Eosinophilic Esophagitis
A Review for the Primary Care Practitioner

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KEYWORDS

• EoE review • Primary care practitioner • PCP • Esophageal • GERD and EoE

KEY POINTS

- Keep eosinophilic esophagitis in the differential diagnosis of a patient with upper gastrointestinal symptoms, especially in a patient with atopy.
- Recognize that the presentations may vary with age of the patient and the duration of disease.
- Refer appropriately for endoscopy/gastrointestinal evaluation if patient fails to respond to standard reflux therapy.
- A team effort with a nutritionist, gastroenterologist, and an allergist input will likely be needed.
- Monitor for compliance and complications of therapy.

EOSINOPHILIC ESOPHAGITIS

Introduction

Eosinophilic esophagitis (EoE) is a chronic antigen-mediated inflammatory disorder that is increasingly recognized as a cause of esophageal dysfunction in both adults and children.

Despite increased recognition of this condition, there can still be significant delays in time to diagnosis in both children and adults, which increases the risk of long-term morbidity, including fibrosis and strictures.[1]

Therefore, it is especially important for PCPs to be aware of the spectrum of clinical presentations, keep it in their differential diagnosis, and know how to screen for EoE symptoms in at-risk populations.

Epidemiology

Initially recognized as a distinct clinical entity in the mid-1990s,[2] it has since been increasingly seen as a major cause of esophageal dysfunction and as a source of significant health care burden both in terms of morbidity and cost.[3]

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The incidence of EoE is approximately 7.7/100,000 per year in adults and 6.6/100,000 per year in children.

EoE affects an estimated 34.4/100,000 people in Europe and North America. Since the mid-1990s there has been a significant increase in the overall prevalence of EoE for both age groups not fully explained by the increased recognition of the condition or change in diagnostic criteria.[4]

Prevalence rates in children increased from 19.1 (95% confidence interval [CI], 7.9–35.2) to 34.4 (95% CI, 22.3–49.2) patients per 100,000 inhabitants over 4 years, whereas for adults they grew from 32.5 (95% CI, 12.4–62.2) to 42.2 (95% CI, 31.1–55) patients per 100,000 inhabitants.[5]

Depending on the prevalence estimate, health care costs attributable to EoE range from $350 to $947 million/year.[3]

EoE can occur in any age group and has a 3:1 male to female predominance. The age at presentation is biphasic. The mean age at diagnosis in children is between 6 and 10 years, whereas in adults it occurs most commonly in the third and fourth decades.[6–8] There is an average delay in diagnosis of 4 years.

Most patients with EoE have an atopic history, and heritability has been established, with a recent multicenter analysis showing that 6.5% of patients had a parent or a sibling with EoE.[5]

In adult EoE patients, the prevalence of any atopic condition is 20% to 80%.[9] Children with EoE have a prevalence of 30% to 50% and 50% to 75% for asthma and allergic rhinitis. Furthermore, children with EoE are more likely to have environmental allergies and immunoglobulin E (IgE)-mediated food allergy (eg, urticaria, anaphylaxis). Moreover, a family history of an atopic disorder is found in more than 50% of patients with EoE.[10,11]

EoE also develops in association with some inherited connective tissue disorders that exhibit hypermobility, but this is rare.[12]

A family history of EoE increases an individual's risk for the condition.[13] Interestingly, the risk varies by the particular relationship with a higher risk if the father or brother is affected. A father affected gives a 2.4% individual risk (recurrence risk ratio: 43), and a brother affected gives a 3.5% individual risk (recurrence risk ratio: 64).[14]

DISCUSSION

Clinical Presentation

The clinical presentation of the individual patient to the PCP may be varied depending on the age of the patient, chronicity of disease, and prior treatments (**Table 1**). Solid food dysphagia and food impaction are more common in adults and adolescents and nausea, vomiting, heart burn, and abdominal pain in younger children. It is also a differential in exercise-induced chest pain in adults.[15] Failure to thrive and feeding refusal is seen in infants and toddlers. Food impaction has a high correlation with EoE, with studies demonstrating up to 36% of individuals presenting with food impaction having EoE.[16]

When assessing for dysphagia it is important to recognize that many patients may have subconsciously developed compensatory eating behaviors over years to minimize symptoms. So close questioning on eating habits is important to elicit. It is important to ask whether the patient has been eating slowly, chewing excessively, drinking copious amounts of fluids, repeating swallows, avoiding certain foods, and crushing or avoiding pills.

Making the diagnosis further challenging is the overlap of gastrointestinal reflux disease (GERD) and EoE as well as subset of patients with EoE who respond to PPIs. Therefore, a high index of suspicion must be maintained by the PCP in patients who are refractory to standard therapy for GERD and have commonly associated conditions or present with food impaction.

Table 1
Most common presenting symptoms of eosinophilic esophagitis by age

Age	Infants/Younger Children	Older Children/Adolescents	Adults
Symptoms	Feeding refusal Delayed feeding skills Textural preferences Vomiting chronic nausea/abdominal pain Regurgitation Irritability	Preference for soft/liquid diet Heartburn Abdominal pain Vomiting Dysphagia/choking/food sticking Fear/anxiety with meal Food impaction	Dysphagia Chest/upper abdominal pain Heartburn

Pathophysiology

Major players in the pathology of eosinophilic esophagitis are activated eosinophils, mast cells, and Th2 cytokines. This disease does not seem to be IgE mediated (Fig. 1).[17]

An impaired esophageal epithelial barrier initiates a cascade of self-propagating events. Increased permeability of the esophageal lining is theorized due to altered functioning of desmoglein-1, calpain 14, and eotaxin. The increased presence of thymic stromal lymphopoietin acts on the antigen-presenting cells and induces CD4 cells to differentiate into mainly Th2 (T helper cells) and to a lesser extent Th1 cells.

Activated eosinophils in the epithelium release T-cell–activating cytokines, which induce Th2 cell differentiation and also degranulate and release preformed granule proteins. The preformed granules include eosinophil cationic protein, major basic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin, which cause inflammation and edema. In addition, along with mast cells, eosinophils release TGF-β1,

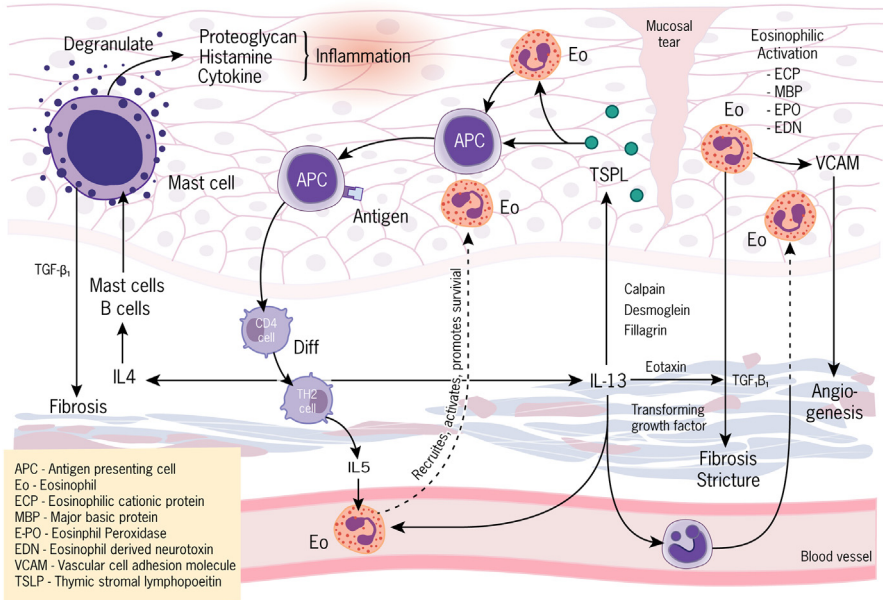

Fig. 1. Pathophysiology of eosinophilic esophagitis. APC, antigen presenting cell; ECP, eosinophilic cationic protein; EDN, eosinophil derived neurotoxin; Eo, eosinophil; E-PO, eosinophil peroxidase; MBP, major basic protein; TSLP, thymic stromal lymphopoeitin; VCAM, vascular cell adhesion molecule. (*Reprinted with permission*, Cleveland Clinic Foundation ©2023. All Rights Reserved.)

which stimulates epithelial cells to undergo mesenchymal changes causing subepithelial fibrosis. Eosinophils also release vascular cell adhesion molecule, which increases angiogenesis.[18]

Antigen-presenting cells and T-cell–activating cytokines induce the differentiation of CD4 cells both locally and systemically. Activated Th2 cells release interleukin-4 (IL-4), IL-5, and IL-13. IL-4 recruits mast cells that release histamine, cytokines, serine proteases (tryptase, chymase), and proteoglycans causing local inflammation. Mast cells also release TGF-β1, which induces epithelial fibrosis. IL-4 also induces release of periostin, a profibrotic agent. IL-5 is a key cytokine involved in proliferation and survival of eosinophils. IL-13 induces the secretion of eotaxin in the esophageal epithelium, which increases the recruitment, retention, and activation of eosinophils to the esophagus. It also induces the secretion of proteolytic enzymes calpain 14, desmoglein, and filaggrin affecting epithelial integrity.[19]

Evaluation and Diagnosis

Patients who present with any of the aforementioned symptoms should be further queried about all the potential symptoms of EoE. It is also helpful to ask about risk factors for EoE, such as a personal history of other atopic conditions, even if resolved, and any family history of EoE, severe GERD, food impactions/dysphagia, or need for esophageal dilatations.

Patients who may present for routine preventative care and have conditions associated with an increased risk of EoE should be screened with a targeted review of systems for evidence of dysphagia and the other gastrointestinal manifestations of EoE.

All patients suspected of having EoE should be referred to gastroenterology for an esophagogastroduodenoscopy (EGD) to establish the diagnosis. Although not diagnostic, certain gross endoscopic findings are frequently seen in patients with EoE. These include **E**xudates, **R**ings, **E**dema, **F**urrows, **S**trictures, and trachealization. The first 4 findings are used to generate an eosinophilic esophagitis endoscopic reference score (**Table 2**), which is a classification system used routinely in clinical practice to assess severity of disease. However, biopsy is necessary to establish the diagnosis and assess response to treatment.[20–22] Maximum sensitivity is achieved by obtaining multiple biopsies from proximal and/or mid- and distal esophagus.

Original diagnostic criteria required that eosinophils be present despite the patient being on a high-dose proton pump inhibitor (PPI) for 8 weeks. However, this criterion was removed in the updated guidelines in 2018 due to evidence that EoE and GERD can co-exist and perhaps potentiate each other. Some patients with EoE and no evidence of GERD respond to PPIs (formerly known as PPI-responsive esophageal eosinophilia, now classified as a subset of EoE), and PPIs have a nonacid–mediated mechanism of action that contributes to their effectiveness in EoE.

Criteria for Diagnosis

Criteria for diagnosis are based on the AGREE[23] group consensus statement from 2018 and has 3 components:

1. Clinical symptoms of esophageal dysfunction;
2. An esophageal eosinophil count of more than or equal to 15 eosinophils/high-power field, and
3. Exclusion of other possible causes of esophageal eosinophilia.

Differential Diagnosis

It is important to be aware of other causes of esophageal eosinophilia as well as the possibility of a concurrent diagnosis. The differential is quite broad; however, GERD

Table 2
Eosinophilic esophagitis endoscopic reference scores

		Major Features	Minor Features		
Fixed rings	Grade 0	None	Crepe-paper esophagus (mucosal fragility or laceration passage of endoscope)	Grade 0	Absent
	Grade 1	Mild (subtle circumferential ridges)		Grade 1	Present
	Grade 2	Moderate (distinct rings, permits passage of endoscope)			
	Grade 3	Severe (distinct rings, do not permit passage, of endoscope)			
Exudates	Grade 0	None			
	Grade 1	Mild (<10% of the esophageal surface area)			
	Grade 2	Severe (>10% of the esophageal surface area)			
Edema	Grade 0	Absent (distinct vascularity present)			
	Grade 1	Loss of clarity or absence of vascular markings			
Furrows	Grade 0	Absent			
	Grade 1	Present			
Stricture	Grade 0	Absent			
	Grade 1	Present			

From Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013;62(4):489-495.

is the most common condition that can not only mimic but also coexist with EoE. Other conditions in the differential diagnosis include achalasia, eosinophilic gastrointestinal disease, hyper eosinophilic syndrome, Crohn disease, celiac disease, vasculitis, connective tissue disorders, and infections.

Management

The goal of therapy is both symptomatic and histologic resolution of symptoms and reduction in the long-term sequelae of untreated EoE.

As with most chronic disease management, a patient-centered approach with treatment streamlined to make it as nondisruptive to the patients as possible is preferred. Which treatment strategy is chosen is based on shared decision-making between the practitioners and family. In addition, a multidisciplinary approach with a team composed of an allergist, a gastroenterologist, a dietitian, and the primary care practitioner is preferred.

New guidelines were released in 2020 from the American Gastroenterological Association (AGA) and the Joint Task Force for Allergy-Immunology Practice Parameters, which provided recommendations for the management of EoE in pediatric and adult patients (**Table 3**). The only strong recommendation was the recommendation for the use of topical steroids over no treatment. The rest of the recommendations were conditional and included use of PPIs over no treatment, use of topical rather than systemic steroids, and the use of elemental, empirical elimination diets or allergy testing–based elimination diet over no treatment. Importantly, continuing treatment after remission was also a conditional recommendation.[24]

Use of anti-IL-3, IL-4, or IL-5, montelukast, and antitumor necrosis factor therapy was only recommended in the context of clinical trials, and anti-IgE therapy was not recommended.[24] *Of note, as of May 2022, dupilumab (anti-IL-4/IL-13) was granted Food and Drug Administration (FDA) approval for the treatment of EoE in those 12 years and older.*

The 3 main modalities currently in use for EoE are diet, medications, and endoscopic dilatation (**Table 4**).

Dietary Modalities

- Elemental diets consisting of exclusively amino acid–based formula are highly effective—93.6% resolution compared with placebo (13.3%) in 6 observational studies.[5] However, they are difficult to sustain and poorly palatable. A disruption of children's developmental feeding progress and need for gastrostomy tubes are possible downsides.[5,25]
- Empirical elimination diets consist of removing food groups that are commonly implicated in EoE (**Table 5**). The traditional 6-food elimination diet includes elimination of milk, wheat, soy, egg, nuts, and fish/seafood from diet. This induces remission in approximately 67% of patents compared with 13% with placebo noted in 9 observational studies. It requires repeated endoscopy to assess for response, as each food group is then reintroduced. Elimination diets of 2 and 4 food are less effective[5,26]; however, a recent study looked at a step-up approach to therapy in which participants began with a 2-food elimination diet (milk, gluten) and if no response after 6 weeks, went to a 4-food elimination. Nonresponders at 6 weeks then went to the 6-food elimination. The results showed remission rates of 43% with 2-food elimination, 60% with 4-food elimination, and 79% with 6-food elimination, with greater than 90% of the 2- and 4-food group responders having 1 to 2 food triggers. Endoscopic procedures and diagnostic times were reduced by 20% with this step-up strategy.[27]

Table 3
AAAAI/ACAAI joint task force on allergy/immunology practice parameters and AGA release guideline on the management of eosinophilic esophagitis

Recommendation	Strength of Recommendation	Quality of Evidence
In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment	Strong	Moderate
In patients with EoE, the AGA/JTF suggests topical glucocorticosteroids rather than oral glucocorticosteroids	Conditional	Moderate
In patients with EoE, the AGA/JTF suggests using elemental diet over no treatment	Conditional	Moderate
In patients with EoE, the AGA/JTF suggests using an empirical, 6-food elimination diet over no treatment	Conditional	Low
Testing-based elimination diet over no treatment	Conditional	Very low
In patients with EoE in remission after short-term topical glucocorticosteroids, the AGA/JTF suggests continuation of topical glucocorticosteroids over discontinuation	Conditional	Very low
In adult patients with dysphagia from a very low-quality endoscopic dilation over no dilation	Conditional	Very low
In patients with EoE, the AGA/JTF recommends using anti-IL-5 therapy for EoE only in the context of a clinical trial	No recommendation	Knowledge gap
In patients with EoE, the AGA/JTF recommends using anti-IL-13 or anti-IL-4 receptor therapy for EoE only in the context of a clinical trial[a]	No recommendation	Knowledge gap
In patients with EoE, the AGA/JTF suggests against the use of anti-IgE therapy for EoE	Conditional	Very low
In patients with EoE the AGA/JTF suggests using montelukast, cromolyn sodium, immunomodulators, and anti-TNF for EoE only in the context of a clinical trial	No recommendation	Knowledge gap

Abbreviation: TNF, tumor necrosis factor.
[a] Dupixent is an anti-IL-4, IL-13 agent FDA approved on May 20, 2022.

- Allergy testing–based elimination diets consist of eliminating foods that are positive on skin and/or atopy patch testing. Because EoE is not IgE mediated and atopy patch testing for foods is not standardized, this is less effective than the previous 2 dietary approaches. However, 50.8% of patients respond to this approach compared with 13.3% to placebo. This approach has largely fallen out of favor.

Medications

Before May 2022 there were no medications approved by FDA for EoE. In May 2022 dupilumab, a monoclonal antibody against IL-4 and IL-13, became the first FDA-approved medication for the treatment of EoE in patients older than 12 years and 40 kg (88 lbs) in weight. Topical steroids and PPIs are most commonly used for first-line management.

Table 4
Current treatment options for eosinophilic esophagitis

	Treatment	Mode of Action	Dose	Formulation	Efficacy vs Placebo	Side Effects	Clinical Considerations
Diet[a]	Elemental	Avoids allergen	Individualized	Amino acid–based formula	93.60%	Unpalatable	Needs support to ensure adherence; cost, IgE-mediated food sensitivity on reintroduction
	6-food Elimination diet	Avoids allergen	—	Eliminate milk, wheat, soy, egg, nuts, fish/seafood	67.90%	—	Needs support to ensure adherence; dairy and wheat are the most common culprits.
	Allergy testing–based elimination diet	Avoids allergen	—	Eliminate allergens in diet	50.80%	—	Needs patient motivation, less effective than 6-food elimination
Drugs	Proton pump inhibitors	Anti-inflammatory omeprazole maintains mucosal integrity	20 mg BID	Capsule	41.70%	Diarrhea including cliff	Easily available, low-cost, well-tolerated needs higher doses than in treatment of GERD
Tropical corticosteroids	Fluticasone	Anti-inflammatory	440–880 UG BID	Inhaler-swallow	64.90%	Oral and esophageal candidiasis	Adrenal suppression off-label use.
	Budesonide	—	1–2 mg BID	Slurry	—	—	—
	Dupilumab	Biological anti-IL-4 and IL-13	300 mg weekly	Subcutaneous injection	60.00%	Respiratory infection arthralgia	12 y and clear weighing at least 40 kg. Avoid live vaccines; pregnancy registry

[a] See text for additional diets.

Table 5
Common food triggers in eosinophilic esophagitis

Children	Adults
• Milk	• Wheat
• Wheat	• Milk
• Egg	• Soy
• Soy	• Egg
• Corn ("other grains")	• Corn ("other grains")
• Beef ("meats")	• Beef ("meats")

Topical Steroids

Topical steroids include either fluticasone via inhaler swallowed 88 to 440 μg twice daily in children and 440 to 880 ug twice daily in adults, or oral viscous budesonide (budesonide nebulizer solution mixed in vehicle such as honey, applesauce, maple syrup, or sucralose to make slurry), 0.5 to 1 mg twice daily in children and 1 to 2 mg in adults. They have shown to induce remission in 65% of patients versus 13.3% with placebo.

It is important to be aware of the risk of esophageal candidiasis with this therapy and treat the patient appropriately should they develop odynophagia.

Adrenal suppression (1.4%) with a higher dose of 2 mg bid of budesonide has been reported in a cohort of 318 patients followed-up for 8 weeks.[5]

Proton Pump Inhibitors

PPIs are traditionally needed in higher doses than in the management of GERD and result in remission in approximately 41% of patient's versus 13.3% with placebo.[5] PPIs both maintain mucosal integrity by reducing acidity and are also proposed to have antiinflammatory effect by reducing release of eotaxin-3 in response to IL-13[28] (**Fig. 2**).

Endoscopy with Dilatation

Endoscopy with dilatation is needed in more advanced stenotic disease. Dilatation provides immediate and long-term relief but does not address the underlying process. There is risk of esophageal perforation but much less than initially thought. The optimal role of dilatation is controversial.

Monitoring Therapy

Current criteria for monitoring treatment response requires an endoscopy after initiation of treatment and after changes in treatment; however, less invasive procedures to assess response and esophageal function show promise.[5]

Assessment of response has been demonstrated with use of an esophageal capsule with mesh attached to a string for esophageal scrapings, an esophageal string, or transnasal endoscopy as alternatives to traditional endoscopy. Esophageal function can be assessed using a gene sequence or functional luminal imaging probe a US FDA–approved measuring tool to measure pressure and distensibility of the esophagus and risk of stenosis.[5] There are no guidelines for routine EGD surveillance after remission has been achieved.

Duration of Therapy

Current guidelines favor ongoing treatment, as there is disease recurrence when treatment is discontinued. Therefore, close monitoring of patients by either the PCP, allergist, or gastroenterologist for adherence to treatment, recurrence of symptoms, and possible side effects and complications of therapy is needed.

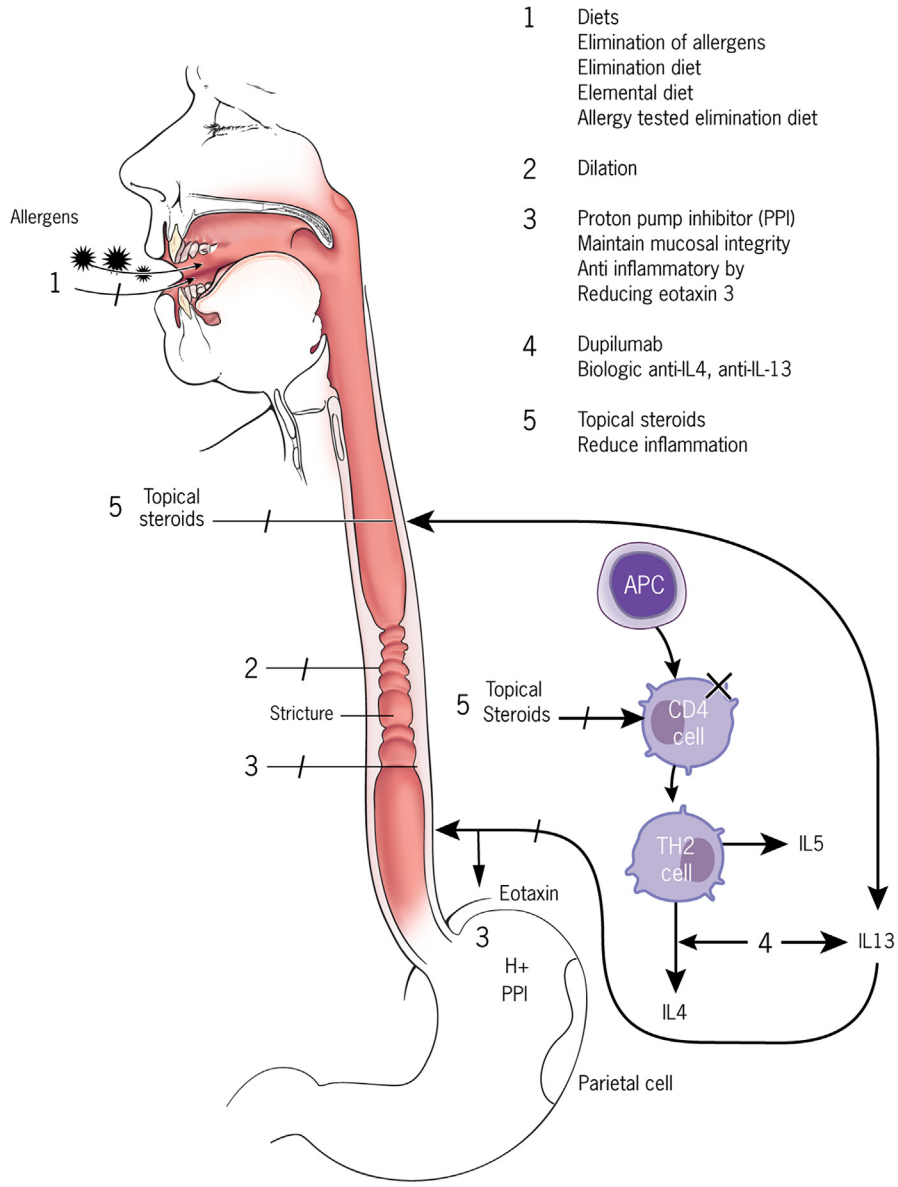

Fig. 2. Mechanism of action of medications eosinophilic esophagitis. (*Reprinted with permission*, Cleveland Clinic Foundation ©2023. All Rights Reserved.)

SUMMARY

With the increase in prevalence of EoE in the general population, this is a condition primary care practitioners will increasingly encounter in their practice. Increased awareness of the condition, maintaining a high index of suspicion, appropriate referral for endoscopy, and partnering with the patient and with specialists in gastroenterology and allergy immunology are essential to provide the best clinical outcome.

CLINICS CARE POINTS

- Keep EoE in mind when patients present with symptoms such as dysphagia, food impaction, unexplained vomiting, abdominal pain, food refusal, or failure to thrive, especially if they have other atopic conditions.
- Keep EoE in mind in patients with GERD that is refractory to standard treatment.
- Screen periodically for EoE in patients with atopic conditions.
- Gastroenterology referral is needed for diagnosis by EGD with biopsies; allergists can suspect and help manage but cannot diagnose EoE.
- The most common trigger foods are milk, wheat, egg, soy, grains, and meats. There are numerous dietary elimination options, but with all, adherence is challenging and nutritional support is critical.
- PPIs are now considered an effective treatment option for EoE and are safe.
- Dupilumab is an FDA-approved medication for patients aged 12 years and older and who weigh at least 40 kg (88 lbs).

DISCLOSURE

The authors have nothing to disclose.

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