Molina-Infante J, Arias A, Barrio J, et al. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. *J Allergy Clin Immunol*. 2014;134:1093–1099.
23. Van Rhijn BD, Vlieg-Boerstra BJ, Versteeg SA, et al. Evaluation of allergen-microarray-guided dietary intervention as treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2015;136:1095–1097.
24. Warners MJ, Vlieg-Boerstra BJ, Verheij J, et al. Elemental diet decreases inflammation and improves symptoms in adult eosinophilic oesophagitis patients. *Aliment Pharmacol Ther*. 2017;45:777–787.
25. Warners MJ, Vlieg-Boerstra BJ, Verheij J, et al. Esophageal and small intestinal mucosal integrity in eosinophilic esophagitis and response to an elemental diet. *Am J Gastroenterol*. 2017. [Epub ahead of print]. Doi:10.1038/ajg.2017.107.
26. Sawas T, Dhalla S, Sayyar M, et al. Systematic review with meta-analysis: pharmacological interventions for eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2015;41:797–806.
27. Tan ND, Xiao YL, Chen MH. Steroids therapy for eosinophilic esophagitis: systematic review and meta-analysis. *J Dig Dis*. 2015;16:431–442.
28. Chuang M-YA, Chinnaratha MA, Hancock DG, et al. Topical steroid therapy for the treatment of eosinophilic esophagitis (EoE): a systematic review and meta-analysis. *Clin Transl Gastroenterol*. 2015;6:e82.
29. Murali AR, Gupta A, Attar BM, et al. Topical steroids in eosinophilic esophagitis: systematic review and meta-analysis of placebo-controlled randomized clinical trials. *J Gastroenterol Hepatol*. 2016;31:1111–1119.
30. Sherrill JD, Kc K, Wu D, et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. *Mucosal Immunol*. 2014;7:718–729.



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This paper can be cited using the date of access and the unique DOI number which can be found in the footnotes.

31. Katzka DA, Tadi R, Smyrk TC, et al. Effects of topical steroids on tight junction proteins and spongiosis in esophageal epithelia of patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2014;12:1824–1829.
32. 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;110:1289–1297.
33. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol*. 2007;120:1292–1300.
34. Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology*. 2012;143:321–324.
35. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol*. 2008;6:165–173.
36. Netzer P, Gschossmann JM, Straumann A, et al. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol*. 2007;19:865–869.
37. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol*. 2008;122:425–427.
38. 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;56:3551–3558.
39. Alexander JA, Ravi K, Enders FT, et al. Montelukast does not maintain symptom remission after topical steroid therapy for eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2017;15:214–221.
40. 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.
41. 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;129:456–463.
42. 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;135:500–507.
43. Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy Eur J Allergy Clin Immunol*. 2013;68:375–385.
44. Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology*. 2014;147:602–609.
45. Dellon ES, Gibbs WB, Rubinas TC, et al. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. *Gastrointest Endosc*. 2010;71:706–712.
46. 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;105:1062–1070.
47. Dougherty M, Runge TM, Eluri S, et al. Esophageal dilation with either bougie or balloon technique as a treatment for eosinophilic esophagitis: a systematic review and meta-analysis. *Gastrointest Endosc*. 2017. [Epub ahead of print]. Doi:10.1016/j.gie.2017.04.028.
48. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology*. 2009;137:1238–1249.
49. 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;46:1049–1055.
50. Zuo L, Fulkerson PC, Finkelman FD, et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R alpha 2-inhibited pathway. *J Immunol*. 2010;185:660–669.
51. Dellon ES, Kim HP, Sperry SLW, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc*. 2014;79:577–585.
52. Rajan J, Newbury RO, Anilkumar A, et al. Long-term assessment of esophageal remodeling in patients with pediatric eosinophilic esophagitis treated with topical corticosteroids. *J Allergy Clin Immunol*. 2016;137:147–156.
53. Van Rhijn BD, Van Ree R, Versteeg SA, et al. Birch pollen sensitization with cross-reactivity to food allergens predominates in adults with eosinophilic esophagitis. *Allergy Eur J Allergy Clin Immunol*. 2013;68:1475–1481.
54. Simon D, Straumann A, Dahinden C, et al. Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis. *Allergy Eur J Allergy Clin Immunol*. 2013;68:945–948.
55. Erwin EA, James HR, Gutekunst HM, et al. Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2010;104:496–502.
56. Sugnanam KKN, Collins JT, Smith PK, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy Eur J Allergy Clin Immunol*. 2007;62:1257–1260.
57. Rodríguez-Sánchez J, Gõmez Torrijos E, Lõpez Viedma B, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. *Allergy Eur J Allergy Clin Immunol*. 2014;69:936–942.
58. Molina-Infante J, Martin-Noguerol E, Alvarado-Arenas M, et al. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. *J Allergy Clin Immunol*. 2012;130:1200–1202.
59. Wolf WA, Jerath MR, Sperry SLW, et al. Dietary elimination therapy is an effective option for adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2014;12:1272–1279.
60. Wright BL, Kulis M, Guo R, et al. Food-specific IgG4 is associated with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2016;138:1190–1192.
61. Simon D, Cianferoni A, Spergel JM, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy Eur J Allergy Clin Immunol*. 2016;71:611–620.
62. 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.
63. Malerba G, Lauciello MC, Scherpbier T, et al. Linkage analysis of chromosome 12 markers in Italian families with atopic asthmatic children. *Am J Respir Crit Care Med*. 2000;162:1587–1590.
64. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest*. 2006;116:536–547.
65. Blanchard C, Stucke EM, Burwinkel K, et al. Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. *J Immunol*. 2010;184:4033–4041.
66. Rothenberg ME, Spergel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet*. 2010;42:289–291.
67. Aceves SS, Newbury RO, Chen D, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy Eur J Allergy Clin Immunol*. 2010;65:109–116.
68. Sherrill JD, Gao PS, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with


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eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010;126: 160–165.
69. Ziegler SF. The role of thymic stromal lymphopoietin (TSLP) in allergic disorders. *Curr Opin Immunol*. 2010;22:795–799.
70. Rodríguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: Robust risk factors in atopic disease. *J Allergy Clin Immunol*. 2009; 123:1361–1370.
71. Sherrill JD, Rothenberg ME. Genetic dissection of eosinophilic esophagitis provides insight into disease pathogenesis and treatment strategies. *J Allergy Clin Immunol*. 2011;128:23–32.
72. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. *Gastroenterology*. 2013;145:1289–1299.
73. Mohammad AA, Wu SZ, Ibrahim O, et al. Prevalence of atopic comorbidities in eosinophilic esophagitis: a case-control study of 449 patients. *J Am Acad Dermatol*. 2017;76: 559–560.
74. Holgate ST. The epithelium takes centre stage in asthma and atopic dermatitis. *Trends Immunol*. 2007;28:248–251.
75. Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. *Nat Rev Immunol*. 2004;4: 978–988.
76. Tobey NA, Carson JL, Alkiek RA, et al. Dilated intercellular spaces: a morphological feature of acid reflux—damaged human esophageal epithelium. *Gastroenterology*. 1996;111: 1200–1205.
77. Weijenborg PW, Smout AJPM, Verseijden C, et al. Hypersensitivity to acid is associated with impaired esophageal mucosal integrity in patients with gastroesophageal reflux disease with and without esophagitis. *Am J Physiol Gastrointest Liver Physiol*. 2014;307:323–329.
78. Woodland P, Sifrim D. Esophageal mucosal integrity in nonerosive reflux disease. *J Clin Gastroenterol*. 2014;48: 6–12.
79. Bredenoord AJ, Hemmink GJM, Smout AJPM. Relationship between gastro-oesophageal reflux pattern and severity of mucosal damage. *Neurogastroenterol Motil*. 2009;21: 807–812.
80. Krarup AL, Villadsen GE, Mejlgaard E, et al. Acid hypersensitivity in patients with eosinophilic oesophagitis. *Scand J Gastroenterol*. 2010;45:273–281.
81. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol*. 2007;102: 1301–1306.
82. Hirano I. Eosinophilic esophagitis and gastroesophageal reflux disease: there and back again. *Clin Gastroenterol Hepatol*. 2011;9:99–101.
83. Molina-Infante J, Van Rhijn BD. Interactions between gastro-oesophageal reflux disease and eosinophilic oesophagitis. *Best Pract Res Clin Gastroenterol*. 2015;29:749–758.
84. Van Rhijn BD, Kessing BF, Smout AJ, et al. Oesophageal baseline impedance values are decreased in patients with eosinophilic oesophagitis. *United European Gastroenterol J*. 2013;1:242–248.
85. Abdulnour-Nakhoul SM, Al-Tawil Y, Gyftopoulos AA, et al. Alterations in junctional proteins, inflammatory mediators and extracellular matrix molecules in eosinophilic esophagitis. *Clin Immunol*. 2013;148:265–278.
86. Aalfs AS, Oktarina DAM, Diercks GFH, et al. Staphylococcal scalded skin syndrome: loss of desmoglein 1 in patient skin. *Eur J Dermatology*. 2010;20:451–456.
87. Samuelov L, Sarig O, Harmon RM, et al. Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat Genet*. 2013;45:1244–1248.
88. Sandilands A, Sutherland C, Irvine AD, et al. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci*. 2009;122:1285–1294.
89. Marietta EV, Geno DM, Smyrk TC, et al. Presence of intraepithelial food antigen in patients with active eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2016;45:427–433.
90. Mueller S, Aigner T, Neureiter D, et al. Eosinophil infiltration and degranulation in oesophageal mucosa from adult patients with eosinophilic oesophagitis: a retrospective and comparative study on pathological biopsy. *J Clin Pathol*. 2006;59:1175–1180.
91. Abonia JP, Blanchard C, Butz BB, et al. Involvement of mast cells in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010;126:140–149.
92. Vicario M, Blanchard C, Stringer KF, et al. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut*. 2010;59:12–20.
93. Noti M, Wojno EDT, Kim BS, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med*. 2013;19:1005–1013.
94. Straumann A, Bauer M, Fischer B, et al. Idiopathic eosinophilic esophagitis is associated with a TH2-type allergic inflammatory response. *J Allergy Clin Immunol*. 2001;108: 954–961.
95. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology*. 2002; 122:1216–1225.
96. Aceves SS, Chen D, Newbury RO, et al. 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: 1198–1204.
97. Iwakura N, Fujiwara Y, Tanaka F, et al. Basophil infiltration in eosinophilic oesophagitis and proton pump inhibitor-responsive oesophageal eosinophilia. *Aliment Pharmacol Ther*. 2015;41:776–784.
98. Mulder DJ, Pooni A, Mak N, et al. Antigen presentation and MHC class II expression by human esophageal epithelial cells: role in eosinophilic esophagitis. *Am J Pathol*. 2011;178: 744–753.
99. Chandramouleeswaran PM, Shen D, Lee AJ, et al. Preferential secretion of thymic stromal lymphopoietin (TSLP) by terminally differentiated esophageal epithelial cells: relevance to eosinophilic esophagitis (EoE). *PLoS One*. 2016;11: e0150968.
100. Blanchard C, Rothenberg ME. Chapter 3 biology of the eosinophil. *Adv Immunol*. 2009;101:81–121.
101. Konikoff MR, Blanchard C, Kirby C, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006;4:1328–1336.
102. Mulder DJ, Pacheco I, Hurlbut DJ, et al. FGF9-induced proliferative response to eosinophilic inflammation in oesophagitis. *Gut*. 2009;58:166–173.
103. Otani IM, Anilkumar AA, Newbury RO, et al. Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2013;131:1576–1582.
104. 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;145:1230–1236.
105. Van Rhijn BD, Oors JM, Smout AJPM, et al. Prevalence of esophageal motility abnormalities increases with longer disease duration in adult patients with eosinophilic esophagitis. *Neurogastroenterol Motil*. 2014;26:1349–1355.
106. Le-Carlson M, Seki S, Abarbanel D, et al. Markers of antigen presentation and activation on eosinophils and T cells in the esophageal tissue of patients with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2013;56:257–262.
107. Arias A, Lucendo AJ, Martínez-Fernández P, et al. Dietary treatment modulates mast cell phenotype, density, and activity in adult eosinophilic oesophagitis. *Clin Exp Allergy*. 2016;46:78–91.
108. Chehade M, Sampson HA, Morotti RA, et al. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2007;45:319–328.


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109. Hsu Blatman KS, Gonsalves N, Hirano I, et al. Expression of mast cell associated genes is upregulated in adult eosinophilic esophagitis and responds to steroid or dietary therapy. *J Allergy Clin Immunol*. 2017;127:1307–1308.
110. Mishra A, Schlotman J, Wang M, et al. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. *J Leukoc Biol*. 2007;81:916–924.
111. Kelly-Welch AE, Hanson EM, Boothby MR, et al. Interleukin-4 and interleukin-13 signaling connections maps. *Science*. 2003;300:1527–1528.
112. Davis BP, Rothenberg ME. Mechanisms of disease of eosinophilic esophagitis. *Annu Rev Pathol*. 2016;11:365–393.
113. Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology*. 2003;125:1419–1427.
114. Akei HS, Mishra A, Blanchard C, et al. Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. *Gastroenterology*. 2005;129:985–994.
115. Blanchard C, Mingler MK, McBride M, et al. Periostin facilitates eosinophil tissue infiltration in allergic lung and esophageal responses. *Mucosal Immunol*. 2008;1:289–296.
116. Blanchard C, Mishra A, Saito-Akei H, et al. Inhibition of human interleukin-13-induced respiratory and oesophageal inflammation by anti-human-interleukin-13 antibody (CAT-354). *Clin Exp Allergy*. 2005;35:1096–1103.
117. Roman S, Hirano I, Kwiatek MA, et al. Manometric features of eosinophilic esophagitis in esophageal pressure topography. *Neurogastroenterol Motil*. 2011;23:208–215.
118. Martín Martín L, Santander C, Lopez Martín MC, et al. Esophageal motor abnormalities in eosinophilic esophagitis identified by high-resolution manometry. *J Gastroenterol Hepatol*. 2011;26:1447–1450.
119. Nennstiel S, Bajbouj M, Becker V, et al. High-resolution manometry in patients with eosinophilic esophagitis under topical steroid therapy-a prospective observational study (HIMEOS-study). *Neurogastroenterol Motil*. 2016;28: 599–607.
120. Colizzo JM, Clayton SB, Richter JE. Intrabolus pressure on high-resolution manometry distinguishes fibrostenotic and inflammatory phenotypes of eosinophilic esophagitis. *Dis Esophagus*. 2016;29:551–557.
121. Von Arnim U, Kandulski A, Weigt J, et al. Correlation of high-resolution manometric findings with symptoms of dysphagia and endoscopic features in adults with eosinophilic esophagitis. *Dig Dis*. 2017. [Epub ahead of print]. Doi:10.1159/000458407.
122. Kwiatek MA, Hirano I, Kahrilas PJ, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology*. 2011;140:82–90.
123. 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.
124. 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.
125. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: Improvement with an amino acid-based formula. *Gastroenterology*. 1995;109:1503–1512.
126. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol*. 2003;98:777–782.
127. Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol*. 2013;108:759–766.
128. 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: 1097–1102.
129. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology*. 2012;142:1451–1459.
130. Lucendo AJ, Arias Á, 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.
131. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol*. 2005;95:336–343.
132. Lieberman JA, Morotti RA, Konstantinou GN, et al. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy Eur J Allergy Clin Immunol*. 2012;67:1299–1307.
133. Abu-Sultaneh SMA, Durst P, Maynard V, et al. Fluticasone and food allergen elimination reverse sub-epithelial fibrosis in children with eosinophilic esophagitis. *Dig Dis Sci*. 2011; 56:97–102.
134. Boeckxstaens G, El-Serag HB, Smout AJPM, et al. Symptomatic reflux disease: the present, the past and the future. *Gut*. 2014;63:1185–1193.
135. Kessing BF, Bredenoord AJ, Weijenborg PW, et al. Esophageal acid exposure decreases intraluminal baseline impedance levels. *Am J Gastroenterol*. 2011;106:2093–2097.
136. 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: 824–832.
137. 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.
138. Huo X, Zhang X, Yu C, et al. In oesophageal squamous cells exposed to acidic bile salt medium, omeprazole inhibits IL-8 expression through effects on nuclear factor-κB and activator protein-1. *Gut*. 2014;63:1042–1052.
139. Wen T, Dellon ES, Moawad FJ, et al. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol*. 2015;135:187–197.
140. Molina-Infante J, Rivas MD, Hernandez-Alonso M, et al. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. *Aliment Pharmacol Ther*. 2014;40: 955–965.
141. Park JY, Zhang X, Nguyen N, et al. Proton pump inhibitors decrease eotaxin-3 expression in the proximal esophagus of children with esophageal eosinophilia. *PLoS One*. 2014; 9:e101391.
142. Dranove JE, Horn DS, Davis MA, et al. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *J Pediatr*. 2009; 154:96–100.
143. Peterson KA, Thomas KL, Hilden K, et al. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig Dis Sci*. 2010;55:1313–1319.
144. Moawad FJ, Veerappan GR, Dias JA, et al. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol*. 2013;108:366–372.
145. Warners MJ, van Rhijn BD, Curvers WL, et al. PPI-responsive esophageal eosinophilia cannot be distinguished from eosinophilic esophagitis by endoscopic signs. *Eur J Gastroenterol Hepatol*. 2015;27:506–511.
146. Moawad FJ, Schoepfer AM, Safroneeva E, et al. Eosinophilic oesophagitis and proton pump inhibitor-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. *Aliment Pharmacol Ther*. 2014;39: 603–608.
147. Jiao D, Ishimura N, Maruyama R, et al. Similarities and differences among eosinophilic esophagitis, proton-pump inhibitor-responsive esophageal eosinophilia, and reflux esophagitis:


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comparisons of clinical, endoscopic, and histopathological findings in Japanese patients. *J Gastroenterol*. 2017;52:203–210.
148. Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. *Am J Gastroenterol*. 2013;108:1854–1860.
149. Molina-Infante J, Rodriguez-Sanchez J, Martinek J, et al. Long-term loss of response in proton pump inhibitor-responsive esophageal eosinophilia is uncommon and influenced by CYP2C19 genotype and rhinoconjunctivitis. *Am J Gastroenterol*. 2015;110:1567–1575.
150. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology*. 2006;131:1381–1391.
151. 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.
152. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology*. 2010;139:1526–1537.
153. 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.
154. Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. *Gastroenterology*. 2014;147:324–333.
155. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology*. 2010;139:418–429.
156. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2011;9:400–409.
157. Kavitt RT, Ates F, Slaughter JC, et al. Randomized controlled trial comparing esophageal dilation to no dilation among adults with esophageal eosinophilia and dysphagia. *Dis Esophagus*. 2016;29:983–991.
158. Hanania N, Noonan M, Corren J, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax*. 2015;70:748–756.
159. He R, Oyoshi MK, Wang JYT, et al. The prostaglandin D2 receptor CRTH2 is important for allergic skin inflammation after epicutaneous antigen challenge. *J Allergy Clin Immunol*. 2010;126:784–790.
160. Barnes N, Pavord I, Chuchalin A, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. *Clin Exp Allergy*. 2012;42:38–48.
161. Mutalithas K, Guillen C, Day C, et al. CRTH2 expression on T cells in asthma. *Clin Exp Immunol*. 2010;161:34–40.
162. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368:2455–2466.
163. Gómez-Garre D, Martín-Ventura JL, Granados R, et al. Losartan improves resistance artery lesions and prevents CTGF and TGF-β production in mild hypertensive patients. *Kidney Int*. 2006;69:1237–1244.
164. Bolar N, Van Laer L, Loeys BL. Marfan syndrome: from gene to therapy. *Curr Opin Pediatr*. 2012;24:498–504.


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