# Clinical Evaluation of the Child with Eosinophilic Esophagitis

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**KEYWORDS**

- Eosinophilic esophagitis • Pediatric eosinophilic esophagitis
- Transnasal endoscopy

**KEY POINTS**

- Clinical symptoms of eosinophilic esophagitis (EoE) vary based on age with feeding difficulties, vomiting, and/or abdominal pain as common presenting symptoms in children and with dysphagia and food impactions being more common in adolescents and adults.
- Histologic evidence of an eosinophil predominant esophageal inflammation is required for diagnosis. Less-invasive monitoring methods without the requirement for anesthesia such as transnasal endoscopy have emerged to monitor disease or response to therapies.
- First-line treatments for EoE include medications (proton pump inhibitors and swallowed topical steroids) dietary therapy and esophageal dilation. As esophageal dilation does not address underlying inflammation, it is not recommended as monotherapy in children.
- Dupilumab, a monoclonal antibody that blocks IL-4 receptor alpha, is approved for treatment of EoE in patients $\geq$12 years of age and $\geq$40 kg. At present, it is typically used in specific clinical scenarios.

## INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated disease characterized clinically by symptoms related to esophageal dysfunction and histologically

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by eosinophil-predominant esophageal inflammation.[1] The prevalence in Western countries is estimated to be 0.4% among children and adults.[2] The pathophysiology is multifaceted and likely due to a complex interplay of genetic, heritable, environmental, and cellular factors.[3] Patients with EoE are more often male and frequently have comorbid atopic conditions, such as immunoglobulin E (IgE)-mediated food allergies, atopic dermatitis, asthma, and/or allergic rhinitis.[2]

Symptoms differ depending on age with feeding difficulties, vomiting and/or abdominal pain, and reflux symptoms as common presenting symptoms in children and with dysphagia and food impactions being more common in adolescents and adults.[2] In addition to clinical symptoms, pathologic evidence on esophageal biopsies is also required for diagnosis, defined as $\geq$ 15 eosinophils per high powered field in the esophageal mucosa after ruling out other causes of esophageal eosinophilia.[1,2] Previous diagnostic criteria for EoE required demonstrating persistent esophageal eosinophilia following treatment with high-dose proton pump inhibitor (PPI) therapy, theoretically ruling out gastroesophageal reflux disease (GERD).[1] However, more recent studies demonstrate that PPIs may treat EoE based on their anti-inflammatory properties in a subset of patients.[4] Therefore, guidelines for EoE were recently updated to list PPIs as a treatment option for EoE.[4] Complications of untreated EoE include malnutrition, feeding difficulties, esophageal stricture formation, and food impaction.[2] EoE is unfortunately rarely outgrown, and thus requires chronic treatment.[2]

## EPIDEMIOLOGY

Since the initial descriptions of EoE as it is known today in the mid-1990s,[5] EoE has emerged from an initially rare disease to one that is increasing in incidence and prevalence[6–8] which seems to outpace increased knowledge about EoE.[9] A recent systematic review and meta-analysis identified a pooled prevalence rate of 22.7/100,000 persons with a higher prevalence in adults (43.4/100,000) than in children (29.5/100,000).[10] However, significant heterogeneity among included studies existed, particularly due to the difference in definition based on responsiveness to PPIs.[10] Prevalence of EoE also varies based on location as it is more commonly reported in North America, Western Europe, and Australia and less often reported in other areas of the world.[9]

EoE has a clear male predominance with a male-to-female ratio of nearly 3:1[11] and a strong familial pattern as evidenced by concordance of 58% in monozygotic twins.[12] However, a concordance of 36% in dizygotic twins and 2.4% in non-twin siblings[12] demonstrates the effects of genetic and environmental influences.[3] Additionally identified risk factors include genetic variants, cellular pathology (ie, impaired epithelial barrier), atopic status, and environmental factors such as cesarean birth and antibiotics.[3]

Children diagnosed with EoE are more likely to be White, non-Hispanic[11] and from English-speaking, socioeconomically advantaged neighborhoods.[13,14] However, as this is not the case in other atopic diseases, it is unclear if this reflects the true epidemiology of EoE or results from discrepant health care access and other barriers.[13]

## CLINICAL SYMPTOMS

The clinical symptoms of EoE are due to esophageal dysfunction, vary according to patient age and can often be nonspecific such as abdominal pain and/or vomiting.[2] Food refusal, vomiting, and failure to thrive are common in the infant population. Vomiting, abdominal pain, heartburn, regurgitation, and feeding refusal/aversion are often

reported in school age children with dysphagia, food impactions, and heartburn being more prevalent in older children, adolescent, and adult patients.[15,16] Patients often develop compensatory mechanisms such as avoiding certain foods with denser textures, taking smaller bites, chewing foods for a prolonged period and using sauces or liquids to lubricate food.[17] Clinical symptoms often do not correlate with histologic findings.[18]

EoE is frequently associated with other atopic diseases as 68% of patients also have another allergic disease such as rhinitis, asthma, and/or atopic dermatitis. In addition, other food allergies have been reported including oral allergy syndrome, urticaria, or diarrhea. Many patients also have a high frequency of aero-allergen sensitization and more than 50% have IgE-mediated food allergen sensitization. Allergic airway diseases often precede the development of EoE suggesting that the initial sensitization might take place in the airways.[19]

A few studies suggest that ethnicity may also impact presenting symptoms. Recent literature has demonstrated that pediatric Black patients are more likely to present with multiple atopic comorbidities and failure to thrive/poor growth while non-Black patients were more likely to present with abdominal pain.[20] Similarly, a recent retrospective chart review demonstrated that Black children when compared with White children were younger at diagnosis and at first dilation, arguing for greater disease severity at diagnosis.[13] However, these results have not been confirmed and may reflect discrepancies in access to care as opposed to inherent differences in symptomatology.[13]

Clinical scoring systems for EoE have been difficult to create. Owing to the differing clinical symptoms based on age, the Pediatric Eosinophilic Esophagitis System Score, the only validated outcome measure of pediatric patients with EoE, incorporates symptoms such as nausea and abdominal pain which differ from adult outcome measures that focus more on dysphagia.[21,22] A recently proposed Index of Severity for Eosinophilic Esophagitis for patients with known EoE incorporates 3 domains: symptoms, endoscopy, and histology to assess EoE as inactive, mild active, moderate active, or severe active.[22] Although specific symptoms are not specified due to the variance based on age, the severity is based on frequency (ie, weekly to multiple times/day) and complications such as malnutrition with body mass < 5% or decreased growth trajectory indicating severe disease.[22]

## PHYSICAL EXAMINATION

There are no pathognomonic clinical examination findings that are diagnostic of EoE. In the pediatric population, particular attention to growth is needed as up to 30% of children have evidence of failure to thrive secondary to malnutrition.[23,24] As most patients with EoE will have comorbid conditions, it is also prudent to assess for evidence of atopic comorbidities on examination as their presence may impact management of EoE (discussed in more detail in the next section).[25]

## ENDOSCOPIC FINDINGS

Esophagogastroduodenoscopy (EGD) with biopsy is required for the diagnosis of EoE.[26] In pediatrics, EGD is typically done under general anesthesia or conscious sedation. Although there are no pathognomonic endoscopic markers to make the diagnosis of EoE, several endoscopic findings have been associated with EoE including longitudinal furrows, edema, white exudate, esophageal rings, esophageal stricture or narrow caliber esophagus, and crepe paper mucosa. Longitudinal furrows, edema and exudate reflect acute inflammatory changes in the esophagus, whereas

the features of esophageal rings, stricture and crepe paper mucosa reflect chronic fibrotic features. The Endoscopic Reference Score (EREFS Score) is a standardized assessment tool that provides a numerical score at the time of EGD to grade the presence and severity of endoscopic findings including Edema, Rings, Exudate, Furrows and Stricture.[27] The EREFS has been shown to correlate with histologic features in order to be used with histology as an outcome measure to assess treatment response.[28,29]

## HISTOLOGIC FEATURES AND DIAGNOSTIC CRITERIA

The diagnosis of EoE requires both symptoms of esophageal dysfunction and histologic confirmation.[26] Esophageal mucosal biopsies are obtained from the esophagus at multiple levels for histologic evaluation. Normally, the esophagus is devoid of eosinophils. In EoE, esophageal eosinophilia is present in the esophageal mucosa (defined as $\geq$ 15 eosinophils per high powered field), but other histologic changes can also be seen in EoE including basal cell hyperplasia, rete peg elongation, lamina propria fibrosis, eosinophilic microabscesses, and dilated intercellular spaces.[26,30] The EoE Histologic Severity Score is a histologic scoring system that has been developed to provide a broad assessment of histologic features in addition to peak eosinophil count.[30,31] The histologic features are given a grade for degree of activity and stage for degree of the specimen involved.[30,31] This scoring system has been shown to correlate with peak eosinophil count.[30]

## COMPLICATIONS OF EOSINOPHILIC ESOPHAGITIS

EoE is a chronic disease that requires long-term management.[2] The goal of treatment of EoE is to improve symptoms, quality of life, and prevent disease progression and potential complications. The delay in the diagnosis of EoE or untreated EoE can lead to remodeling of the esophagus and increase the risk for development of esophageal stricture.[32] One study noted that with each additional year of undiagnosed EoE, the risk of stricture increased by 9%.[33] Potential complications of EoE include esophageal strictures that may require endoscopic dilation and acute food impactions that may require urgent endoscopic removal. In the pediatric population, additional complications of untreated EoE include malnutrition/failure to thrive and persistent feeding difficulties.[2,34]

## TREATMENT

Treatment of EoE includes medications (ie, PPI or swallowed topical corticosteroid [TCS]), dietary therapy, or esophageal dilation. Dupilumab, a monoclonal antibody, has been recently approved for patients $\geq$12 years and at least 40 kg.[35–37] Although some current guidelines recommend selecting one therapy among PPI therapy, TCS, and dietary therapy as an initial treatment, a significant number of clinicians continue to follow the recommendations adopted from the original guidelines that suggest initial therapy should utilize aggressive PPI therapy as a first-line treatment.[38,39] These guidelines were written before the approval of dupilumab which is the only FDA-approved therapy for EoE. Despite its FDA approval, currently most clinicians generally consider dupilumab as either a step up therapy for patients who fail other treatment options or as first-line therapy in specific clinical contexts (discussed in the next section).[40]

Multidisciplinary care in EoE has been associated with high patient satisfaction and high quality care.[41] In addition to a gastroenterologist and allergist, comprehensive

multidisciplinary care in pediatric EoE may include a dietician and an occupational/speech therapist with an expertise in feeding dysfunction. Dieticians with an expertise in EoE are instrumental in implementation of dietary therapy and evaluation of potential nutritional deficiencies.[24] Similarly, feeding specialists can assist with maladaptive feeding behaviors commonly encountered in pediatric EoE.[42]

### *Proton Pump Inhibitors*

PPIs are a class of medications commonly used in the treatment of GERD. In 2007, because GERD had been demonstrated to be a cause for esophageal eosinophilia, the original consensus guidelines for the definition of EoE recommended to rule out GERD with a trial of PPI.[26] If esophageal eosinophilia persisted despite PPI therapy, the etiology was then likely related to food antigens. There is substantial evidence that PPIs decrease esophageal eosinophilia in children, adolescents, and adults.[43] Patients with esophageal eosinophilia who respond to PPI have similar clinical, histologic, and molecular features as those with food-driven EoE.[43] Therefore, in 2018, consensus guidelines were updated to recommend that PPIs be considered a treatment of esophageal eosinophilia rather than part of the diagnostic criteria.[43] A meta-analysis including both pediatric and adult studies showed a 61% clinical response and 50% histologic response to PPI.[44]

### *Swallowed Topical Corticosteroids*

TCSs have been shown to reduce esophageal eosinophilia in patients with EoE. They are typically administered either as an oral viscous budesonide slurry or by using a metered dose inhaler, such as fluticasone or ciclesonide that is swallowed. When topical steroids are given by metered dose inhaler, patients are instructed to puff the medication into their mouth and swallow rather than inhale it. When given as a viscous solution, patients mix the budesonide liquid with a mixing agent, typically sucralose (Splenda), to make a viscous slurry that they then swallow.[45] They then do not eat or drink for at least 30 minutes. These medications are provided to coat the esophagus to achieve a topical anti-inflammatory effect. The efficacy of TCS ranges from 60% to 90%.[46–52]

### *Esophageal Dilation*

Esophageal dilation is an important therapeutic modality in the treatment of EoE.[53] It is used when patients have esophageal strictures or narrowing.[53,54] Esophageal dilation is typically performed via bougie dilators or through the scope balloon dilators.[53,55–57] Medications and diet elimination reduce or eliminate esophageal eosinophilia, whereas esophageal dilation does not, and is typically used concomitantly with medical therapy. Chest pain is the most common complication post esophageal dilation and complications of bleeding and perforation are exceedingly rare.[53,55–57]

### *Dietary Therapy*

Dietary therapy was the first therapy utilized for EoE and has been shown to decrease esophageal eosinophilia. Standard elimination diets for EoE include elemental diets utilizing amino acid-based formulas, directed diets based on allergy testing, or empiric dietary elimination diets.[34] The elemental diet consists of exclusive feeding with an amino acid-based formula with high success rates, up to 90% in children and 94% in adults[58]; however, this diet is highly restrictive due to poor palatability, social implications, and often requiring placement of a gastrostomy tube, limiting its practical use for treatment of EoE.[34]

Targeted allergy testing-directed diets, include diets in which foods are removed based on positive IgE-mediated and/or atopy patch allergy testing. This method of food removal has generally been unsuccessful in identifying EoE triggers with an efficacy of approximately 45%.[39,58,59]

Empiric elimination diets consist of avoiding foods that are deemed the most likely cause of food allergens in EoE without allergy testing.[34] Commonly recommended empiric elimination diets are the 6-food elimination diet (6FED) consisting of avoidance of cow's milk, wheat, egg, soy, peanut/tree nuts and fish/shellfish; 4 food elimination diet (4FED) with avoidance of cow's milk, egg, wheat, and soy/legumes; 2 food elimination diet (2FED) with avoidance of cow's milk and wheat; and the 1 food elimination diet (1FED) with avoidance of cow's milk. In general, the more restrictive the diet the more successful with efficacy of the 6FED reported as high as 74%,[34] the 4FED up to 64%,[60] the 2FED 43%,[61] and 51% in the 1FED.[62] However, the success rate of empiric elimination diets varies greatly based on the study and, in general, is more efficacious in pediatric patients than adult patients.[58,59] For example, a recent prospective observational study of 41 pediatric patients who underwent the 1FED demonstrated histologic remission in 51%,[62] whereas a recent randomized multicenter open label trial of adult patients demonstrated success in 34% of patients on the 1FED.[63]

The decision about which diet to select is based on shared decision making between the physician and patient/family. Because a dissociation between clinical symptoms and histologic findings is common,[18] it is almost always essential that mucosal biopsies be obtained after introduction or change in any therapy or food elimination or reintroduction to assess histology and treatment success.[34] Therefore, extensive elimination diets are typically accompanied by an increased number of EGDs with subsequent food reintroductions. As the majority of patients with EoE only has 1 to 2 food triggers, beginning with a less restrictive diet may be a reasonable approach.[64] Molina-Infante et al. noted a 20% reduction in endoscopies when using a step-up approach as opposed to a step-down approach to dietary therapy. [61] Other factors such as the age, nutritional status and social/financial factors may weigh into the decision on selecting dietary therapy as a treatment and the specific type of diet.[34]

### *Biologic Therapy/Dupilumab*

Dupilumab is a monoclonal antibody that blocks IL-4 receptor alpha, thereby inhibiting IL-4 and IL-13, two key cytokines in allergic inflammation. As of June 2022, dupilumab was approved for treatment of EoE in patients $\geq$12 years of age and $\geq$40 kg due to improvement in clinical symptoms, histologic inflammation and endoscopic findings in pivotal clinical studies.[35–37] More specifically, in the phase 3 randomized placebo-controlled trial by Dellon and colleagues, 60% of patients who received dupilumab 300 mg every week achieved histologic remission as defined by the primary endpoint ($\leq$6 eos/hpf) compared to 5% in the placebo group ($P < .001$) with a secondary endpoint (<15 eos/hpf) noted in?? 75% increase compared to placebo. Similar histologic findings were noted in every other week dosing. Clinical symptoms were assessed by the Dysphagia Symptom Questionnaire with a significant improvement in symptoms with weekly dupilumab dosing but not every other week dosing.[37] The most common reported adverse event in the dupilumab group was injection-site reactions with conjunctivitis being rare (a common adverse event of dupilumab in other conditions). Of note, a majority of this cohort (70%) had previously tried additional therapeutic options for EoE such as dietary therapy or TCS and 89% had a comorbid atopic condition.[37] Clinical trials in a younger age group for EoE are currently ongoing.[65]

Although dupilumab is the only FDA-approved therapy for EoE, there is strong evidence to support the initial use of either dietary therapy or medical therapy (PPI or TCS).[39] Given the refractory nature of the population studied that lead to dupilumab's approval and the cost of the therapy, the initial use of dupilumab in specific clinical scenarios may be reasonable. Following its approval, Aceves and colleagues suggested consideration of dupilumab as a first-line agent in patients with comorbid atopic conditions that would qualify them for dupilumab, or patients with a strong preference to avoid diet therapy or swallowed topical steroid therapy.[40] They otherwise recommended dupilumab as a step up therapy for patients who are difficult to treat, exhibiting poor growth, on severe dietary restriction/elemental diet, with significant esophageal stricture, refractory to current therapy, or experiencing adverse effects (ie, iatrogenic adrenal insufficiency) to current therapy.[40]

## EVALUATION OF ATOPIC COMORBIDITIES

The majority of patients with EoE has atopic comorbidities with EoE being a late manifestation of the atopic march.[66] Evaluation of comorbidities is necessary in providing comprehensive care as their presence may impact management decisions regarding EoE. Patients with EoE have a higher prevalence of IgE-mediated food allergy than the general population (10%–60% compared with 8%[25,67–71]). Additionally, up to 4% of patients have biopsy-confirmed EoE to the same foods that they outgrew as an IgE-mediated allergy.[72] Oral immunotherapy (OIT), a treatment of IgE-mediated food allergy which is discussed further sections, has also been associated with development of EoE in 3% to 5% of cases.[73,74] Knowledge of comorbid IgE-mediated food allergies may impact the treatment decision for EoE. For example, if many common EoE trigger foods are already avoided, an empiric elimination may be less successful[34] or may render dietary therapy difficult due to concerns for further nutritional compromise and quality of life.[34]

Allergic rhinitis is similarly more common in pediatric patients with EoE compared with those without (30%–93%[25,71,75,76] compared with 13%[77]). Although food allergens are the culprit in the majority of patients with EoE, aeroallergens are a trigger in a small subset of patients[78] with rare case reports of patients with primarily aeroallergen-driven EoE.[79] Aeroallergen-exacerbated EoE has been noted to occur in approximately 3% to 5% of patients,[80,81] characterized by patients who respond to typical treatment for EoE but have clinical and histologic flares coinciding with the pollen season. In these cases, knowledge of their aeroallergen-sensitization profile may impact decisions on timing of endoscopies.[78] Pesek and colleagues noted that pediatric patients sensitized to perennial aeroallergens are less likely to respond to traditional therapies,[82] highlighting that perennial aeroallergen exposure may contribute to disease in treatment refractory patients. Therefore, a comprehensive evaluation and management of allergic rhinitis is essential in providing care to patients with EoE.

Atopic dermatitis and/or asthma both have an increased prevalence in EoE compared with the general population (20%–55% vs[25,71,76,83] 12.5%,[84] and 35%–60%[25,71,76] compared with 7%[85] respectively). Knowledge of the severity of any associated atopic disease may aid in the treatment decision of patients with EoE. As previously discussed, dupilumab is currently approved for EoE (≥12 years of age and ≥40 kg),[37] atopic dermatitis (≥6 months with moderate-to-severe atopic dermatitis whose disease is not controlled on topical therapies[86]), asthma (patients ≥ 6 years of age with moderate-to-severe eosinophilic asthma[87]), chronic rhinosinusitis with nasal polyposis (≥18 years) and prurigo nodularis (≥18 years).[40] Therefore, pediatric

patients with EoE who also have comorbid atopic dermatitis and/or asthma which require biologic therapy may be ideal candidates for dupilumab.[40] Given dupilumab's approval in patients younger than 12 years for other atopic indications, patients with comorbid EoE < 12 years of age have received it with associated clinical and histologic remission.[88]

## NOVEL METHODS FOR DISEASE MONITORING IN EOSINOPHILIC ESOPHAGITIS

Performing an EGD to obtain esophageal biopsies is an important tool in assessing response to treatment.[26] Of note, as already discussed, symptom improvement reported by patients do not correlate with histologic improvement.[89] As a result, EGD to obtain biopsies continues to be the gold standard to assess for response to treatment. In pediatrics, EGD is time consuming, expensive, and has risks associated with general anesthesia. To date, no serum biomarkers exist that accurately depict disease activity. This has led to the development of less invasive methods of disease monitoring, such as unsedated transnasal endoscopy (TNE).[90,91] In pediatrics, unsedated TNE uses an ultra-thin endoscope introduced through the nasal cavity and into the esophagus to perform endoscopic examination and obtain biopsies while utilizing distraction techniques such as virtual reality to improve tolerability of the procedure.[90,91] The advantages to unsedated TNE are that it requires no anesthesia or sedation, is lower cost, requires less time for recovery and less time away from school or work.[90] Innovative methods of disease monitoring that do not require endoscopy include the esophageal string test (EST), Cytosponge, and blind esophageal brushings.[92–96] These techniques obtain esophageal luminal effluents to assess the esophagus without the need for endoscopy. The EST is a weighted gelatin capsule with nylon string attached.[92,93] Patients swallow the capsule allowing the string to unwind in the esophagus and after 1 hour the string is retrieved and the esophageal eluate is evaluated.[92,93] The Cytosponge is a capsule that dissolves in the stomach after being swallowed and releases an expandable sponge.[94,95] The sponge is retrieved from the esophagus with the attached cord and as it is being retrieved, the sponge collects cells from the esophageal mucosa.[94,95] Blind esophageal brushings obtain esophageal effluent from a cytology brush inserted through a nasogastric tube.[96] Of these less-invasive techniques, TNE is the first to be used more commonly in clinical practice while the others are currently being used in the research setting. Finally, the disadvantages of these techniques include the inability of visualizing the esophagus or detecting the presence of an esophageal stricture, the possibility of not obtaining enough esophageal tissue, and the inability of evaluating the stomach and duodenum.

## RELATIONSHIP WITH ORAL IMMUNOTHERAPY

EoE is a known side effect of OIT, a treatment for IgE-mediated food allergy, with a prevalence of biopsy-confirmed EoE after initiation in approximately 3% to 5% of cases.[73,74] Because gastrointestinal symptoms are a common occurrence after OIT, and patients are not routinely biopsied, prevalence estimates based on symptoms characteristic of EoE and/or biopsy findings may be as high as 8% to 14%.[74,97] EoE in the setting of OIT typically resolves with cessation of therapy[73]; however, there are cases of patients whose EoE persists despite discontinuation of OIT.[98]

Much is still unknown about the use of OIT and the development of EoE. Because patients with IgE-mediated food allergies are at increased risk of EoE,[97] and because patients are not routinely biopsied prior to initiation of OIT, it is not fully understood whether there is subclinical esophageal disease before the initiation of OIT. Thus, it may be impossible to know whether EoE would have developed irrespective of OIT

or if EoE is induced by OIT. To further investigate this relationship, Wright and colleagues performed baseline endoscopies on 21 adults before initiation of peanut OIT and noted that while all patients were clinically asymptomatic (thus not meeting diagnostic criteria for EoE), 24% had ≥5 eos/hpf and 14% had ≥ 15 eos/hpf.[99] Those patients underwent serial endoscopic biopsies following dose escalation and on maintenance therapy, noted that OIT-induced or exacerbated esophageal eosinophilia was common in the treatment group, but was typically transient and not correlated with gastrointestinal symptoms.[100] However, one patient did develop EoE (dysphagia accompanied by esophageal eosinophilia) and OIT was discontinued.[100]

At present, the optimal management of EoE during OIT or pursuing OIT in patients with known EoE is unknown.[101] However, particularly given the recent approval of dupilumab, shared decision making may be a reasonable approach based on balancing the risks the patient/family attributes to IgE-mediated food allergy (ie, anaphylaxis, quality of life) compared with risks of management of EoE (ie, chronic disease requiring medications and endoscopic evaluation).[101]

## SUMMARY

EoE is a chronic antigen-mediated condition of increasing prevalence characterized by clinical symptoms of esophageal dysfunction and histologic findings of eosinophilic predominant inflammation on endoscopy.[1] In the pediatric population, particular attention to symptoms such as chronic vomiting, feeding difficulties, abdominal pain, reflux, and poor growth is needed as characteristic symptoms such as dysphagia and food impaction are not common until adolescence/adulthood.[2] Recent advances in treatment of EoE include approval of dupilumab for treatment in patients ≥12 years of age and ≥40 kg.[37] Novel methods for monitoring EoE, such as the TNE and EST, allow for a less-invasive approach to assess responses to treatment without the requirement for general anesthesia, addressing a long-term need in EoE.[102] These less-invasive methods may additionally aid in future efforts to better understand questions such as the relationship between OIT and EoE, identification of patients at risk for fibrostenotic disease and optimal management of clinically symptomatic patients.

## DISCLOSURE

M. Bauer, has served as a consult for Sanofi. N. Nguyen, has served as a consultant for Regeneron/Sanofi and is on the advisory board for EvoEndo. C.A. Liacouras, has served a speaker and consultant for Abbott; a speaker for Regeneron and a speaker for Sanofi.

## REFERENCES

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128(1):3–20, e26; quiz 21-22.
2. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015;373(17):1640–8.
3. O'Shea KM, Aceves SS, Dellon ES, et al. Pathophysiology of eosinophilic esophagitis. Gastroenterology 2018;154(2):333–45.
4. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology 2018;155(4):1022–33.e1010.

5. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995;109(5):1503–12.
6. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? J Allergy Clin Immunol 2005;115(2):418–9.
7. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol 2009;7(10):1055–61.
8. van Rhijn BD, Verheij J, Smout AJ, et al. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. Neuro Gastroenterol Motil 2013;25(1):47–52.e45.
9. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology 2018;154(2):319–32.e313.
10. 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(1):3–15.
11. Mansoor E, Cooper GS. The 2010-2015 Prevalence of eosinophilic esophagitis in the USA: a population-based study. Dig Dis Sci 2016;61(10):2928–34.
12. 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(5):1084–92.e1081.
13. Mehta P, Pan Z, Zhou W, et al. Examining disparities in pediatric eosinophilic esophagitis. J Allergy Clin Immunol Pract 2023;11(9):2855–9.
14. McGowan EC, Keller JP, Dellon ES, et al. Prevalence and geographic distribution of pediatric eosinophilic esophagitis in the 2012 US Medicaid population. J Allergy Clin Immunol Pract 2020;8(8):2796–8.e2794.
15. Barni S, Arasi S, Mastrorilli C, et al. Pediatric eosinophilic esophagitis: a review for the clinician. Ital J Pediatr 2021;47(1):230.
16. Spergel JM, Brown-Whitehorn TA, Muir A, et al. Medical algorithm: Diagnosis and treatment of eosinophilic esophagitis in children. Allergy 2020;75(6):1522–4.
17. Hirano I, Furuta GT. Approaches and challenges to management of pediatric and adult patients with eosinophilic esophagitis. Gastroenterology 2020;158(4):840–51.
18. Pentiuk S, Putnam PE, Collins MH, et al. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2009;48(2):152–60.
19. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr 2009;48(1):30–6.
20. Edwards-Salmon S, Moraczewski J, Offerle T, et al. Comparing Eosinophilic Esophagitis in a Black and Non-Black Pediatric Cohort. J Pediatr Gastroenterol Nutr 2022;75(4):485–90.
21. Collins MH, Martin LJ, Wen T, et al. Eosinophilic esophagitis histology remission score: significant relations to measures of disease activity and symptoms. J Pediatr Gastroenterol Nutr 2020;70(5):598–603.
22. Dellon ES, Khoury P, Muir AB, et al. A clinical severity index for eosinophilic esophagitis: development, consensus, and future directions. Gastroenterology 2022;163(1):59–76.

23. Chehade M, Sampson HA, Morotti RA, et al. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2007;45(3):319–28.
24. Groetch M, Venter C, Skypala I, et al. Dietary therapy and nutrition management of eosinophilic esophagitis: a work group report of the american academy of allergy, asthma, and immunology. J Allergy Clin Immunol Pract 2017;5(2):312–24.e329.
25. Cianferoni A, Warren CM, Brown-Whitehorn T, et al. Eosinophilic esophagitis and allergic comorbidities in a US-population-based study. Allergy 2020;75(6):1466–9.
26. 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(4):1342–63.
27. 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(4):489–95.
28. Wechsler JB, Bolton SM, Amsden K, et al. Eosinophilic esophagitis reference score accurately identifies disease activity and treatment effects in children. Clin Gastroenterol Hepatol 2018;16(7):1056–63.
29. Hiremath G, Correa H, Acra S, et al. Correlation of endoscopic signs and mucosal alterations in children with eosinophilic esophagitis. Gastrointest Endosc 2020;91(4):785–794 e781.
30. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus 2017;30(3):1–8.
31. Warners MJ, Ambarus CA, Bredenoord AJ, et al. Reliability of histologic assessment in patients with eosinophilic oesophagitis. Aliment Pharmacol Ther 2018;47(7):940–50.
32. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, et al. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol 2018;113(6):836–44.
33. 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(6):1230–6, e1231-1232.
34. Chehade M, Brown S. Elimination diets for eosinophilic esophagitis: making the best choice. Expet Rev Clin Immunol 2020;16(7):679–87.
35. Al-Horani RA, Chiles R. First therapeutic approval for eosinophilic esophagitis. Gastroenterol Insights 2022;13(3):238–44.
36. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. Gastroenterology 2020;158(1):111–22.e110.
37. Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab in adults and adolescents with eosinophilic esophagitis. N Engl J Med 2022;387(25):2317–30.
38. 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(3):335–58.
39. Hirano I, Chan ES, Rank MA, et al. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis. Gastroenterology 2020;158(6):1776–86.

40. Aceves SS, Dellon ES, Greenhawt M, et al. Clinical guidance for the use of dupilumab in eosinophilic esophagitis: a yardstick. Ann Allergy Asthma Immunol 2023;130(3):371–8.
41. Sauer BG, West A, McGowan EC. Multidisciplinary eosinophilic esophagitis care: a model for comprehensive patient-centered care through shared decision making between gastroenterology, allergy, and nutrition. Clin Gastroenterol Hepatol 2021;19(11):2226–9.
42. Mehta P, Furuta GT, Brennan T, et al. Nutritional state and feeding behaviors of children with eosinophilic esophagitis and gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2018;66(4):603–8.
43. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference. Gastroenterology 2018;155(4):1022–33, e10.
44. Lucendo AJ, Arias A, 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(1):13–22 e11.
45. Aceves SS, Dohil R, Newbury RO, et al. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2005;116(3):705–6.
46. 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(5):1381–91.
47. Aceves SS, Bastian JF, Newbury RO, et al. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol 2007;102(10):2271–9, quiz 2280.
48. 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(2):418–29.
49. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139(5):1526–37, 1537 e1521.
50. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2015;13(1):66–76 e63.
51. Dellon ES, Woosley JT, Arrington A, et al. Efficacy of budesonide vs fluticasone for initial treatment of eosinophilic esophagitis in a randomized controlled trial. Gastroenterology 2019;157(1):65–73 e65.
52. Dellon ES, Lucendo AJ, Schlag C, et al. Fluticasone propionate orally disintegrating tablet (APT-1011) for eosinophilic esophagitis: randomized controlled trial. Clin Gastroenterol Hepatol 2022;20(11):2485–2494 e2415.
53. Richter JE. Esophageal dilation in eosinophilic esophagitis. Best Pract Res Clin Gastroenterol 2015;29(5):815–28.
54. Gentile N, Katzka D, Ravi K, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. Aliment Pharmacol Ther 2014;40(11–12):1333–40.
55. Runge TM, Eluri S, Cotton CC, et al. Outcomes of esophageal dilation in eosinophilic esophagitis: safety, efficacy, and persistence of the fibrostenotic phenotype. Am J Gastroenterol 2016;111(2):206–13.

56. Menard-Katcher C, Furuta GT, Kramer RE. Dilation of pediatric eosinophilic esophagitis: adverse events and short-term outcomes. J Pediatr Gastroenterol Nutr 2017;64(5):701–6.
57. 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;86(4):581–591 e583.
58. Arias A, 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(7):1639–48.
59. Mayerhofer C, Kavallar AM, Aldrian D, et al. Efficacy of elimination diets in eosinophilic esophagitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2023;21(9):2197–210.e2193.
60. Kagalwalla AF, Wechsler JB, Amsden K, et al. Efficacy of a 4-food elimination diet for children with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2017;15(11):1698–707.e1697.
61. Molina-Infante J, Arias Á, Alcedo J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: The 2-4-6 study. J Allergy Clin Immunol 2018;141(4):1365–72.
62. Wechsler JB, Schwartz S, Arva NC, et al. A single-food milk elimination diet is effective for treatment of eosinophilic esophagitis in children. Clin Gastroenterol Hepatol 2022;20(8):1748–56.e1711.
63. Kliewer KL, Gonsalves N, Dellon ES, et al. One-food versus six-food elimination diet therapy for the treatment of eosinophilic oesophagitis: a multicentre, randomised, open-label trial. Lancet Gastroenterol Hepatol 2023;8(5):408–21.
64. Spergel J, Aceves SS. Allergic components of eosinophilic esophagitis. J Allergy Clin Immunol 2018;142(1):1–8.
65. Available at: clinicaltrials.gov/study/NCT04394351.
66. Hill DA, Grundmeier RW, Ramos M, et al. Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March. J Allergy Clin Immunol Pract 2018;6(5):1528–33.
67. Guajardo JR, Plotnick LM, Fende JM, et al. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. J Pediatr 2002;141(4):576–81.
68. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol 2005;3(12):1198–206.
69. Jyonouchi S, Brown-Whitehorn TA, Spergel JM. Association of eosinophilic gastrointestinal disorders with other atopic disorders. Immunol Allergy Clin 2009;29(1):85–97, x.
70. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011;128(1):e9–17.
71. Capucilli P, Cianferoni A, Grundmeier RW, et al. Comparison of comorbid diagnoses in children with and without eosinophilic esophagitis in a large population. Ann Allergy Asthma Immunol 2018;121(6):711–6.
72. Maggadottir SM, Hill DA, Ruymann K, et al. Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. J Allergy Clin Immunol 2014;133(5):1487–9, 1489.e1481.
73. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014;113(6):624–9.

74. Petroni D, Spergel JM. Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy. Ann Allergy Asthma Immunol 2018;120(3):237–40.e234.
75. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. J Allergy Clin Immunol 2007;119(3):731–8.
76. Sugnanam KK, Collins JT, Smith PK, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. Allergy 2007;62(11):1257–60.
77. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol 2020;146(4):721–67.
78. Egan M, Atkins D. What is the relationship between eosinophilic esophagitis (EOE) and aeroallergens? implications for allergen immunotherapy. Curr Allergy Asthma Rep 2018;18(8):43.
79. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. J Allergy Clin Immunol 2003;112(4):796–7.
80. Ram G, Lee J, Ott M, et al. Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis. Ann Allergy Asthma Immunol 2015;115(3):224–8.e221.
81. Reed CC, Iglesia EGA, Commins SP, et al. Seasonal exacerbation of eosinophilic esophagitis histologic activity in adults and children implicates role of aeroallergens. Ann Allergy Asthma Immunol 2019;122(3):296–301.
82. Pesek RD, Rettiganti M, O'Brien E, et al. Effects of allergen sensitization on response to therapy in children with eosinophilic esophagitis. Ann Allergy Asthma Immunol 2017;119(2):177–83.
83. Brown-Whitehorn TF, Spergel JM. The link between allergies and eosinophilic esophagitis: implications for management strategies. Expet Rev Clin Immunol 2010;6(1):101–9.
84. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS Data Brief 2013;121:1–8.
85. Pate CA, Zahran HS, Malilay J, et al. The shifting prevalence of asthma and allergic disease in US children. Ann Allergy Asthma Immunol 2022;129(4):481–9.
86. Paller AS, Simpson EL, Siegfried EC, et al. Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2022;400(10356):908–19.
87. Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. N Engl J Med 2021;385(24):2230–40.
88. Spergel BL, Ruffner MA, Godwin BC, et al. Improvement in eosinophilic esophagitis when using dupilumab for other indications or compassionate use. Ann Allergy Asthma Immunol 2022;128(5):589–93.
89. Safroneeva E, Straumann A, Coslovsky M, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. Gastroenterology 2016;150(3):581–590 e584.
90. Nguyen N, Lavery WJ, Capocelli KE, et al. Transnasal endoscopy in unsedated children with eosinophilic esophagitis using virtual reality video goggles. Clin Gastroenterol Hepatol 2019;17(12):2455–62.
91. Friedlander JA, DeBoer EM, Soden JS, et al. Unsedated transnasal esophagoscopy for monitoring therapy in pediatric eosinophilic esophagitis. Gastrointest Endosc 2016;83(2):299–306 e291.

92. Furuta GT, Kagalwalla AF, Lee JJ, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. Gut 2013;62(10):1395–405.
93. Ackerman SJ, Kagalwalla AF, Hirano I, et al. One-hour esophageal string test: a nonendoscopic minimally invasive test that accurately detects disease activity in eosinophilic esophagitis. Am J Gastroenterol 2019;114(10):1614–25.
94. Katzka DA, Geno DM, Ravi A, et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2015;13(1):77–83 e72.
95. Katzka DA, Smyrk TC, Alexander JA, et al. Accuracy and safety of the cytosponge for assessing histologic activity in eosinophilic esophagitis: a two-center study. Am J Gastroenterol 2017;112(10):1538–44.
96. Smadi Y, Deb C, Bornstein J, et al. Blind esophageal brushing offers a safe and accurate method to monitor inflammation in children and young adults with eosinophilic esophagitis. Dis Esophagus 2018;31(12). https://doi.org/10.1093/dote/doy056.
97. Hill DA, Dudley JW, Spergel JM. The prevalence of eosinophilic esophagitis in pediatric patients with ige-mediated food allergy. J Allergy Clin Immunol Pract 2017;5(2):369–75.
98. Hamant L, Freeman C, Garg S, et al. Eosinophilic esophagitis may persist after discontinuation of oral immunotherapy. Ann Allergy Asthma Immunol 2021;126(3):299–302.
99. Wright BL, Fernandez-Becker NQ, Kambham N, et al. Baseline gastrointestinal eosinophilia is common in oral immunotherapy subjects with ige-mediated peanut allergy. Front Immunol 2018;9:2624.
100. Wright BL, Fernandez-Becker NQ, Kambham N, et al. Gastrointestinal eosinophil responses in a longitudinal, randomized trial of peanut oral immunotherapy. Clin Gastroenterol Hepatol 2021;19(6):1151–9.e1114.
101. Chu DK, Spergel JM, Vickery BP. Management of eosinophilic esophagitis during oral immunotherapy. J Allergy Clin Immunol Pract 2021;9(9):3282–7.
102. Nguyen N, Mark J, Furuta GT. Emerging role of transnasal endoscopy in children and adults. Clin Gastroenterol Hepatol 2022;20(3):501–4.