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Pediatric Eosinophilic Esophagitis: Updates for the Primary Care Setting

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Abstract

Purpose of Review: Eosinophilic esophagitis (EoE) is a multifactorial, non-IgE mediated inflammatory disorder of the esophagus and is the most common cause of food impaction in the pediatric population. The purpose of this review is to describe the current recommendations for diagnosis and management of EoE.

Recent Findings: New data has associated EoE with other the other allergic disorders of the atopic march as well as several risk factors which predispose to allergic conditions. A subset of patients with esophageal eosinophilia respond to proton pump inhibitor (PPI) therapy with a partial or complete resolution of esophageal eosinophilia. Therefore, some patients can be treated with PPI alone. If this is unsuccessful, dietary elimination and swallowed steroid therapy are recommended for long-term management. There is a growing appreciation that untreated esophageal inflammation can lead to complications of fibrosis and stricture formation.

Summary: The current review will focus on the diagnosis and management of EoE in the pediatric population. Identification and diagnosis of pediatric patients with EoE is critical to prevent long-term esophageal complications.

Keywords

primary care; medical home; eosinophilic esophagitis (EoE); food allergy; non-IgE mediated food allergy; children; pediatrics

Introduction:

Eosinophilic esophagitis (EoE) is characterized by chronic inflammation of the esophageal mucosa and classically presents with symptoms of esophageal dysfunction and histologic evidence of mucosal eosinophilic inflammation. It is a histopathologic diagnosis requiring 15 or greater intraepithelial eosinophils present per high powered field on the esophageal biopsy [1]. EoE is increasingly a cause of esophageal food impaction and stricture worldwide. Pediatricians must be able to recognize symptoms suggestive of EoE and

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understand the specific health care needs of the pediatric EoE population. The current clinical evidence underlying the diagnosis and management of this increasingly common atopic disorder is presented in this review.

Epidemiology:

Case reports of EoE were first described in the 1970s. Ultimately in the early 1990s evidence pointed to EoE as a distinct non-IgE mediated food allergy syndrome [2,3]. EoE occurs at a prevalence of 1/2000 persons in the US [4]. Estimates of the prevalence from other countries including The Netherlands, Denmark, Spain and Canada are within a similar range [5–9]. Population based studies in the US suggest that the incidence of EoE is rising over time [10,11]. This can in part be attributed to increased awareness of the diagnosis. However, recent data in a large pediatric primary care birth cohort suggests that the presence of allergic comorbidities positively correlates with risk of developing EoE [12]. Similar to other atopic disease, the incidence of EoE is increasing as it is a part of the atopic march and its development is influenced by early-life factors [13,14].

EoE is characterized by a male predominance of approximately 70% [4,15,16]. One proposed mechanism for this is inheritance of risk-associated single-nucleotide polymorphisms within TSLP receptor on pseudoautosomal regions Xp22.3/Yp11.3 in male patients with EoE [17]. A similar association was not seen in females. There is also Caucasian predominance in presentation of EoE even after controlling for referral and population basis, suggesting unique pathologic and protective factors may exist [4,11,15,18]. Some studies suggest that African Americans may be more likely to present with grossly normal esophagus on endoscopy, highlighting the need for all patients suspected of EoE to have biopsies collected per diagnostic guidelines [19].

In the majority of cases, EoE is a multifactorial condition and the genome wide-array studies that have outlined specific risk alleles associated with EoE have been recently reviewed elsewhere [20]. However, there have been studies which associating specific genetic disorders with EoE. Therefore, it is important to look for these related syndromes in EoE patients, and screen for EoE in patients with these syndromes. For example, EoE patients have an 8-fold risk for connective tissue diseases including Marfan's and Loeys-Dietz syndrome [21]. Therefore, patients with EoE should be screened for hypermobility. Severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome and Netherton syndrome both present with eosinophilic esophagitis [22–24]. These specific associations are thought to reduce epithelial barrier integrity, leading to increased transit of esophageal contents into the submucosa. Eosinophilic esophagitis has been described as a feature in 65% of a cohort of patients with autosomal dominant hyper IgE syndrome caused by *STAT3* mutation and in case reports of CVID [25,26].

Presentation:

EoE can present at any age from infancy through adulthood, including elderly patients [4]. EoE is a chronic disease, and data from pediatric cohorts demonstrate less than 1% spontaneous remission [27]. The presenting symptoms of EoE vary based on the patient's

age and developmental level [15,28,29]. Importantly, symptoms do not correlate with disease severity and may be absent or mild even with relatively severe inflammation present. The converse is also true. The presenting symptoms of EoE by age are summarized in Table 1.

Many patients develop coping strategies to facilitate eating. These include avoiding dry or textured foods, prolonging meal times, cutting foods into small pieces and washing food down with liquid. Patients and parents may be unaware of these behaviors. Screening for them can be helpful in determining affected feeding behaviors, which can occur at presentation or throughout the course of disease. Dysphagia which is not responsive to medical therapy is suggestive of fixed fibrosis and should be investigated by barium swallow. If confirmed, treatment with oral steroids may be tried in the pediatric population or balloon dilation can be used to improve the caliber of the fibrotic segment.

EoE is strongly associated with co-morbid atopic conditions which require close medical management in addition to their EoE. In case cohorts, 26–50% of EoE patients have concomitant asthma, 30–90% have associated allergic rhinitis, 19–55% have atopic dermatitis and IgE-mediated food allergy is 9.8–68% in the EoE population [4,15,29–32]. The presence of IgE-mediated food allergy in addition to EoE reduces options for dietary management. Further, patients with seasonal allergic rhinitis can have seasonal flares of their eosinophilic esophagitis. These are associated with the pollen season and can be treated with intranasal corticosteroids [33]. There are reports of resolution of these symptoms with immunotherapy for some patients [27,33]. As atopic conditions can develop over time, it is essential that medical providers caring remain vigilant for signs of new or poorly controlled atopic conditions in EoE patients.

Diagnosis:

The differential diagnosis of esophageal mucosal eosinophilia is broad (Table 2). Diagnosis of EoE requires the presence of greater than 15 eosinophils per high powered field in at least one of four esophageal biopsies (Table 3). These biopsies should be obtained from multiple positions in the esophagus due to the patchy nature of inflammation in EoE, and antral and duodenal biopsies are recommended to narrow the differential diagnosis [34]. It is important to note that inflammation can be present when the gross endoscopic appearance of the esophagus is normal and therefore histopathologic analysis cannot be deferred. An updated diagnostic algorithm for EoE is shown in Figure 1.

Therapy:

The aim of EoE therapy is to reduce symptoms, induce histologic remission and prevent long-term complications including stricture formation and esophageal fibrosis [11,35]. In pediatric practice the two main therapies for EoE are dietary exclusion and swallowed steroids. Esophageal dilation plays a limited role in the management of pediatric EoE as fibrostenotic disease is seen less commonly in the pediatric EoE population than in adults.

Proton pump inhibitor:

As noted in Table 2, reflux can contribute to esophageal eosinophilia. Current guidelines suggest therapy with PPI prior to endoscopy is no longer necessary for diagnosis (Figure 1), and use of PPI as first line therapy for esophageal eosinophilia [1,36]. It is now well-established that subset of patients will have resolution of esophageal eosinophilia with higher doses of proton pump inhibitor (PPI) alone. This has been termed PPI-responsive esophageal eosinophilia (PPI-REE). The distinction between PPI-REE and EoE is critically important. If a patient has a normal endoscopy while on a high-dose PPI, eosinophilia and symptoms may return if the PPI is discontinued. In our center, 37% of children with a diagnosis of EoE and unresponsive to therapy with diet or steroids had complete or near complete response when treated with a PPI [37,38]. This demonstrates that PPI is not interchangeable with other therapy modalities for EoE. Recent studies suggest underlying similarities in mucosal gene expression changes in PPI-REE and EoE, [39,40]. and that high-dose PPI may have anti-inflammatory effects within the esophageal mucosa in addition to the known proton pump inhibitory effect [41,42].

Dietary elimination:

Dietary elimination or swallowed steroids are the mainstay of therapy for children with EoE that is completely controlled with PPI alone. Kelly et al in 1995 first identified EoE as a food allergy disorder by successfully treating 10 children with EoE using elemental formula [43]. This was the first demonstration that dietary elimination can be used to induce clinical and histologic remission in EoE. Following this study, there have been a number of attempts to optimize dietary therapy for EoE and minimize the number of followup endoscopies. The three types of diet are elemental diet, targeted elimination by allergy testing and empirical elimination. The most effective is an elemental diet, which primarily consists of an amino-acid based formula. On meta-analysis, elemental diet resulted in remission rate of 90.8% (95% CI 84.7–95.5) and was effective as treatment with oral steroids [44]. However, it is very difficult for the majority of patients to adhere to a diet consisting of strictly elemental formula. Some providers will liberalize this to include fruits and vegetables.

In targeted therapy various allergy testing methods including skin prick test and specific IgE to foods have been tried to predict foods causing EoE reactions. These IgE tests are helpful to predict risk for IgE-mediated food reactions, however they are not useful for food allergen identification or prediction of disease activity in EoE [45–50]. [51]. Targeted food elimination using a combination of food skin testing with food patch testing has been shown to have equal overall efficacy to empiric six-food elimination diets [49,50,52]. However, this approach has low negative predictive value for major allergens like milk [49]. Therefore, at this time, the clinical standard for determining patients' response to changes in EoE therapy remains endoscopy with biopsy [36,53]. Skin prick testing should be performed for patients with symptoms suggestive of IgE-mediated food allergy or allergic rhinoconjunctivitis.

The third option is empiric elimination. The most notable is the 6-food group elimination diet (SFED) which eliminates all products containing milk, wheat, egg, soy, peanut, tree nut, as well as fish and shellfish. This resulted in a 74% response rate in children [54]. Subsequent studies have demonstrated an efficacy between 50–70% [44,54,55]. However,

this may be unnecessarily restrictive because at the time of presentation with EoE, many toddler and school age children likely not have incorporated all of these food groups into their diets in significant amounts. Most children's EoE is triggered by 1–3 foods, and a careful dietary history helps to identify the potential food triggers eaten in the child's diet. [54–56]. In the pediatric population, foods removed from the diet to manage EoE can often be sequentially reintroduced after a period of avoidance with careful monitoring symptoms and biopsies after each dietary change [54–56]. Although less common, IgE-mediated food reactions have been described in EoE patients reintroducing foods after long periods of avoidance [57]. Co-management of dietary restriction and reintroduction with an allergist familiar with pediatric EoE is recommended to assist patients in identifying potentially causative foods and counseling regarding strict food avoidance.

The risks associated with dietary elimination include risk for nutritional deficiency, decreased quality of life, increased complexity of therapy need for greater number of endoscopies and increased expense [58]. At each visit, children should have their growth parameters monitored and should be screened for recurrence of esophageal symptoms such as chest or abdominal pain, dysphagia, vomiting, food refusal, slow eating, and over-chewing. Consultation with a nutritionist familiar with the management of EoE is recommended for patients on elemental or elimination diets.

Topical Steroid Therapy:

There is currently not an FDA-approved topical steroid formulation for the treatment of eosinophilic esophagitis, but it is a mainstay of medical management nonetheless. Topical steroid treatment induces remission in 50–90% of patients [1,36,59–64]. Topical steroids reduce mucosal inflammation, eosinophil counts and may also reduce fibrosis progression in patients responding to therapy [59,60,65]. Side effects include oral and esophageal candidiasis, risk of growth suppression and risk of adrenal suppression [66–68].

Swallowed budesonide or swallowed fluticasone propionate are the two formulations typically used for EoE. Budesonide as a 0.5 mg or 1 mg Pulmicort Respule® can be mixed with five packets of sucralose (Splenda™) to create a viscous slurry which can be swallowed. Small volumes of applesauce or honey can be used as an alternative vehicle if Splenda is not tolerated [69]. Fluticasone propionate should be swallowed from the inhaler directly without a spacer. Children younger than 8 should swallow 2 puffs of 110 mcg twice daily and patients over 8 should swallow two puffs of 220 mcg twice daily. All patients should be instructed to avoid rinsing the mouth, brushing teeth and food or drink for 30 minutes after administering swallowed steroids.

Oral Steroid Therapy:

Oral steroids are not a first-line therapy for EoE. Short courses of steroids may be appropriate for EoE pediatric patients with severe weight loss unable to tolerate oral intake due to dysphagia, or prior to attempting dilation if narrowing is seen on barium swallow. Due to the systemic side effect profile they are not recommended for long-term use [1,36].

Esophageal Dilation:

Esophageal strictures are one of the most severe complications of EoE, and can lead to food impaction. The risk of esophageal stricture increases with the amount of time EoE has been left untreated, and medical treatment of EoE is associated with decreased risk of impactions over time. [70,71]. In a cohort of adult patients, a 10-year increase in age of presentation was associated with a 2.1 (95% CI, 1.7–2.7) odds ratio of esophageal fibrosis [72]. The risk of stricture formation in the pediatric population is generally thought to be less than in the adult population. However, there is loss of esophageal distensibility in pediatric patients with EoE which correlated with active disease, lamina propria fibrosis and fibrotic phenotype [73]. This suggests that fibrosis may begin earlier than suspected and that control of EoE activity in childhood is important to prevent long-term complications.

Symptoms of esophageal stricture include persistent dysphagia and odynophagia, feelings of delayed esophageal transit and sensations of food impaction or “sticking” in the esophagus. Patients with esophageal stricture are likely to have compensatory eating behaviors including prolonged, careful chewing, frequent sips of fluid and cutting food into very small pieces. It is important to screen EoE patients at every visit for these symptoms and behaviors. If an irreversible stricture is suspected, a barium esophagram should be ordered to determine the degree of narrowing prior to upper endoscopy.

Biologics:

Patients with EoE often have other atopic disorders and there is a subset of patients who do not respond well to either steroids or diet. Therefore, there is significant interest in identifying targeted therapy to treat EoE. EoE is characterized by Th2-type inflammation, and as such, many of these efforts have focused on the development of monoclonal antibodies which halt the progression of Th2-type inflammation. A number of these have not been advanced to trials in a pediatric population due to lack of promising results in pediatric and adult cohorts. Omalizumab (anti-immunoglobulin E), anti-CRTH2 on Th2 cells agents RDBPCT and OC000459, reslizumab and mepolizumab have been tried in EoE with mixed results [74–77]. Mepolizumab and reslizumab (anti-IL5) are approved for the treatment of severe eosinophilic asthma. [78]. In adult EoE populations, mepolizumab decreased serum eosinophil counts and decreased the esophageal biopsy eosinophil mean and peak counts [74,79]. However, patients' symptom scores did not improve. Spergel et al conducted a prospective randomized control trial in children 5–18 years of age with PPI-nonresponsive EoE that showed histological improvement without improvement in clinical symptoms [75]. Assa'ad et al performed a multicenter, randomized, double blind trial of mepolizumab in EoE patients ages 2–17 which demonstrated that treatment with mepolizumab was safe and decreased mucosal eosinophilia [76]. However, again there was no improvement in clinical symptom scores using a pediatric symptom-specific score. More recent, data has been presented showing promise for anti-IL-4 (dupilumab) in EoE [77]. Dupilumab is currently approved by the FDA for treatment of adults with moderate to severe eczema.

Conclusion:

EoE is a non-IgE mediated complex disorder of esophageal mucosal inflammation. The diagnosis of EoE relies on accurate histopathologic diagnosis by biopsies obtained via endoscopy. In the last several years, there has been a growing recognition PPI treatment likely plays an anti-inflammatory role in some patients with esophageal eosinophilia in addition to the known role of PPI in preventing gastric acid hypersecretion. However, it is currently not possible to predict which subset of patients will respond to treatment with a PPI. Therefore, trial of high-dose PPI is recommended as the first-line therapy. For patients with non-PPI responsive EoE, mainstays of therapy are swallowed steroids or dietary avoidance of food antigen triggers. There is a need to better understand the natural history of EoE. However, our current understanding is that it is a chronic nonfatal disease that can result in esophageal fibrosis, stricture and food impaction if left untreated. There are currently no biomarkers that reliably substitute for biopsy to predict disease activity in EoE.

As in the care of all children, the role of the primary care physician remains important for children with EoE even though they will also receive specialist care. In addition to all age-appropriate routine care and health screening, additional screening for growth and nutritional concerns, development of atopic comorbidities, and psychosocial concerns is recommended. If the diet is restricted, it is helpful to work with the patient's allergist and nutritionist to explore all possible varieties and textures of a food that may be available to EoE patients to maximize flexibility in the prescribed diet. The primary care physician plays a vital role in encouraging compliance and recognizing disease flares that require specialist intervention. Therefore, the PCP can have significant influence on the successfulness of EoE patients' therapy.

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Abbreviations Used:

EoE	eosinophilic esophagitis
PPI	proton pump inhibitor
PPI-REE	proton pump inhibitor-responsive esophageal eosinophilia
GERD	gastroesophageal reflux disease
IgE	immunoglobulin E
US	United States

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Key Points:

- Symptoms of esophageal dysfunction vary by age, and should raise concern for eosinophilic esophagitis (EoE)
- Diagnosis of EoE should be made when symptoms of esophageal dysfunction are present and esophageal biopsy confirms at least 15 eosinophils per high powered field on biopsy in the absence of additional disorders which could cause esophageal eosinophilia (Table 2)
- Consensus criteria for EoE have been recently updated to reflect evidence that proton pump inhibitors (PPI) are likely better classified as a treatment option for EoE.
- Some EoE patients may be managed successfully using PPI, dietary exclusion or swallowed steroid as monotherapy. However, some patients may benefit from a combination of modalities.

Figure 1:

Updated diagnostic schematic for EoE. Patients typically require reevaluation using endoscopy and esophageal biopsy to determine the efficacy of the therapy that has been chosen.

Table 1:

Presenting symptoms of eosinophilic esophagitis by age

	Symptoms
Infants	Reflux & vomiting Weight loss & failure to thrive Coughing Food refusal
Children	Prolonged chewing & over-lubricating food; "Slow eating" Decreased appetite, food refusal, selective eating Chest pain or heartburn Abdominal pain or nausea Nausea, Vomiting Choking/gagging, feeling food is "sticking," throat pain
Adolescents & Adults	Nausea, vomiting, abdominal pain Dysphagia and retrosternal pain Food or medication impaction

Table 2:

Differential Diagnosis of esophageal eosinophilia

Gastroesophageal reflux disease
PPI-Responsive esophageal eosinophilia
Eosinophilic esophagitis, with or without other eosinophilic GI disorders present
Crohn’s disease
Celiac disease
Connective tissue disease
Infection
Hypereosinophilic syndrome
Drug hypersensitivity
Graft versus host disease
Achalasia
Pemphigus vegetans

Modified from Furuta et al [80]. and Liacouras et al [1].

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Table 3:**Diagnosis of eosinophilic esophagitis:**

Clinical symptoms of esophageal dysfunction (see Table 1)
15 eosinophils in one or more high powered field on esophageal biopsy
Lack of response to high-dose (2mg/kg/day) proton pump inhibitor
Normal pH monitoring of distal esophagus

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