

Pearls and pitfalls in the management of eosinophilic esophagitis

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ABSTRACT

Background: Eosinophilic esophagitis is a newly recognized condition driven by allergen exposure. The management of eosinophilic esophagitis can be a challenge for the practicing allergist.

Objective: Provide the allergist with the skills needed to effectively manage eosinophilic esophagitis.

Methods: A literature review of the important aspects of evaluation and management.

Results: More effective care of patients with eosinophilic esophagitis.

Conclusion: This review provided the allergist who sees patients with eosinophilic esophagitis some additional tools to help avoid the pitfalls and use the pearls in disease management.

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Eosinophilic esophagitis (EoE) is a chronic disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil predominant inflammation. EoE is a disease with a growing recognition by both primary care physicians and specialists. Treatment goals for EoE are the resolution of clinical symptoms and eosinophilic inflammation, maintenance of remission, and avoidance of potential complications, including food impactions. This review focused on some of the most important aspects in the clinical evaluation and treatment of both children and adults with EoE.

DIAGNOSIS OF EoE

Asthma, allergic rhinitis, atopic dermatitis, and food allergy are prevalent in patients with EoE.¹ EoE can be a late manifestation of the allergic march.² Most allergists see patients of all ages and provide care for their patients over many years; therefore, allergists should include an age-specific EoE history as part of their ongoing assessment, particularly in the adolescent patient when the symptom of dysphagia most often develops.³ Symptoms of EoE change with age (Table 1). In toddlers, the common symptoms are recurrent vom-

iting and food refusal. Children can also experience abdominal discomfort. Solid food dysphagia can be recognized in younger children, although this most commonly presents in the preteen to young adult years.⁴ Solid food dysphagia most probably represents progression of disease from inflammation seen in young children to the onset of fibrotic disease seen in older children and adults.⁵ Adult patients often do not report symptoms during their school-age years, which suggests that some patients have the onset of EoE as adults.

When a patient with EoE is referred to the allergist for evaluation, it is important to review both the endoscopic and histologic findings. These may often include more than one endoscopy and biopsy report. As much data as possible should be gathered. The endoscopic evaluation will determine the endoscopist's assessment of disease severity. The use of standardized nomenclature that characterizes the severity of the inflammation is becoming more common.⁶ When reading histology reports, one should be certain that there is adequate information to support the diagnosis. Ideally, there should be enumeration of the eosinophils and location of the biopsy. Biopsy specimens from more than one location in the esophagus (proximal and distal) helps support the diagnosis. Eosinophil counts of >15 per high power field are consistent with a diagnosis of EoE. Additional histologic findings, although not diagnostic, are often found. These include a thickened mucosa with basal layer hyperplasia.⁷ Occasionally, patients are referred with a diagnosis of EoE that has not been confirmed histologically; however, histologic confirmation, along with symptoms characteristic of

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Table 1 Common symptoms associated with eosinophilic esophagitis

Adolescents and Adults	Children
Solid food dysphagia	Nausea and vomiting
Food bolus impaction	Regurgitation
Heartburn	Heartburn
Chest pain	Abdominal pain
Abdominal pain	Chest pain
Overcutting food	Anorexia, feeding refusal, failure to thrive
Overchewing food	Overcutting food
Early satiety	Overchewing food
Excessive meal times	Early satiety
Drinking liquids with dry foods	Solid food dysphagia

EoE, are essential for appropriate diagnosis and management.

COMPREHENSIVE APPROACH TO THE MANAGEMENT OF EoE

The therapeutic approach to the patient should begin with a discussion of expected goals and preferences for children and adults with EoE. Parents of young children may wish to explore diet to avoid medical therapy. Busy adolescents and young adults may prefer medical therapy to avoid elimination diets. In older children and adults, when dysphagia is such a dominant feature, treatment goals are generally easily achieved, including elimination of dysphasia and normalization of histology. Treatment goals are more difficult in younger children because symptoms are variable; young children cannot provide much information about symptoms; and symptom change is harder to quantify clinically. Areas of therapy for discussion with families and adult patients include the use of proton-pump inhibitors, off-label use of corticosteroids preparations, and diet therapy. In addition, for patients being evaluated for the first time, the allergist should address the comorbid conditions associated with EoE, including asthma, allergic rhinitis, pollen food allergy syndrome, atopic dermatitis, and IgE-mediated food anaphylaxis.

PROTON-PUMP INHIBITOR THERAPY

Early studies in patients with eosinophilic infiltration of the esophagus revealed that some patients responded histologically and symptomatically to the use of a proton-pump inhibitor. This gave rise to the notion that this may be a condition separate from EoE. These early studies deemed these patients who responded to proton-pump inhibitors as having proton-pump inhib-

itor responsive esophageal eosinophilia.⁸ From this came the recommendation that all patients should undergo an 8- to 12-week trial of a high-dose proton-pump inhibitor followed by an endoscopy before establishing the diagnosis of EoE.⁹ There is recent evidence, however, that symptomatically, endoscopically, histologically, and genetically proton-pump inhibitor responsive esophageal eosinophilia is indistinguishable from EoE.¹⁰ A recent international consensus concludes that proton-pump inhibitor trials are not required for a diagnosis of EoE. A proton-pump inhibitor may be a treatment option. Dietary avoidance or swallowed topical glucocorticosteroids are starting options as well.¹¹

SWALLOWED CORTICOSTEROIDS

Currently, there are no approved topical corticosteroid preparations for EoE; however, multiple randomized controlled trials have shown the efficacy of using off-label adapted preparations of both fluticasone and budesonide (Table 2).^{12–18} One of the most common failures of therapy is the inappropriate use of medication. Patients may often receive a prescription for a metered-dose inhaler that contains fluticasone without appropriate instructions for use. It is a challenge for patients to swallow the mist from a metered-dose inhaler. A fluticasone alternative to delivering corticosteroids to the esophagus is the fluticasone diskus 250 µg, which results in a 75% improvement rate for histologic, clinical, and endoscopic findings.¹⁹ Budesonide ampules made into a slurry are effective therapy. Splenda (Splenda Heartland Consumer Products Carmel, Indiana) was the original vehicle used to thicken the budesonide to form a slurry²⁰; however, other vehicles have been used to thicken the budesonide. The most common are honey and applesauce.²¹ For some families, the cost of fluticasone or budesonide may be excessive. An alternative is to use compounding pharmacies to prepare a budesonide slurry from powdered budesonide, which is often more cost effective.

DIETARY THERAPY

Since the early observation that children with severe esophageal eosinophilia and persistent gastroesophageal reflux disease (GERD) refractory to medical and surgical therapy responded to an elemental diet,²² specialists have been searching for ways to identify culprit foods that cause EoE. Since that publication almost 25 years ago, a debate is still ongoing as to the best methods to choose a diet to resolve both symptoms and esophageal inflammation in EoE. The debate centers on empiric diets or test-directed diets. Multiple trials from both Europe and the United States have compared and contrasted these different approaches.^{23,24}

Table 2 Practical use of off-label corticosteroid preparations for EoE: Initiate therapy with either budesonide slurry or fluticasone

Preparation	Children	Adolescents	Adults
Budesonide	1 mg daily	1–2 mg b.i.d.	1–2 mg b.i.d.
Fluticasone metered-dose inhaler	88–440 µg b.i.d.	880–1760 µg bid	880–1760 µg b.i.d.
Fluticasone powder#			250 µg b.i.d.

EoE = eosinophilic esophagitis; b.i.d. = twice a day.

Instructions:

- For patients taking swallowed steroids once daily, a bedtime dose is recommended. For patients using swallowed steroids bid the first dose is in the morning. The second dose is at bedtime. Bedtime dosing increases esophageal contact time and improves effectiveness.
- Demonstrate the use of specific formulation (liquid, powder, inhaler) to the patient in the office or by using instructional videos available on YouTube (San Bruno, CA).
- Avoid having patients eat or drink for 30 min after administration.
- Avoid having patients rinse their mouth immediately after administration (different from instructions given for use in asthma).

#Consider using fluticasone powder (Flovent Diskus, GlaxoSmithKlein Research Park Triangle, NC) by removing the interior strip and using the powder contained within the diskus formulation placed directly on tongue.

Table 3 Practical considerations in discussing elimination diet therapy

Emphasize the long-term goal of managing disease by identifying a single or small number of food triggers
Discuss the potential for food aversion and eating-associated anxiety
Discuss the need for multiple serial endoscopic examinations over a period of several months during reintroduction
Discuss practical implications of a child on a restricted diet and assess parental motivation
Review the practical limitations for work, travel, holidays, and college that may impact timing of diet initiation or adherence
Consider available resources for optimizing adherence to an elimination diet (i.e., dietician to address nutritional concerns, food substitutes, meal planning, food labeling, and access to shopping for specialty items)
Discuss options if there is no histologic response to initial diet elimination (i.e., expanded diet elimination vs topical steroids)

Empiric diets are begun with food elimination based on removing food historically associated with immunoglobulin E (IgE) mediated allergy and do not rely on allergy testing. An endoscopy is required after 6–8 weeks on the diet. If the biopsy is normal, then reintroduction is begun with subsequent endoscopies and biopsies. A recent multicenter study evaluated a four-food empiric diet in children by removing egg, milk, wheat, and soy. This elimination diet was effective in 64% of the children.²⁵ On reintroduction, 62% had one culprit food identified. Numerous empiric diets have been studied in adults. European investigators use different food group eliminations than American investigators. However most elimination diets in adults remove all the major allergens, including egg, milk,

wheat, soy, fish, and nuts. These diets are generally effective in ~65% of adults with EoE.²⁶

Test-directed elimination diets are not without challenges (Table 3). Numerous studies have been done by using Prick Skin Testing (PST) and atopy patch testing to direct the diet.²⁷ These have generally resulted in resolution of disease in 40–70% of children. Reproducibility is an issue because there is a high variability in PST-directed diet results. The best results reported for children came from one center where a test-directed diet by using PST plus atopy patch testing along with milk elimination reported symptom and histologic response in 77% of pediatric patients.²⁸ The use of serum-specific IgE to foods, including component testing as a guide to direct diet therapy in EoE has not been effective.

tive and generally is not considered part of the routine evaluation in EoE.²⁹

Atopy patch testing in children to identify culprit foods in EoE was conceived to explore the possibility of determining a delayed reaction to foods. The techniques and both positive and negative predictive values of patch testing in children have been extensively reviewed.³⁰ However, a lack of standardized testing material, difficulty of test interpretation, lack of controlled studies, and a requirement for multiple visits all have led to significantly less use in EoE evaluation. A small study of atopy patch testing in adults did not reliably predict food triggers in EoE.³¹ In patients deemed candidates for food elimination, a consultation with a dietitian is helpful. When access to a dietitian skilled in EoE is not readily available, there are references that provide physicians with instructions for patients to manage appropriate food eliminations, preparation, and substitutions.³² During the 2017 Eastern Allergy Conference, a pro-con debate on diet versus medical therapy in EoE reinforced the notion that a singular approach to EoE management has yet to be found.³³

EVALUATION AND MANAGEMENT OF COMORBIDITIES

The driving factor for EoE is considered to be non-IgE-mediated food sensitivity.³⁴ However, the majority of patients have IgE-mediated comorbidities that contribute to suboptimal control of EoE if not addressed.³⁵ Their evaluation and management are important in the care of children and adults with EoE.³⁶ In a recent large multicenter analysis, 91% of patients with EoE were atopic.³ Two recent cross-sectional analyses compared children and adults with EoE to children and adults in a large primary care network. Among children with EoE, 60% had allergic rhinitis and 59% had asthma.³⁷ Among the adults, 36% had asthma, 70% had allergic rhinitis, 24% had food allergy, and 34% had pollen food allergy syndrome (PFAS).³⁸ PFAS had a remarkable 600-fold increase in patients with EoE compared with the control population.

Allergic Rhinitis

Evidence that environmental allergen exposure plays a role in EoE is more controversial than for food-driven EoE. A recent meta-analysis indicated that there is a weak correlation between pollen exposure and EoE.³⁹ However, a number of studies indicated a stronger correlation, including seasonal exacerbations of EoE,^{40,41} and the finding of eosinophils in the esophagus of subjects with atopy but no EoE during the pollen season.⁴² Taken together, this argues for a careful evaluation, including history-driven environmental allergy testing in patients

with EoE. There is a case report of a patient having improvement in the patient's EoE when on immunotherapy.⁴³ However, before any recommendations on the usefulness of subcutaneous immunotherapy (SCIT) in EoE are made, prospective studies will be required.

PFAS

PFAS is a common finding in patients with EoE compared with the general population.³⁸ In addition, PFAS is significantly higher in patients with EoE and allergic rhinitis compared with patients with allergic rhinitis and no EoE.⁴⁴ A case report implicated PFAS as the cause of EoE in an adult male.⁴⁵ Although suspected mechanisms have been postulated,⁴⁴ further work is needed to gain more insight as to mechanisms. Patients with EoE should be questioned carefully about PFAS. It would seem reasonable to avoid those foods that cause obvious symptoms.

Asthma

Asthma, as with other atopic diseases, is frequently found in children and adults with EoE.^{3,37} EoE and asthma are both thought to be associated and possibly affected by GERD. However, a well-defined common pathway has not been identified.⁴⁶

Food Allergy

The prevalence of IgE-mediated food allergy in children and adults with EoE has been established mostly through chart reviews.^{3,37} One multicenter pediatric study of children with EoE used data from The Consortium for Food Allergy Research.³ In that study, 67% reported food allergy and 27% reported anaphylaxis.³

However, in the evaluation of patients with EoE and their comorbidities, allergists are faced with the task of distinguishing IgE-mediated food allergy from non-IgE-mediated food allergy and their role in pathogenesis. Traditionally, the term "food allergy" is associated with IgE-mediated disease. However, now confusion results from the term "food allergy" being used to characterize both IgE- and non-IgE-mediated reactions. In a recent review, EoE was characterized as a non-IgE-mediated food allergy based primarily on the inability of PST to consistently predict culprit foods that cause EoE.³⁴

An understanding of these distinctions is necessary to manage various scenarios in patients with EoE. Establishing the presence of well-documented IgE-mediated reactions can predict the clinical presentation. One recent study found distinct differences in the presentation of EoE in children with clinically documented IgE-mediated food allergy compared with those with no IgE-mediated food allergy. The 29% with immediate hypersensitivity to foods presented at a younger

age, had more comorbid allergic diseases, and had more dysphagia.⁴⁷

An IgE-mediated food allergy can be lost, only to be the causative factor of EoE years later. In one study, 17 of 84 patients who outgrew IgE-mediated food allergy developed EoE to the same food.⁴⁸ The average time to symptoms of EoE was 2.4 years after reintroduction.⁴⁸ Although rare, some patients placed on an empiric avoidance diet for EoE can develop IgE-mediated allergies to a previously tolerated food.⁴⁹ Also, the approval of oral immunotherapy (OIT) to food will most probably be available in the next few years. Up to 2.7% of children who receive OIT for food allergy have been diagnosed with EoE.⁵⁰

Summary Approach to Comorbidities

There seemed to be an undefined link between EoE and IgE-mediated disease.⁵¹ This should place at the forefront of the evaluation of the patient with EoE, a history-driven selection of those skin tests best suited to define comorbidities and disease pathogenesis.

CONCLUSION

The Allergist and EoE: Past, Present, and Future

Since the original recognition of EoE, allergists have played a well-defined role in identifying and documenting the clinical characterizes and comorbidities of EoE and in uncovering its pathogenesis. Initially, allergists sought to identify food triggers with a variety of allergy tests. Although initially seeming to be a more-effective way of choosing an elimination diet than an empiric diet, allergy testing unfortunately has limitations in regard to diet selection. However, we now recognize that patients with EoE are most often atopic, and untreated comorbid allergic disease likely impacts EoE control.⁵² A number of recent publications have addressed the important interplay between atopy and EoE.^{52,53} A well-reasoned thorough approach that identifies and appropriately treats the coexistent atopic disease in patients is key to successful EoE management.⁵² As our specialty moves forward, there will be new challenges, including an increased incidence of EoE in the allergic population, increased use of sublingual immunotherapy, commercialization of food OIT, and introduction of new biologic agents for which the allergist is most knowledgeable. These challenges and others will require that allergists add effective management of EoE to their knowledge base, just as they do with all common atopic disorders.

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