Eosinophilic esophagitis in children: Updates and practical aspects of management for allergists in a non–tertiary care private practice setup

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ABSTRACT

Background: *Eosinophilic esophagitis (EoE) is a chronic immune and/or antigen-mediated disease characterized by eosinophilic infiltration of mucosa (≥15 eosinophils per high power field) without any secondary etiology. Non–immunoglobulin E mediated mechanisms predominate in EoE.*

Objective: *This review concentrated on a stepwise approach for the allergist working in non–tertiary care private practice.*

Methods: *A medical literature search that focused on several areas of the latest developments in the diagnosis and management of EoE was conducted.*

Results: *There has been a steady increase in the prevalence and incidence of EoE. Clinical symptoms can vary from dysphagia to failure to thrive, depending on the age at presentation; some children develop adaptive behaviors to compensate for dysphagia, such as food preferences and slow eating. The diagnosis is based on a high index of clinical suspicion and is confirmed with endoscopy with biopsies after ruling out other causes of esophageal eosinophilia. Treatment options may include dietary therapy, pharmacologic therapies, or combination therapy. Therapeutic options may also include endoscopic dilation for stricturing disease.*

Conclusion: *Providers should be aware of recent recommendation changes in the diagnostic workup, the role of skin-prick testing, and role of the proton-pump inhibitor as first-line therapy for EoE. Also, clinicians should be aware of the emerging role of empiric dietary therapy as a preferable therapeutic option when compared with the testing-directed diet and the elemental diet. Furthermore, topical glucocorticoid therapies are available, and new developing therapies are being investigated. Reevaluation of esophageal mucosa with biopsies is required approximately 2 months after therapy for a response and after a change in therapies to confirm continued resolution.*

(Allergy Asthma Proc 43:5–11, 2022; doi: 10.2500/aap.2022.43.210084)

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophilic infiltration of mucosa (≥15 eosinophils per high power field) without any secondary etiology.[1]

METHODS

A medical literature search by using the PubMed database was conducted. The search focused on several areas of the latest developments in the diagnosis and management of EoE. The search included available literature with key search terms such as Eosinophilic esophagitis and EoE diagnosis and treatment, EoE reference score, skin test, topical steroids, and elimination diet. The selection of articles was based on the relevance for the pediatric allergist with the objective to provide a concise stepwise approach for the management of children with EoE. Reviews and searches of existing literature are exempt from IRB review.

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No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

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EPIDEMIOLOGY

The prevalence of EoE is much higher in the Western hemisphere when compared with Japan and China.[2] Recent epidemiologic data showed an increase in the prevalence of EoE in recent years. A large meta-analysis evaluated an incidence of 5.1 cases per 100,000 persons per year and a prevalence of 19.1 cases per 100,000 persons per year.[3] Children with EoE have a higher prevalence of asthma and allergic rhinitis (30–50% and 50–75%, respectively) when compared with the overall pediatric population.[4]

PATHOPHYSIOLOGY

There is evidence that the disease is associated with T-helper type 2 cell immune responses, which are typical of other atopic conditions. Elevated levels of the T-helper type 2 cell cytokines interleukin (IL) 4, IL-5, IL-13, and IL-33 are involved in the recruitment of eosinophils into the esophageal tissue, which leads to the remodeling and to subepithelial fibrosis.[5,6] EoE is also

believed to represent a heterogeneous immunoglobulin E (IgE) and non–IgE-mediated immune response to food and environmental allergens. Non–IgE-mediated mechanisms predominate in EoE.[7–9]

CLINICAL PRESENTATION IN CHILDREN

Symptoms vary from feeding difficulties, vomiting, and growth issues in young children to abdominal pain, dysphagia, and food impaction in older children and adolescents. Children with EoE can develop adaptive behavior by masking their dysphagia symptoms with slow eating, excessive chewing, taking small bites, drinking excessively with foods, and avoiding hard-textured foods.[10]

DIAGNOSTICS

Endoscopy

Characteristic morphologic features in the esophagus may include linear furrows, edema, stacked circular rings, white plaques, attenuation of the subepithelial vascular pattern, and, sometimes, strictures.[11–13] However, a normal appearance is seen in ~30% of patients.[12] Recently, an endoscopic functional luminal imaging probe was being evaluated to assess esophageal wall compliance.[12] The endoscopic reference score, in combination with histologic findings, has been used for children undergoing diagnosis and posttreatment assessment.[14]

Histology

The major diagnostic criterion is of at least 15 eosinophils/hpf (peak value) in at least one biopsy specimen.[1] Biopsy specimens should be obtained from several areas of the esophagus. An allergist should also review the pathology report to evaluate eosinophil density, basal zone hyperplasia, and other histologic findings.[15]

Other Laboratory Tests

Of patients with EoE, 50–60% will have an elevated serum IgE level.[16] A mild peripheral eosinophilia is seen in approximately half of patients with EoE.[17] Genetic testing for the EoE molecular transcriptome is commercially available, but its role in clinical management is still evolving.[18]

DIFFERENTIAL DIAGNOSIS

For the diagnosis of EoE, it is essential to exclude other causes of eosinophilic infiltration. The main differential diagnosis includes conditions such as gastroesophageal reflux disease, eosinophilic gastroenteritis, Crohn disease with esophageal involvement, connective tissue diseases, infections (fungal, viral, and parasitic), drug reactions, hypereosinophilic syndrome, achalasia, graft-versus-host disease, allergic vasculitis, drug injury, drug hypersensitivity, celiac disease, vasculitis, carcinoma, and food sensitivities.

OBJECTIVES OF MANAGEMENT STRATEGIES OF EoE IN CHILDREN

There are three objectives of management of EoE in children:

- Histologic improvement in esophageal eosinophilia and remission of inflammation, which may prevent remodeling and fibrosis (not all patients develop fibrosis)
- Subjective improvement and improvement in clinical symptoms
- Restoration of normal growth and development

Despite the lack of U.S. Food and Drug Administration approved remedies for EoE, three forms of therapies are currently used in pediatric clinical practice: dietary management, medications (topical steroids and proton-pump inhibitors [PPI]), and esophageal dilation.

ROLE OF FOOD ALLERGY IN EoE

Patients are referred to an allergist to perform food allergy tests to identify foods that cause EoE. It is critical to clarify the role of "allergies" in the pathogenesis of EoE. The mechanism of food allergy can vary from immediate IgE-mediated hypersensitivity to more chronic non–IgE-mediated response.[19] The pathogenesis of EoE seems to mostly be a non–IgE-mediated delayed, cell-mediated hypersensitivity response.[20] Because the mechanism has not been shown to rely only on an IgE-mediated pathway, the diagnostic accuracy of IgE-mediated tests (skin-prick and serum-specific IgE tests) is insufficient to develop effective elimination dietary plans for patients with EoE. Despite a predominant non-IgE mechanism involved in the pathogenesis of EoE, IgE sensitization to foods does occur, which requires skin-prick testing in a limited number of cases.[21–23]

DIETARY THERAPY

Dietary elimination may cause resolution of symptoms, esophageal eosinophilia, and, in some cases, esophageal subepithelial fibrosis.[24] The three primary choices for initial dietary avoidance of potential food allergen triggers in patients with EoE are an empiric elimination diet, a testing-directed diet, and an elemental diet.

Empiric Elimination Diet

This is the most-often advised dietary approach for EoE. The initial form of empiric elimination diet was proposed in the form of a six foods elimination diet

(SFED) that account for the majority of foods involved in EoE (milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish).[25,26] However, compliance with such a restrictive dietary approach is difficult, especially in children, which raises the question of availability of a less-restrictive dietary protocol as the initial step. Later studies[27] showed that fish/shellfish and peanuts/tree nuts are rare triggers for EoE. Therefore, subsequent data showed a more favorable compliance with a four-food group elimination diet (FFED): milk, egg, soy, and wheat.[27] There is also an option of a two-food elimination diet (milk and wheat elimination only), followed by increasing the number of eliminated to FFED and SFED if required.[28] Recently, a one-food elimination diet (milk) was tried successfully in children.[29]

Testing-Directed Elimination Diet

This approach is dietary elimination based on allergy testing (skin-prick or serum-specific IgE testing, and atopy patch testing). Skin-prick testing and serum-specific IgE testing, the two most valuable tests used in IgE-mediated food allergy, have been reported in numerous studies to have poor correlation to disease activity in EoE when used alone.[23,30–32] Therefore, skin-prick and serum-specific IgE testing are not invariably recommended to direct dietary therapy for therapy of EoE. The use of atopy patch testing has shown promise in some centers but has not been extensively reproducible.[22,30,31] Testing for IgE-mediated food allergies in patients with EoE is primarily used to identify patients who either have a history of or are at risk for developing acute allergic reactions to foods.[32,33]

Elemental Diet

The elemental diet, which consists of an amino acid–based formula, has been found to be the most effective form of dietary therapy; however, it is challenging to maintain due to the unpleasant taste and monotony and, therefore, rarely used.[34]

Potential of Having IgE Sensitization and Reaction During Reintroduction

Patients with EoE have the potential to develop IgE-mediated food allergy and even anaphylaxis on reintroduction after a prolonged period of the food(s) withheld. A possible mechanism is the loss of tolerance on removal of various foods.[32,33,35,36] Potential risk factors for developing IgE sensitization and/or anaphylaxis during reintroduction include a history of anaphylaxis, an atopic history (*e.g.*, asthma), moderate-to-severe atopic dermatitis, elevated food-specific IgE levels, or a food skin-prick test > 6 mm, especially if the elevated IgE level or skin-prick test was for an eliminated food. An epinephrine autoinjector is recommended during this period of elimination, followed by an in-office oral provocative food challenge on reintroduction.[32,33,35,37]

PHARMACOLOGIC THERAPY

Acid Suppression

Based on the latest medical literature and guidelines,[11] PPI should be considered the first step in the treatment of patients with EoE.[21] PPIs may benefit patients with esophageal eosinophilia either by reducing acid production[13] in patients with coexistent gastroesophageal reflux disease or by acid-independent, anti-inflammatory effects.[1] They showed clinical response and histologic remission rates of 50–60%.[21]

TOPICAL GLUCOCORTICOIDS

Topical steroids have been extensively studied and have shown efficacy in EoE; however, no formulation of topical glucocorticoids has been approved specifically for EoE in the United States. Among topical glucocorticoids, fluticasone and budesonide showed 60–80% improvement in endoscopic, symptomatic, and histologic outcomes.[38–41]

Adverse Effects

Dry mouth and esophageal candidiasis are the two potential adverse effects[42] as well as herpes esophagitis, cataract, impaired growth in children, and adrenal suppression.[43–45]

Other Topical Steroid Options

Studies with a small sample size and case series have shown mixed results with other topical glucocorticoids (ciclesonide, mometasone furoate) in the treatment of EoE.[46,47]

Role of Systemic Glucocorticoids

Because of the potential for adverse effects, the use of systemic steroid therapy is uncommon and is typically reserved for cases with severe disease or emergency cases of dysphagia in which other approaches are not effective.[48,49] There is no consensus on the duration of therapy; however, based on the previous scientific studies, the investigators suggest a dose of 1 to 2 mg/kg per day in divided doses (maximum 40–60 mg per day) for 2 weeks, with slow weaning over the next 4 weeks, followed by topical steroids.[50]

ROLE OF BIOLOGIC AGENTS IN THE TREATMENT OF EoE

Monoclonal antibody therapy with dupilumab, mepolizumab, and reslizumab has been investigated in various studies with mixed results.[51–54]

ESOPHAGEAL DILATION

Dilation of esophageal strictures is effective for patients who are symptomatic and with dysphagia. It is often reserved for patients for whom more conservative therapy failed but may be required as initial therapy in patients with high-grade strictures.[48]

ROLE OF AEROALLERGENS IN PATHOGENESIS OF EoE

The evidence that environmental allergies are involved in EoE is still unclear. Environmental allergies may contribute to EoE in patients with allergies in two ways. First, exposure of the esophageal mucosa of the patient who is sensitized to the minute amounts of pollen inhaled into the nose or mouth and, subsequently, swallowed, which triggers symptomatic and histologic changes.[55,56] Another possible mechanism is that allergen exposure produces a regional airway response or a more systemic response, with subsequent trafficking of eosinophils into the esophagus.[57] Evaluation and management of comorbid allergic rhinitis and asthma are potentially beneficial. Sublingual or oral routes of immunotherapy are mostly contraindicated in patients with known EoE due to reports of the development of EoE in a small portion of patients on these therapies, with resolution of disease after discontinuation.[58,59]

NATURAL HISTORY OF FOOD ALLERGIES IN EoE

EoE is a chronic disease in the majority of the children, and long-term avoidance of food allergens may be required, in contrast to the pattern seen in classic IgE-mediated food hypersensitivity in which allergies to milk, egg, wheat, and soy are usually outgrown by approximately ages 6 to 8 years.[60]

PRACTICAL RECOMMENDATIONS FOR THE MANAGEMENT OF CHILDREN WITH EoE

Step 1

Step 1 is the diagnosis of EoE.[1] Collaboration with a pediatric gastroenterologist for the diagnosis of EoE based on the diagnostic criteria described above.

Step 2

Step 2 is the discussion with the patient and/or family about further evaluation and management after establishing the diagnosis, with an emphasis on shared decision-making.[61] For instance, there can be long-term psychosocial and nutritional consequences to prolonged avoidance of foods that can lead to malnutrition and failure to thrive, and can impact quality of life and compliance for some families. In addition, multiple endoscopies may be required until a specific eliciting food is identified after 6–12 weeks of avoidance. The family needs to understand the risks and benefits of all options and the costs and risks of various interventions.

Step 3

Step 3 is the role of allergy testing.[22,23,30–33,62] Due to the controversial role of allergy testing in identifying foods that lead to EoE, we recommend food allergy testing (percutaneous skin testing and/or food-specific IgE testing) in patients who either have a history of an immediate reaction to food(s), a clear history and/or association of eczema flare-up related to a food(s), or those who are at higher risk for anaphylaxis during a prolonged period of avoidance (see the section on potential of having IgE sensitization reaction during reintroduction).[32,33,35,37] For these patients, we would prescribe epinephrine and pursue an in-office challenge during reintroduction. We do not perform atopy patch testing for foods. We recommend aeroallergen skin prick testing in patients with subjective and objective evidence of underlying IgE-mediated rhinitis and management with standard medications and/or subcutaneous immunotherapy.

Step 4

We recommend PPI as the primary therapy[21]:

- Dose and duration: Starting dose of 1 mg/kg once day; can increase to twice a day if no improvement in 4–6 weeks or start with a 1-mg/kg twice-daily therapy. The total duration for PPI therapy varies case by case; however, we recommend 8–12 weeks.[63]
- Monitoring progress: A repeated endoscopy is recommended to verify the presence or absence of EoE after establishing a clinical response in the form of symptomatic improvement after 8–12 weeks of therapy with PPI. If there are <15 eosinophils/hpf, then we generally reduce the dose and maintain PPI only once daily. If the patient continues to remain stable and develops no symptoms, then follow-up endoscopy may be performed in 6–12 months. For patients with recurrence of symptoms and/or esophageal eosinophilia of >15 eosinophils/hpf after PPI therapy, alternative therapy can be pursued (Steps 5, 7, and 8).

Step 5

Step 5 is for a patient who does not respond to PPI therapy.[64] Our approach to patients who do not respond or who have a suboptimal response with PPI is to start them on dietary therapy with or without topical steroids. For a better compliance and adherence to dietary therapy, the following step-up approach should be considered. Start with a single-food

elimination diet with milk or a two-foods elimination diet (milk and wheat), which have a success rate of 44–50%.[28,29] Patients who did not respond are moved up to an FFED (milk, egg, soy, and wheat) with a success rate of >60%,[27] and eventually to an SFED (milk, egg, soy, wheat, peanuts/tree nuts, fish/shellfish), with a success rate of > 72%.[26] If no response is observed, then we recommend proceeding with steps 7 to 8. We recommend the elemental diet in limited cases, such as in infants or toddlers in whom diet elimination is not possible; it has been shown to have a success rate of >90%.[34]

Step 6

Step 6 is the reintroduction of foods.[32,33,35] The reintroduction of foods, one at a time, is begun after clinical and histologic remission. The recommended duration of the reintroduction of a food or of several foods in the same group is up to 10 to 12 weeks. After this period, we recommend a repeated biopsy for children who are asymptomatic or nearly asymptomatic. We stop the food if the patient becomes symptomatic during this introduction period and proceed with the introduction of another food or food group after a short interval, of 2 weeks. We stop any further food introduction if the patient becomes symptomatic with the reintroduction trial of several foods and refer these patients to gastroenterologist for reevaluation and/or endoscopy, and to rule out other gastrointestinal pathologies. We recommend an in-office challenge before regular introduction if a patient was high risk for anaphylaxis and/or had a skin-prick test result of >6 mm or an elevated food-specific IgE level.[35,37] This additional step is taken to ensure safety and to avoid any unwanted reaction due to the possible loss of tolerance that occurred on removal of these foods, particularly for high-risk foods such as peanuts, tree nuts, and shellfish.

Step 7

Step 7 is failure of dietary therapy and use of topical steroids.[38–42,65,66] Treatment with topical steroids is probably the best next step, especially in children with a history of nonadherence or the failure of dietary elimination. The two most commonly used topical steroids are budesonide and fluticasone:

- Budesonide can be used by having the respules solution coat the entire length of the esophagus in the form of soft, thickened, oral viscous slurry (0.5 mg twice daily for children ages < 12 years, and up to 1 mg twice daily for adolescents). Viscous budesonide can be compounded by mixing two or four 0.5 mg per 2 mL budesonide respules with sucralose (Splenda, Heartland Food Products Group. Carmel, IN) twice a day or another carrier vehicle (honey, agave nectar or applesauce) twice a day.[65]
- Swallowed fluticasone propionate can be delivered from a metered-dose inhaler without a spacer directly puffed into the mouth to be swallowed (440 μg/day in two divided doses for children ages < 8 years). The dose for older children is 880 μg/day in two divided doses.[39] It is highly recommended to avoid food or drink for 45 minutes after swallowed steroids are administered to prevent the steroid from flushing out of the esophagus.
- Duration of therapy: Induction phase therapy for fluticasone is 6 to 8 weeks. For budesonide, it is 12 weeks, followed by clinical assessment.[65,66] A repeated upper endoscopy is recommended for most patients, especially for those who showed clinical improvement.
- Maintenance phase: Reported relapse rates are between 15% and 90% after stopping treatment.[67] Therefore, a slower taper of doses is recommended over a period of 10–12 weeks after clinical remission has been achieved. We recommend clinical monitoring as the dose is gradually lowered to the lowest effective dose, followed by clinical and endoscopic reassessment. For children with a history of intermittent or seasonal flares, swallowed steroids may be given as needed instead of as daily therapy.

Step 8

Step 8 is failure of swallowed steroid therapy.[68]For patients who did not respond to topical steroids therapy, we recommend combining the dietary elimination therapy with swallowed steroid therapy.[68] In some of these severe cases, we give a trial of oral steroids, especially for patients with severe symptoms, *e.g.*, dysphagia.

ESOPHAGEAL DILATION

Dilation is used only for patients with strictures; this will not treat their EoE. Patients who have high-grade strictures are referred to a gastroenterologist for esophageal dilation.

STRENGTHS AND LIMITATIONS

A particular strength of the outlined recommendations is a detailed, comprehensive, and up-to-date review of the relevant literature. Also, these practical recommendations offer an easy-to-understand stepwise approach in the diagnosis and management of EoE in children for primary care allergists. A few unmet needs and limitations that arose during the development of these recommendations are a lack of a multidisciplinary management protocol for EoE (involving gastroenterologists, pediatricians, allergists, pathologists, and dietitians) and a lack of

structured transition programs from pediatrics to adult specialists. Also, we were not able to provide a management strategy of patients for recalcitrant EoE (refractory to PPI, topical and/or oral steroids, and the elimination diet).

CONCLUSION

The above clinical recommendations are one approach toward diagnosing, evaluating, and treating EoE. Each provider and family will need to determine their own level of comfort.

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