



# The Spectrum of Eosinophilic Esophagitis

# 7

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## Abbreviations

EGD	Esophagogastroduodenoscopy
EndoFLIP	Functional luminal imaging probe
EoE	Eosinophilic esophagitis
EOE-HSS	Eosinophilic esophagitis-specific histological score system
EREFS	Eosinophilic Esophagitis Endoscopic Reference Score
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
PPI	Proton pump inhibitor
QoL	Quality of life
TGF- $\beta$ 1	Transcription growth factor- $\beta$ 1
TH2 T cells	Type 2 helper T cells

## Objectives

1. Review the epidemiology and pathophysiology of eosinophilic esophagitis
2. Assess how a diagnosis of eosinophilic esophagitis is made
3. Differentiate treatment options for the disease
4. Identify emerging directions for eosinophilic esophagitis

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## Definition, Epidemiology, and Incidence/Prevalence

Eosinophilic esophagitis (EoE) was recognized in the early 1990s when several case series reported an esophageal disease of atopic individuals that lacked response to reflux management and had higher association with stricture formation than gastroesophageal reflux disease (GERD). It is a disorder in which the esophageal mucosa is characterized by marked eosinophilia leading to inflammatory type symptoms in children and inflammation as well as fibrosis-induced esophageal symptoms, mainly dysphagia, in adults.

It has since been termed an allergic esophagitis as it is associated with a unique esophageal transcriptome—thought to be induced by food and possibly environmental triggers.

Since discovery, interest and research in EoE have evolved. The first international consensus guidelines were published in 2007 and have since been updated multiple times. The first ICD-9 classification came in 2008. Overall, this disease has a history spanning 25 years and shows continual advancement in knowledge of pathogenesis and treatment of the disorder still today.

EoE is a growing health problem causing a significant burden for healthcare systems. The disease is now a leading cause of esophageal morbidity with estimated annual healthcare cost up to \$1.4 billion in the USA. This appears to be a biologic increase in addition to enhanced diagnosis through awareness and endoscopy. EoE has become the most frequent cause of esophageal food bolus impaction (46–63%), and estimates of up to 25% of patients undergoing esophagogastroduodenoscopy (EGD) for symptoms of dysphagia will have EoE. As EoE is an allergic and esophageal disease of both children and adults, it is managed by gastroenterologists, allergists, pediatricians, and internal medicine providers. As a result, these specialties should be aware of the disease to optimize timely and accurate diagnosis. A protracted diagnostic delay following symptom onset correlates with advanced esophageal stricture formation.

The incidence of EoE is increasing with some studies showing up to 10/100,000 in adults. Prevalence can vary widely in population studies with estimates of the US population ranging from 26 to 90/100,000 individuals depending on recognition and coding. The disease is more common in Caucasians, but can affect all races. A 2016 study assessing over 7000 US patients with EoE found 89.3% were Caucasian, 5.6% were Asian, and 6.1% were African American. Interestingly, there may be some differences in EoE based on race as racial minorities are less likely to have typical endoscopic findings or strictures. This disease also affects men 2–3 times more often than women, which may be explained by a protective effect from estrogen. EoE can occur in all ages, but the majority of patients are under 50 and it has a peak prevalence in 35–39-year-old men. EoE is considered a chronic disease that relapses with treatment cessation. There is no evidence to suggest spontaneous remission or lack of progression. Natural history studies suggest the longer the disease is left untreated, the greater the likelihood that a patient will develop esophageal strictures. Additional evidence for this comes from therapy withdrawal, leading to histologic and symptomatic recurrence. There is evidence that those with longer duration of symptoms preceding diagnosis have increased psychiatric comorbidities of anxiety and depression, and risk of food impaction increases.

## Pathophysiology/Mechanism

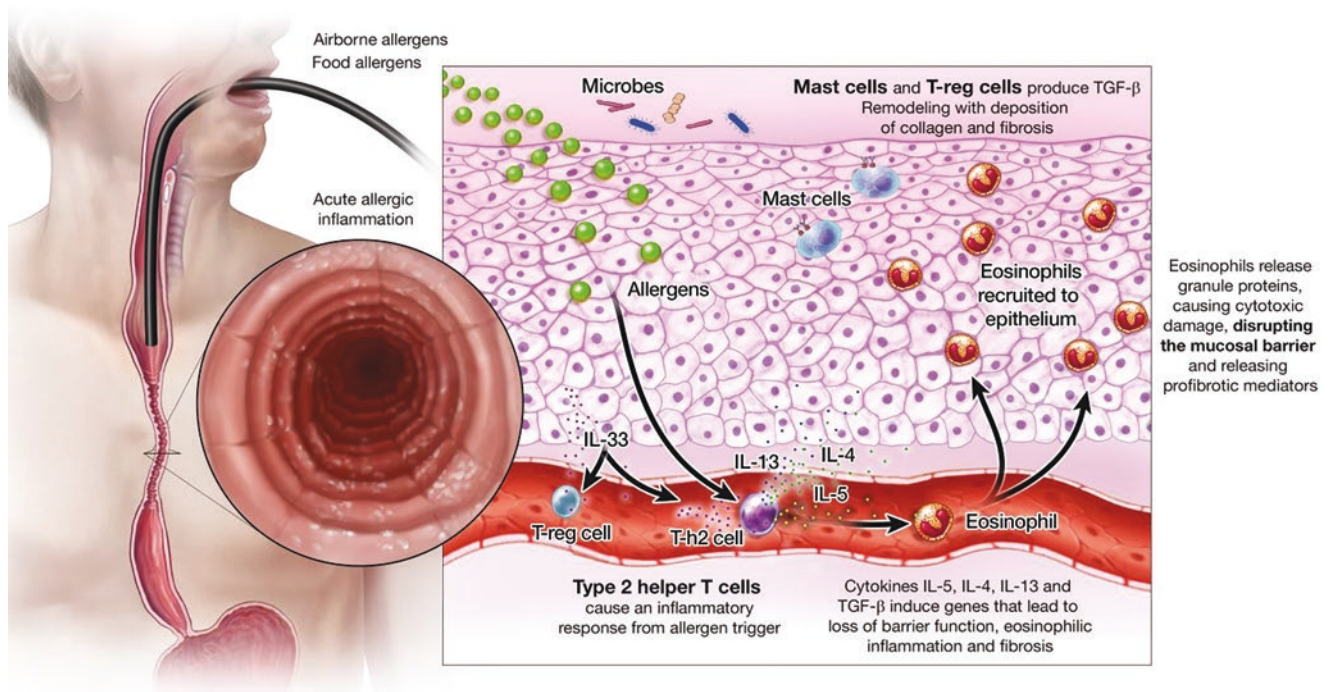
EoE is an aberrant antigenic or immune response where allergens trigger a type 2 helper T cell delayed hypersensitivity reaction to food allergens. While type 2 helper T cells (TH2 T cells) hold a critical role in disease development, there are multiple other cytokines, mediators, and cells involved in the disease development and ultimate sequela of fibrotic remodeling. TH2 T cells are likely induced by thymic stromal lymphopoietin (TSLP) which is released by epithelial cells. This promotion of TH2 T cells leads to stimulation of certain cytokines such as IL-13, IL-4, and IL-5 which induce and upregulate genes. These genes then alter esophageal epithelial barrier function. Lack of invariant natural killer T cells and increase in mucosal mast cells occur. Overall a milieu of cells and mediators create the environment that perpetuates inflammation, with eosinophils releasing granule proteins causing cytotoxic damage, disrupting the mucosal barrier, and leading to profibrotic mediations. Mast cells produce transcription growth factor- $\beta$ 1 (TGF- $\beta$ 1) leading to collagen deposition and increase in smooth muscle mass. Ultimately remodeling of the esopha-

gus occurs leading to narrowing, decreased compliance, and risk of food bolus impaction.

Patients with EoE express a unique esophageal transcriptome, and this with interplay of environmental factors leads to development of the disease. Altered germ line genetic loci have been identified leading to disease susceptibility including TSLP, calpain-14 (CAPN14), EMSY, LRRC32, STAT6, and ANKRD27. The strongly associated EoE gene, CCL26, has also been identified, which encodes eotaxin-3 which is induced via IL-13. Together these genes support a cellular environment that leads to squamous epithelial cell dysfunction and barrier breakdown. However, this alone does not cause the disease, as epigenetic factors are likely involved as demonstrated in family studies.

There is a strong link between atopic disorders and EoE. EoE patients have higher rates of extraesophageal atopic diseases including asthma, airway hyperresponsiveness, allergic rhinoconjunctivitis, eczema, and IgE-mediated food allergies. Sensitization to ingested allergens is necessary to develop the disease, and there may be some cross-reactivity to aeroallergens. Human data demonstrates that this disease is principally mediated by food antigens as complete withdrawal of inciting food antigens leads to complete normalization of esophageal mucosa and clinical response in most patients. It is still unclear how much antigen exposure is required to initiate eosinophilic inflammation and how long that exposure needs to be.

Environmental exposures have been implied in disease development and are suggested to drive the changing epidemiology, but the exact role is not known. In animal models, priming of the esophagus with subdermal ovalbumin injection or intratracheal instillation of aspergillus is effective in producing EoE. In humans, EoE tends to be of later onset than other atopic diseases such as atopic dermatitis and rhinitis. Some data supports the existence of an allergic march in which patients evolve through various common atopic diseases to eventually develop EoE. Early life exposures including antibiotic use, and cesarian section, have been implicated, while geographic factors such as arid climate, cold climate, and rural setting have been linked to increased risk of disease development. In addition, childhood exposure to microbes, presence of *Helicobacter pylori* infection, and interplay with commensal bacteria may limit food sensitization and provide a protective role in disease development. Overall, however, no proven causality of any one environment exposure has been identified. Nevertheless, these associations suggest a role for abnormal microbiome development in the esophagus and/or gut as an important predisposing factor to



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**Image 7.1** Pathogenesis of EoE

EoE. This is consistent with other atopic diseases such as asthma and atopic dermatitis which have been associated with abnormal bacterial colonies and altered diversity in the intestine (Image 7.1).

## Diagnosis

EoE is a clinicopathologic disorder characterized by symptoms of esophageal dysfunction and eosinophil predominant inflammation with exclusion of secondary causes that could contribute to the esophageal eosinophilia. There is no single test at present that definitively diagnoses EoE. Other diseases that can lead to esophageal eosinophilia need to be considered before a diagnosis of EoE is made. These can include achalasia, connective tissue diseases, graft-versus-host disease, infection, pill esophagitis, Crohn's disease, drug hypersensitivity, and, most frequently, gastroesophageal reflux disease. Furthermore, with both GERD and EoE now being common, these may coexist in some patients.

- A critical aspect of diagnosis in EoE is symptoms. These can sometimes be blatant, and other times subtle given that the disease can be insidious in onset and patients frequently develop compensatory eating behaviors to minimize symptoms. In children, symptoms most commonly

include abdominal or epigastric pain, nausea, difficulty feeding, food avoidance, vomiting, and failure to thrive. These symptoms reflect the inflammatory changes of EoE. Adults often present with dysphagia, which is the predominant symptom and reflects the fibrotic nature of the disease. This can transpire with or without food bolus impaction. Heartburn and chest pain are also frequent symptoms of esophageal dysfunction in adults and children. As the type, severity, and compensation for symptoms can be varied in EoE, validated questionnaires such as the dietary screener questionnaire (DSQ) and eosinophilic esophagitis activity index (EEsAI) have been developed to better define and quantitate symptoms. These questionnaires are routinely used in clinical trials but are now being used or adopted for use in clinical practice. Some specific questions eosinophilic esophagitis (EoE) diagnosis that can easily be incorporated into office visits and can help determine if a patient is symptomatic include:

- Do you excessively chew your food?
- Do you have to repetitively swallow to get food to pass?
- Are you the last person at the table to finish during a meal?
- Do you avoid foods with a certain food texture?
- Do you modify your foods? Examples would include cutting to extra small pieces or pureeing.

- Do you lubricate your foods with sauces or condiments?
- Do you need liquids present to complete a meal?
- Do you avoid pills?
- Do you completely avoid social situations where eating will take place? Do you go to social events but avoid eating during the social setting?

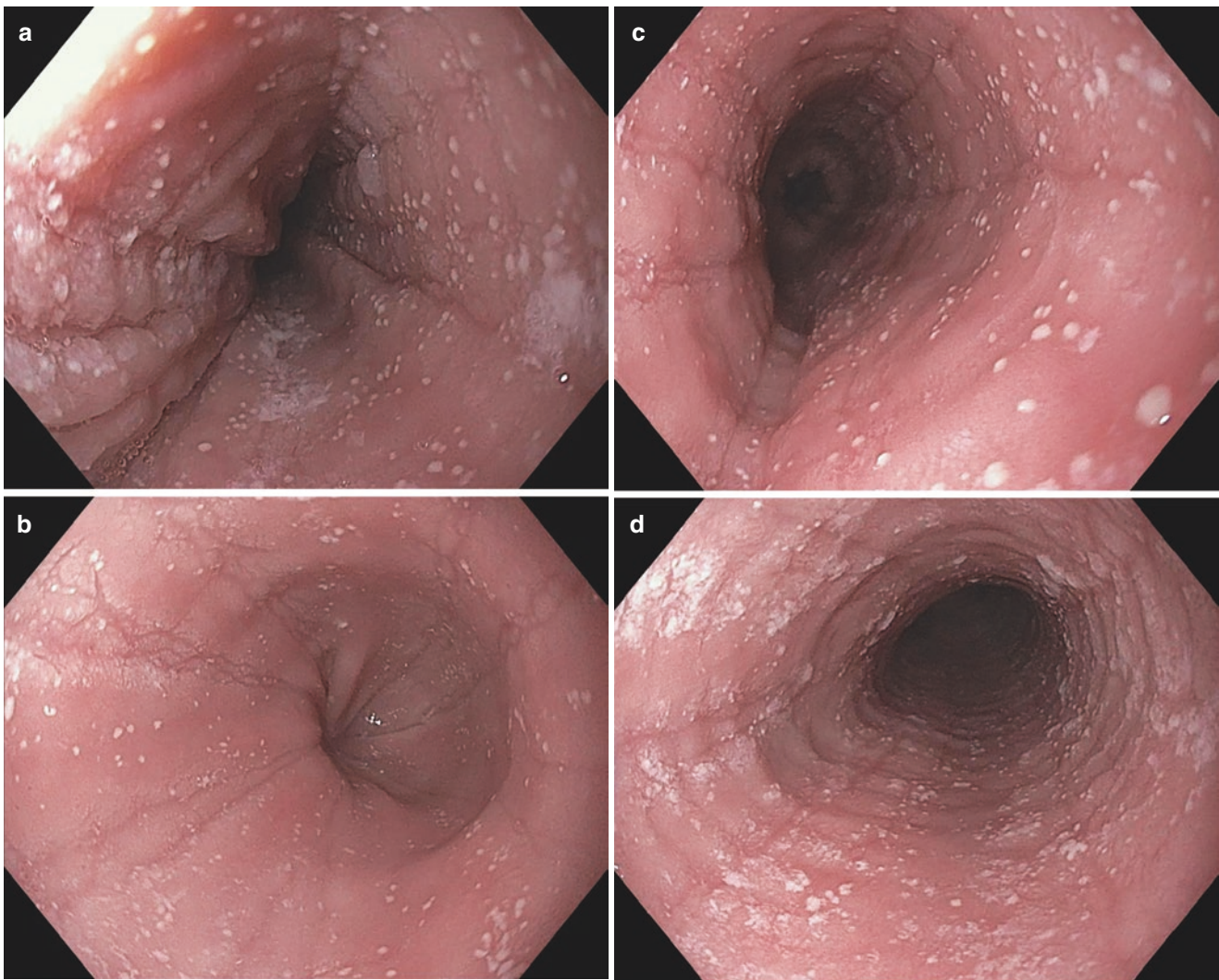
Upper endoscopy with esophageal biopsies is required to confirm the diagnosis of EoE. Gross endoscopic inspection of an esophagus with EoE can display numerous traits suggestive of the diagnosis. Endoscopy findings include white plaques or exudates on the surface of the esophagus; decreased vascularity or pallor to the tissue; fragile mucosa that tears with endoscope passage termed “crepe-paper” mucosa; rings, strictures, or narrowing of the esophageal lumen; linear tracts or furrows; and firmness sensed during biopsy, which has been called “tug sign.” To create a universal language, allow for consistency in description, and standardize reporting of what an endoscopist sees during the procedure, the EoE Endoscopic Reference Score (EREFS) was devised. This scoring system has been validated, and an elevated score is highly predictive of active disease, while it decreases with histologic remission. EREFS is an acronym for Edema, Rings, Exudates, Furrows, and Stricture(s) (Table 7.1, Image 7.2a,b).

Unlike the rest of the GI tract, the esophageal mucosa is normally devoid of eosinophils. Histopathologic studies have shown that equal or greater to 15 eosinophils per high-powered field approaches 100% sensitivity and 96% specificity for the disease. This number is still used in clinical guidelines for diagnosis to date, and peak eosinophil count remains the most widely used histologic assessment tool used to assess the disorder. An eosinophil count below 15 is also used to define remission. Eosinophilic inflammation is patchy and variable in location in EoE. Usually, 2–4 biopsies obtained from at least 2 different locations in the esophagus are recommended for diagnosis and assessment of activity. Five biopsies have been shown to have 100% sensitivity. The distal esophagus is considered around 3–5 cm from the gastroesophageal junction, and mid proximal esophagus is considered 10–15 cm from the gastroesophageal junction. The role of routinely obtaining gastric and/or duodenal biopsies in adult EoE patients to rule out coexisting eosinophilic gastroenteritis is controversial. Biopsies should be obtained if patients have other gastrointestinal-related symptoms or other endoscopic abnormalities seen during upper endos-

**Table 7.1** EoE Endoscopic Reference Score (EREFS). Scoring system used during endoscopy to report EoE findings

<b>Edema (loss vascular markings)</b>	
Grade 0	Distinct vascularity
Grade 1	Decreased
Grade 2	Absent
<b>Rings (trachealization)</b>	
Grade 0	None
Grade 1	Mild
Grade 2	Moderate (distinct rings)
Grade 3	Severe (not pass scope)
<b>Exudate (white plaques)</b>	
Grade 0	None
Grade 1	Mild ( $\leq 10\%$ surface area)
Grade 2	Severe ( $> 10\%$ surface area)
<b>Furrows (vertical lines)</b>	
Grade 0	None
Grade 1	Mild
Grade 2	Severe (depth)
<b>Stricture</b>	
Grade 0	Absent
Grade 1	Present

copy. In addition to eosinophilia, there are multiple other characteristics that are found on esophageal biopsy in patients with EoE. These can include basal cell hyperplasia, dilated intercellular spaces (spongiosis), elongation of the vascular papilla, basal zone hyperplasia, superficial eosinophils, eosinophilic microabscesses, and eosinophil degranulation. The formal eosinophilic esophagitis-specific histological score system (EOE-HSS) is utilized frequently during research studies and may be adapted for routine use in practice.



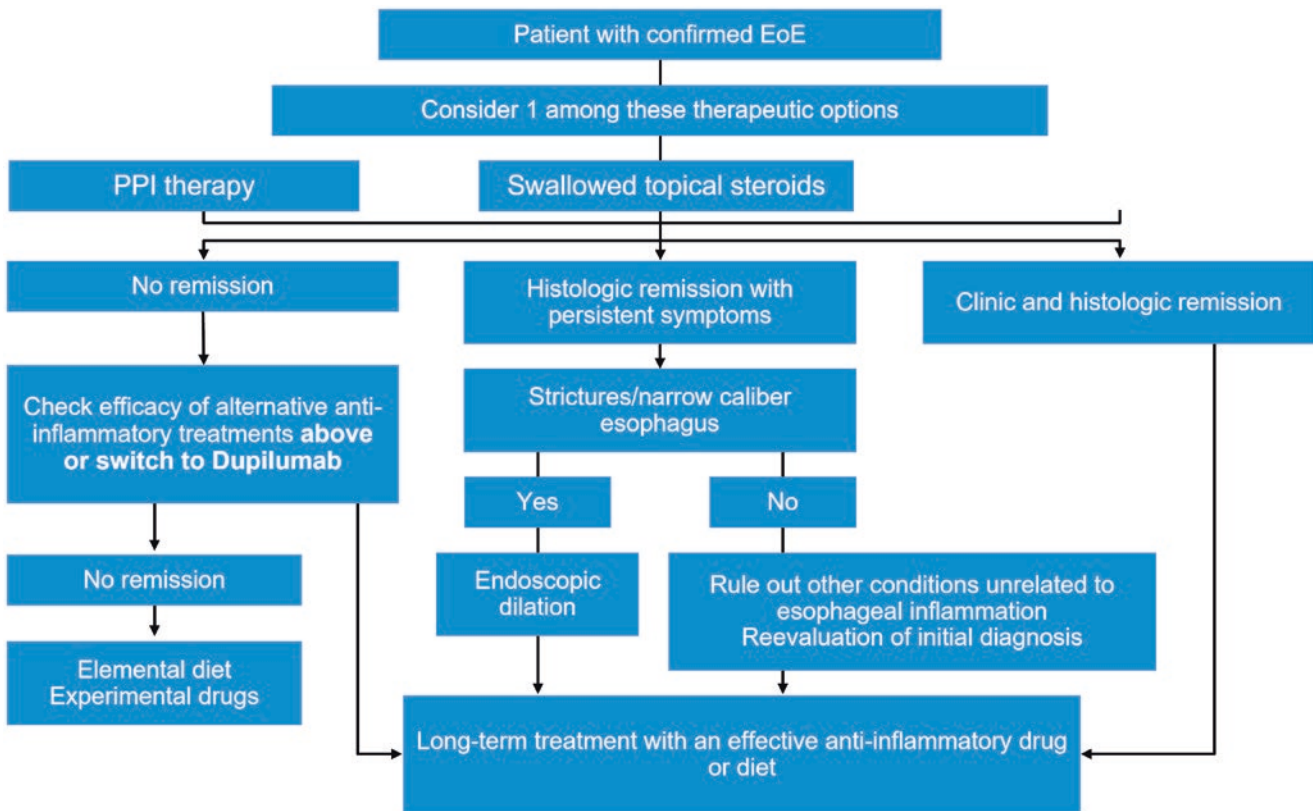
**Image 7.2** (a–d) Endoscopic images of classic EoE findings including edema, fixed rings, exudates, and furrows

## Treatment

EoE has not been found to be associated with esophageal malignancy, nor has it shown any evidence of affecting duration of life expectancy. Despite lack of concern for mortality risk, treatment is important not only for improvement in symptoms and quality of life but to prevent remodeling and fibrosis leading to complications and cost. Treatment endpoints in the literature are variable and can be arbitrary due to a number of factors. For example, symptoms can be non-specific and minimized by compensatory dietary and lifestyle modifications, and histology and symptoms may be discordant. There is also poor correlation of symptoms to eosinophil count. There are also variations in the upper limit of eosinophils per high-power field, due to peak eosinophil count being affected by field size and sampling variability. Other proposed endpoints have been  $<6$  and no eosinophils. This latter measure when occurring with low EREFS score

and reduction of symptoms is defined as deep remission. Histology is not perfect in factors such as subepithelial fibrosis, accounting for other cell mediators, and activity level of the eosinophils is difficult to quantify on biopsies. The degree of esophageal fibrosis and determination of decreased esophageal compliance are not easily measured.

The Food and Drug Administration (FDA) recently approved the first pharmacologic therapy for EoE. Dupilumab is a human monoclonal antibody that binds and inhibits the IL-4 receptor alpha subunit interfering with IL-4 and IL-13 signaling and is highly effective in patients with refractory EoE. Although approved for first line therapy, its precise role in the medical treatment of EoE is evolving. Joint task force guidelines have sought to outline management options for EoE and help standardize practice. In patients with confirmed EoE, first-line therapy options in the USA include proton pump inhibitors (PPIs), swallowed topical steroids, empiric elimination diets, and now dupilumab. When one of these treatment options are



**Image 7.3** Proposed treatment algorithm for EoE

undertaken, it is important to evaluate remission and response to therapy both clinically and histologically. If symptoms persist, one should determine if a stricture or narrow-caliber esophagus is present requiring endoscopic dilation. If the patient is not responsive to therapy as defined by persistent eosinophilia on biopsies, then treatment adherence and correct dosing of pharmacologic therapy needs to be assessed, other conditions unrelated to esophageal inflammation should be ruled out, and the initial diagnosis should be reevaluated. If adherence or correct dosing is not an issue and the disease is confirmed, then an alternative anti-inflammatory treatment should be sought. When first-line therapies are not effective and do not result in remission, then dual therapy versus elemental diet or experimental drugs could be considered. Once clinical and histologic remission is achieved, most experts agree that long-term treatment with the effective anti-inflammatory therapy should be continued (Image 7.3).

Initial therapy choice should take into consideration the severity of symptoms, ability to implement the therapy including dietitian counseling availability, cost of medications, therapy effectiveness, and patient and family preference. For simplification and minimization of potential side effects, monotherapy is usually preferred unless true refractory disease is present or in situations where GERD and EoE occur concomitantly and EoE is nonresponsive to PPI. There are no guidelines stating when repeat histologic assessment should be pursued which usually requires upper endoscopy

though 6–8 weeks is generally used. When a new management plan is initiated or altered, assessment of response should be considered. This is particularly important to emphasize, as symptoms and histology can be conflicting.

## Anti-Inflammatory Treatment and Technical Considerations

### PPIs

Proton pump inhibitors (PPIs) are a first-line treatment option. Previously they were used to classify what was considered to be a separate entity termed PPI-responsive esophageal eosinophilia which is now known to be the same disease as EoE. PPIs work through anti-inflammatory effects with inhibition of key cytokines in the EoE pathway. Effectiveness may also be achieved by inhibiting gastric acid. There have been many clinical studies looking at different PPIs, dosing, timing, and methodology leading to a lot of variability in evidence, and ultimately culminating in the recommendation that PPIs are effective when used at “high daily dose.” Pooled histology response to PPI treatment in adults varies but estimates are around 40–50%. It is unclear if this applies for long-term therapy. There is some data to suggest a higher histologic response to PPI therapy when administered twice daily compared to once daily administration, but this has been

nonsignificant. When reviewing anti-inflammatory treatment options, advantages of PPIs include favorable safety profile, their simplicity in administration, and that they are cost-effective. A major limitation is their lower response rate and concerns with long-term PPI use risk associations.

### Swallowed Topical Steroids

Swallowed topical steroids are currently asthma medications that are repurposed for optimizing esophageal mucosal contact. These are also considered first-line therapy options and are felt to be safe and well tolerated. Without FDA-approved formulations, the two most common options include:

- -Oral aerosolized fluticasone propionate is utilized by puffing a metered dose into the mouth and swallowing. Initial induction dosing for adults is 880 mcg twice daily.
- -Oral viscous budesonide is compounded either by a pharmacy or by the patient at home. If from pharmacy, the slurry comes mixed as oral viscous liquid. If mixing at home, liquid Pulmicort capsules are mixed with sucralose, Splenda, or other sweetened powder to form a 10 cc viscous slurry. Induction dosing is 1–3 mg twice daily.

It is critical to explain to patients how to take the medication correctly. If utilizing aerosolized steroid, patients should breathe, hold, puff, and then swallow to avoid administration into the lungs, which can make the therapy less effective. It should also be used without the spacer. Similarly, budesonide slurry should be placed in and swallowed from the back of the tongue to reduce oral retention. Patients should not eat or drink for 30 minutes after steroid administration. Due to this it is commonly recommended to take medications after an am meal and prior to bedtime. Unfortunately, patients need to be aware of common denial for payment by insurance companies leading to appeals and high out-of-pocket costs for patients. The most common side effect is oral and esophageal candidiasis.

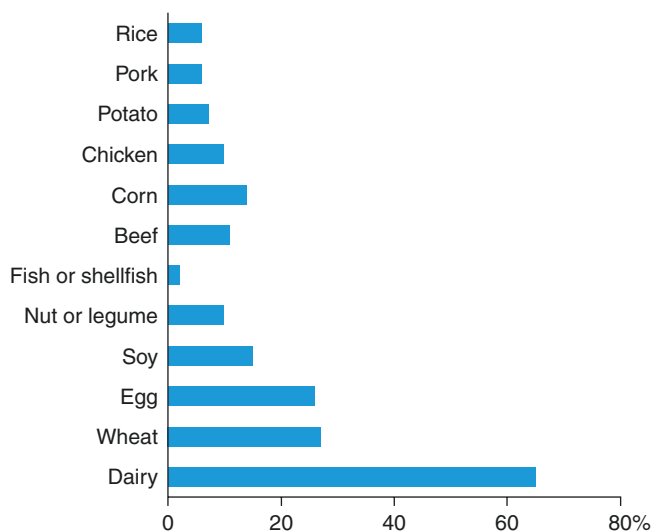
Clinical studies investigating swallowed topical steroids have shown the overall response rate to be 65–70%. A new formulation using an orodissolvable steroid tablet reached 95% efficacy for attaining histologic remission. Steroids are the only treatment option with a strong recommendation in current guidelines due to the availability of randomized controlled trials that demonstrate clear efficacy. When reviewing anti-inflammatory treatment options, the advantage of swallowed topical steroids is a high response rate. Disadvantages to be considered are cost, cumbersome of the therapy with no commercially available preparation, and lack of long-term data on adverse events with these preparations. Use of topical steroids in 2–3-month studies have not demonstrated significant adrenal insufficiency or growth suppression. The asthma literature further suggests that these medications are safe for long-term use.

PPIs and steroids together have a potentially synergistic anti-inflammatory response, with PPIs impairing antigen penetration and steroids blunting the allergic inflammatory response. There is data to suggest PPIs inhibit different cytokines than steroids. Given this knowledge combined therapy may be appropriate for patients who have clear GERD overlap with EoE or those that are refractory to monotherapy.

The most current guidelines for treatment of EoE support the need for long-term maintenance therapy. For both PPIs and swallowed topical steroids, practice often involves starting at a high dose to achieve histologic remission followed by step-down to a maintenance dose. Unfortunately, the required maintenance dose is unclear, but studies suggest half to full dose for maintenance. Less than this leads to relapse in most patients. If remission cannot be maintained with a lower dose of PPI or steroid, the standard dose for initial treatment should be resumed. Some factors associated with risk of relapse with PPI use have included concomitant allergic rhinoconjunctivitis, CYP 2C19 rapid metabolizer genotype, and carriers of certain STAT6 gene variants.

### Diet Elimination

The current mainstay of diet therapy is empiric elimination diets. An elemental diet is effective but often unpalatable and costly. Food allergy testing directed by skin and serum IgE testing unfortunately is poor in identifying diet triggers in EoE. This has led to empiric elimination diets where food triggers are iteratively excluded and/or reintroduced to determine a patient's individual food triggers. These triggers vary from patient to patient. The most common food triggers in EoE in order are milk, gluten, soy, and eggs. Less likely foods such as legumes, corn, and beef may also trigger EoE (Image 7.4).



**Image 7.4** Pooled rates for EOE food trigger prevalence

**Table 7.2** Pros and cons of currently available first-line therapies in EoE

PPI		Steroids		Diet		Dupilumab	
Pros	Cons	Pros	Cons	Pros	Cons	Pros	Cons
Easy to take	PPI risks	Unlimited diet	Expensive	No long term risk	Cost, risks, inconvenience of evaluation period	FDA approved	Expensive
Relatively inexpensive	Lower response rate	Most patients respond	No commercially available preparation	Relatively inexpensive	Long term dietary restriction	Most patients respond	Potential risks
Many of patients also have GERD			Potential risks			Minimal side effects	Insurance coverage

There are a variety of empiric elimination diet strategies currently felt to be acceptable, and choice should be tailored to individual patient preferences, available diet resources, the likelihood of following the diet, and experience. These strategies are based on either step-up or step-down therapy. Various models have been proposed including 1,3-food; 1,4,8-food, 2–4–6 food, milk only, 2-food, 4-food, and 6-food, and extended 6-food elimination diets exist. Step-down approach starting with elimination of six foods typically achieves remission quickly and provides a clear path for reintroduction. While the initial elimination is extensive, it allows subsequent reintroduction, which is encouraging for patients, and clearly identifies triggers when more than one is present. It does, however, require multiple endoscopies to complete. Step-up approach starts with minimal elimination and then increases to more restricted diets in nonresponders. This quickly identifies responders to less restricted diet, and the largest advantage is those who achieve early remission are spared more restrictive diets and endoscopies. Furthermore, some studies suggest that 40% of EoE patients may be effectively treated with elimination of milk and/or gluten only. There is, however, prolonged inflammation in nonresponders due to time requirements which may further impair those patients with severe disease. Further, this approach can include multiple dietary changes to determine triggers, especially if there is more than one.

Regardless of the empiric diet elimination strategy chosen, a registered dietitian can be critical to patient education and compliance. Dietitians can help identify hidden allergens, find suitable food replacements, teach patients to read food labels and understand terminology, and ensure nutritional adequacy when diets are limited. Likely the diet that will be most successful is the one that is personalized in strategy.

## Dupilumab

Dupilumab is the first FDA approved therapy for EoE treatment. The clinical trials investigating dupilumab have shown the overall histologic response rate of eosinophils  $\leq 6$  per high power field to be 60% at 12 weeks and 85% at 52 weeks.

Importantly, patients also demonstrated statistically significant improvement in symptoms during clinical trials. Clinical trial patients were resistant to other medications with all of them failing PPI therapy, 40% having had prior dilation, and 60–70% previously having trialed steroids. This medication is given as a weekly subcutaneous injection. The advantage of dupilumab is it has a high response rate, it is FDA approved, and has minimal reported side effects. Disadvantages to be considered are high cost, and lack of long-term data on adverse events and effectiveness. It's precise role in EoE treatment is evolving but it appears to be an excellent option for those who don't respond to previously considered primary therapy (Table 7.2).

## Dilation and Technical Considerations

Dilation is a key tool for treatment of adult patients with EoE and frequently underutilized in practice. It should always be considered in those with severe rings, focal strictures, or narrow-caliber esophagus. It is safe if performed in incremental fashion and discontinued after revisualization of mucosal disruption. Several dilation sessions are often required. Perforation risk is <1% in meta-analysis review. Dilation does not impact the inflammatory nature of the disease but is effective at improving dysphagia.

It is important to note that visualization of subtle esophageal stricture by endoscopy is limited and literature would suggest that esophagram is more sensitive at detecting strictures compared to endoscopy. Fluoroscopic imaging can be an important tool to estimate esophageal diameter and localize the area of greatest concern with barium tablet. It is used frequently in our practices to assess for narrow-caliber esophagus and in attempts to estimate the degree of fibrosis (Images 7.5 and 7.6).

Both bougie (American or Savary) and controlled radial expansion (CRE) balloons can be employed for esophageal dilation in EoE. Choice may be reflected by availability in one's practice and physician experience. When utilizing bougie dilation in EoE, frequent re-examination for mucosal disruption should be employed as there can be more than one stricture and varying severity of strictures. Balloons can be utilized to dilate a focal stricture but also



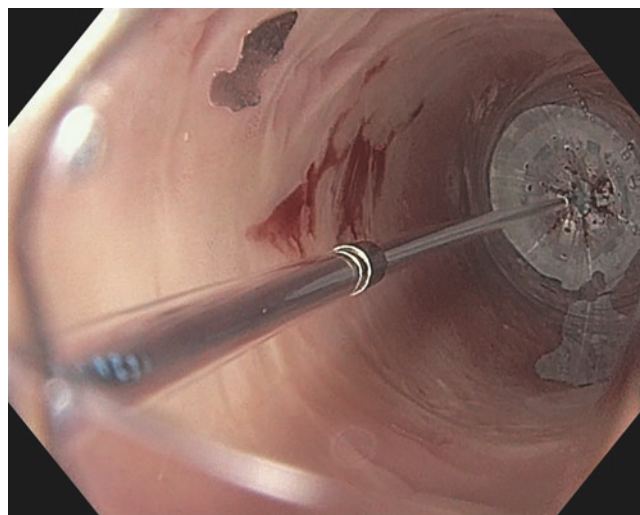


**Image 7.5** Fluoroscopic image of patient with EoE. Fine concentric rings are appreciated throughout the upper half of the esophagus

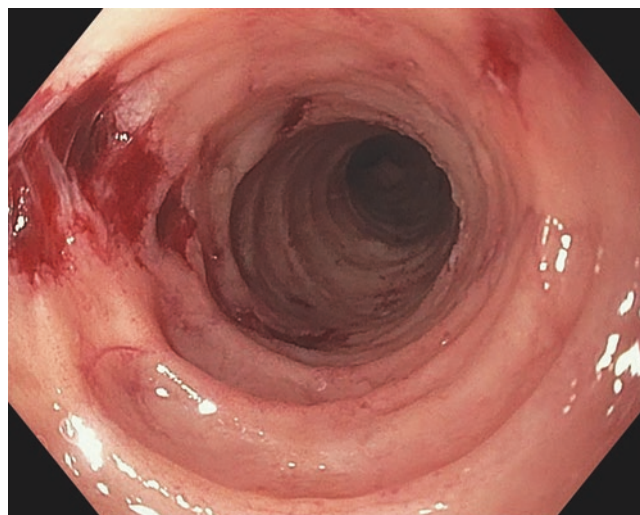


**Image 7.6** Fluoroscopic image of patient with EoE. Severe proximal stricture and narrow-caliber esophagus

dilate the entire esophagus via balloon pull-through technique, performed by pulling the inflated balloon from the gastroesophageal junction to the proximal esophagus. Balloon dilation does allow for direct visualization of mucosal disruption during the dilation but could be more costly if multiple sized balloons need to be utilized (Images 7.7 and 7.8).



**Image 7.7** Dilation with through the scope balloon with direct visualization of tear occurring



**Image 7.8** Post-dilation tear after passing bougie dilator

## Future Directions

Multiple advances continue to be made in the diagnosis and treatment of EoE, and the horizon is bright. Alternatives to endoscopy that have shown promise include transnasal endoscopy, the Cytosponge, and the esophageal string test. All of these allow sampling of the esophageal mucosa without performing standard endoscopy under sedation, but have limitations such as patient tolerability and the inability to perform esophageal dilations.

EoE subtypes have been categorized both phenotypically and by genomic markers predicting more progressive disease, medically refractory disease and severe stricture formation. This will hopefully lend itself to more personal-

ized therapy. Noninvasive biomarkers continue to be tested, and discovery of a circulating blood eosinophil progenitor line in the peripheral blood during allergic inflammation brings hope that we may one day have a blood, saliva, or urine test to determine and monitor degree of disease activity.

Functional luminal imaging probe (EndoFLIP) is a balloon-based technology that utilizes high-resolution impedance planimetry to quantify the change in luminal cross-sectional area during distention. It provides esophageal compliance data by generation of volume pressure curves. Decreased compliance measurements have been shown to correlate with risk of future food bolus impaction. This shows promise for determining degree of fibrosis in the esophageal lumen, data which could help guide therapy based on severity of whole organ function.

Many novel treatment options are showing potential in clinical trials. These include standardized topical steroid formulas and biologic therapies. The European Medicines Agency approved an orodispersible budesonide tablet for short-term EoE treatment. Medications targeting IL-13 and the IL-4 $\alpha$  receptor subunit blocking IL-4 and IL-13 action have both shown significant promise.

Although EoE is a disease that was initially described only 20 years ago, the degree of understanding that has occurred in this disease is formidable. The inflammatory pathway has been carefully elucidated, diagnostic criteria have been refined, and present and evolving therapies show great promise. Nevertheless, there are improvements to be made, particularly in simplifying diagnosis and endpoints of treatment and in optimizing topical and systemic therapies.

### Questions

- Which of the following is not required to make the diagnosis of EoE?
  - Clinical symptoms.
  - Nonresponse to a PPI trial.
  - $\geq 15$  eosinophils per high-power field on esophageal biopsy
  - Mucosal eosinophilia isolated to the esophagus
  - B and D

Answer: B. PPIs were previously used to classify what was considered to be a separate entity termed PPI-responsive esophageal eosinophilia which is now known to be the same disease as EoE.
- Which of the following are challenges in diet elimination therapy?
  - Psychosocial impact of a restricted diet
  - High cost of allergen-free food products
  - Patients must be educated on dietary contamination

- The process usually requires multiple endoscopies
- All of the above

Answer: E. Dietary elimination therapy can be a lengthy process that has a high up-front cost. Patients need to be educated regarding dietary contamination for strict adherence, and it can require multiple endoscopies depending on the underlying trigger.

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