

Clinical Presentation and Approach to Dietary Management of Eosinophilic Esophagitis

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Abstract: Eosinophilic gastrointestinal disorders are a group of disorders that are characterized by chronic eosinophilic inflammation in the gastrointestinal tract, leading to organ dysfunction and clinical symptoms. The disorders are considered immune-mediated and inflammatory, with strong associations to food allergy triggers. The most common eosinophilic gastrointestinal disorder is eosinophilic esophagitis (EoE), which usually presents with dysphagia and food impaction in adults and with heartburn, abdominal pain, and vomiting in children. Treatment strategies consist of medical and dietary therapies. In addition to the clinical presentation of EoE, this article focuses on dietary management, which includes controlling symptoms and bowel inflammation as well as identifying potential food triggers to help tailor a diet for long-term disease management.

Eosinophilic gastrointestinal disorders are a group of disorders that are characterized by chronic eosinophilic inflammation in the gastrointestinal tract, leading to organ dysfunction and clinical symptoms.¹ The most common eosinophilic gastrointestinal disorder is eosinophilic esophagitis (EoE), which is an immune-mediated, antigen-driven disease defined by pathologic eosinophilic inflammation of the esophagus as well as by esophageal dysfunction.² Over the last decade, EoE has gradually been recognized as an important disease by allergists, internists, pediatricians, pathologists, and gastroenterologists who are caring for both pediatric and adult patients. Previously considered a rare condition, EoE has increasingly been reported in many regions, such as North and South America, Europe, Asia, Australia, and the Middle East. The cause of the rise of EoE is thought to be multifactorial and includes a true increasing incidence of EoE in addition to a growing awareness of the condition among physicians.^{3,4} Prior studies have suggested an incidence of EoE of 10.4 per 10,000 population in children and 3.0 per 10,000 population in adults.⁵⁻⁷ The true incidence and prevalence of EoE in the general population may

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be underestimated, as these previous studies evaluated patients with symptoms warranting an upper endoscopy. Esophageal eosinophilia may be more prevalent than suggested, as demonstrated by a population-based study in Sweden that randomly surveyed 3000 adults, 1000 of whom underwent endoscopy with esophageal biopsies.⁸ One percent of all patients who underwent endoscopy and biopsy were found to have histologic eosinophilia meeting the criteria for EoE.⁸ The increase in incidence of EoE also reflects the rising trends in other immunologically driven disorders, such as asthma, atopic dermatitis, and food allergies.⁹

There are many factors behind the pathophysiology of eosinophilic gastrointestinal disorders, including the involvement of food and environmental allergens, acid interplay, and genetic factors. EoE has a male predilection both in the adult and pediatric populations. Results from 323 adult patients with EoE from 13 studies demonstrated that 76% were male, with a mean age of 38 years (range, 14-89 years).² A study of 754 pediatric patients with EoE from 16 studies found that 66% were male, with a mean age of 8.6 years (range, 0.5-21.1 years).^{2,10} White race was the most common, although EoE has been described in patients with varied ethnicities, including African American, Latin American, and Asian.¹⁰ In a case-control study that included 115 patients with EoE and 225 controls, patients with EoE were significantly less likely to have smoked cigarettes or actively used non-steroidal anti-inflammatory drugs (NSAIDs; odds ratio, 0.36 and 0.47, respectively).¹¹ However, there were no significant differences in the rates of smoking or NSAID exposure between patients with or without fibrostenosing disease, or among patients with a posttreatment histologic response. Recent research has suggested that early-life factors, including maternal fever, preterm labor, Caesarean delivery, and antibiotic or acid-suppressant use in infancy, were associated with the risk of pediatric EoE. Interestingly, having a pet in the home was protective. These results implicate early-life exposures in EoE pathogenesis and are being further investigated.¹² Notably, 70% to 80% of patients with EoE have other atopic conditions, such as asthma, allergic rhinitis, atopic dermatitis, or food allergies.²

A familial pattern has been recognized in both the adult and pediatric populations, suggesting a genetic predisposition. In a case series of 381 children with EoE, 5% had siblings with EoE and 7% had a parent with either an esophageal stricture or a known diagnosis of EoE.¹³ Due to these associations, a workup of patients should include a thorough family history.^{11,14,15} A genetic predisposition to EoE is supported by evidence of familial clustering and twin studies, which have revealed a 58% concordance in monozygotic twins and a 36% concordance in dizygotic

twins compared with fraternal siblings.¹⁶ In addition, several genetic variants that may predispose patients to EoE have been identified, particularly on chromosomes 5q22 (*TSLP* gene) and 2p23 (*CAPN14* gene). A genome-wide association study also identified links between EoE and eotaxin-3, a gene encoding an eosinophil-specific chemoattractant.¹⁷

Clinical Features

As with other diseases, some age-related differences in the clinical presentation of EoE are noted between children and adults.^{18,19} The most common presenting symptoms in adults include dysphagia, food impaction, heartburn, and chest pain, with 1 study finding that as many as 50% of adult patients with food impaction were diagnosed with EoE.² Older children and adolescents may also present with dysphagia and food impaction.⁵ Younger children present most commonly with vomiting, heartburn, regurgitation, emesis, feeding dysfunction, and abdominal pain.^{13,20} A delay of diagnosis has been reported in some adults due to prior misdiagnosis of Schatzki rings or gastroesophageal reflux disease (GERD).²¹ In many cases, these patients had undergone repeated endoscopies, esophageal dilations, and a delay in the institution of appropriate medical therapy. One reason for the delay of diagnosis is that prior literature in the pathology community equated the presence of eosinophils in esophageal mucosal biopsies with GERD; therefore, some specimens may have been misclassified as reflux. Due to this overlap, gastroenterologists who suspect a diagnosis of EoE should specifically request tissue eosinophil counts as well as a description of other inflammatory features to help differentiate EoE from GERD. Research is now aimed at a newer histologic scoring system that takes into account additional inflammatory features rather than focusing solely on the eosinophil number.²²

Endoscopic Findings

Patients with EoE have characteristic features on endoscopy suggestive of the diagnosis. The most common endoscopic features in adults with EoE include linear or longitudinal furrows (80%), mucosal rings (64%), small-caliber esophagus (28%), white plaques and/or exudates (16%), and strictures (12%; Figure 1).^{21,23} In a large clinical series of 381 children, the most common endoscopic features were linear furrows (41%), normal appearance (32%), white plaques (15%), and esophageal rings (12%).^{13,20} Some of these features can be subtle, and, therefore, missed on endoscopy; thus, it is advised to take esophageal biopsies in all patients suspected of

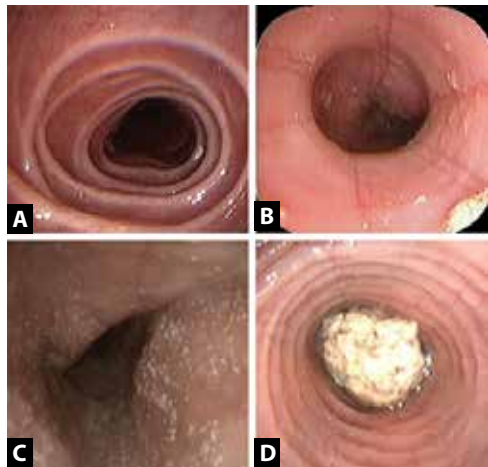


Figure 1. Endoscopic images illustrating concentric mucosal rings (A), linear furrows (B), white plaques (C), and food impaction (D), all common features of eosinophilic esophagitis in adults.²¹

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having EoE irrespective of endoscopic appearance.² The Eosinophilic Esophagitis Endoscopic Reference Score system has been validated and is a helpful tool to objectively characterize endoscopic abnormalities.²⁴

Histologic Features

Although certain endoscopic features are characteristic of EoE, the gold standard for diagnosis continues to be biopsy findings demonstrating histologic changes of increased intramucosal eosinophils in the esophagus without concomitant eosinophilic infiltration in the stomach or duodenum.¹⁰ Additional histologic features of EoE include superficial layering of the eosinophils, eosinophilic microabscesses (clusters of ≥ 4 eosinophils), epithelial hyperplasia, intercellular edema or spongiosis, and degranulation of eosinophils (Figure 2). Other inflammatory cells, such as lymphocytes, polymorphonuclear leukocytes, and mast cells, may be present in the epithelium.²⁵

Subepithelial fibrosis has been demonstrated in biopsies of both children and adults with EoE, suggesting involvement of deeper layers of the esophagus that also likely contribute to esophageal dysfunction.²⁶ Thickening of the deeper layers of the esophagus has also been demonstrated in a study using endoscopic ultrasound to investigate the esophagus.²⁷ This mucosal and submucosal fibrosis has been speculated to lead to esophageal remodeling and decreased compliance of the esophagus, thus contributing to the symptoms of dysphagia even in the

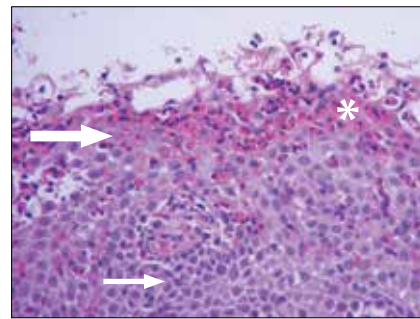


Figure 2. Histologic features in a patient with eosinophilic esophagitis show numerous eosinophils with superficial layering in the esophageal epithelium (large arrow), intercellular edema or spongiosis (small arrow), and microabscesses or clusters of 4 or more eosinophils in a group (star).

absence of an identifiable stricture.²⁸ A newer technique (Functional Luminal Imaging Probe, Crospon) has demonstrated changes in the compliance of the esophageal wall in adults and children, further implicating the role of esophageal fibrosis.^{29,30} The imaging probe has shown improvement in esophageal compliance after treatment with either diet or medication.³¹

Consensus statements suggest using a threshold value of at least 15 eosinophils per high-power field (eos/hpf) to diagnose EoE.^{2,10,32} Research has demonstrated that eosinophilic inflammation of the esophagus may not be evenly distributed within the esophagus.²¹ Therefore, at least 5 biopsies should be obtained from the proximal and distal esophagus to allow a higher diagnostic yield and potentially increase the specificity of the diagnosis, as well as help maximize the sensitivity based on a diagnostic threshold of at least 15 eos/hpf in the adult population.²¹ Although current guidelines are using an absolute threshold of 15 eos/hpf to determine active inflammation, newer histologic scoring tools described previously may have better accuracy in assessing disease activity.^{2,22}

Diagnostic Criteria

Recent consensus recommendations based on a systematic review of the literature and expert opinion have led to certain diagnostic criteria.² EoE is a clinicopathologic disease characterized by (1) the presence of symptoms, including, but not limited to, dysphagia and food impaction in adults and feeding intolerance and GERD symptoms in children; (2) eosinophil-predominant inflammation of at least 15 eos/hpf in the esophageal tissue; (3) eosinophilia isolated to the esophagus after

an adequate high-dose trial of proton pump inhibitors (PPIs); and (4) exclusion of other disorders associated with similar clinical, histologic, or endoscopic features.²

Proton Pump Inhibitor–Responsive Esophageal Eosinophilia

Initial guidelines have suggested that patients with clinical and histologic features compatible with EoE but who respond histologically to a PPI can be described as having PPI-responsive esophageal eosinophilia (PPI-REE).³² There is considerable debate regarding whether this patient population represents a subset of patients with EoE who happen to respond to PPI therapy given the strong overlap of certain clinical, endoscopic, and even genotypic features.^{33–35} In a study that evaluated the differences in major basic protein, tryptase, and eotaxin-3 levels in patients with PPI-REE, with EoE, and in controls, there were significant differences in protein levels when EoE patients were compared with controls, but not when EoE patients were compared with patients with PPI-REE.³⁶ Another study found that clinical and endoscopic features of patients with PPI-REE were indistinguishable from patients with EoE.³⁷ The mechanisms by which PPIs improve esophageal eosinophilia have been shown to be independent of acid suppression and, rather, an effect of blocking eotaxin-3 and its effect on esophageal eosinophil recruitment.³⁸ Given that there is strong evidence that PPI therapy can improve histologic, endoscopic, and symptomatic features in patients with presumed EoE or esophageal eosinophilia, PPI therapy is a helpful first step in the treatment of these disorders.³⁹ Therefore, PPIs can be used as initial therapy for esophageal eosinophilia, and a course of PPI therapy may no longer be needed to confirm the diagnosis of EoE. The basis for this new approach is that some patients who have previously responded to PPI therapy have also responded to elimination diet therapy.⁴⁰

Treatment

The goal of therapy for EoE is not only to improve the clinical symptoms but also to prevent disease progression and complications. In this regard, understanding the natural history of EoE is of great importance. Prior studies suggest that EoE, when untreated, can lead to an increased risk of stricture formation over time, and that earlier identification and treatment may prevent progression to fibrostenosis; thus, maintenance therapy is advocated to prevent ongoing fibrosis.^{41,42} Practical endpoints of treatment are to improve histologic eosinophilia to below the diagnostic threshold (<15 eos/hpf), improve the symptoms of dysphagia, and achieve endoscopic

improvement, including targeting an esophageal diameter of at least 16 to 17 mm.^{2,43}

Dietary Therapy for Eosinophilic Esophagitis

Dietary therapy was first identified as an effective therapeutic approach in children with EoE,⁴³ thereby implicating dietary antigens in the pathogenesis of EoE. This form of therapy has since emerged as a nonpharmacologic, first-line approach to disease management in both adults and children with EoE. Three distinct dietary approaches have been identified: elemental diet, allergy testing–directed diet, and empiric elimination diet.

Elemental Diet

The first study to show improvement in EoE after treatment with an elemental, or amino acid–based, diet was a study in 10 children with suspected GERD and esophageal eosinophilia.⁴⁴ In this landmark study, administration of an elemental diet led to substantial improvement of both symptoms and esophageal eosinophilic inflammation. The effect of a diet devoid of intact dietary protein implied that food allergy was responsible for eosinophilic inflammation. Two prospective, adult studies of elemental diet reported a lower histologic response in approximately 75% of patients, suggesting that non-food allergens may play a role in adults with EoE.^{45,46} However, the adult trials were both limited by a 4-week treatment period, a high patient dropout rate due to palatability of the elemental formula, and nonadherence to the diet protocol. Retrospective cohort studies as well as a meta-analysis have reported superiority of the elemental diet over both the empiric elimination diet and allergy testing–directed diet approaches.^{20,47} Limitations of elemental diet include the palatability of the formula and the lack of meal variety. Although the goal of dietary therapy is to eliminate specific food triggers, another major shortcoming of the elemental diet approach is the length of time and number of endoscopies required to identify specific triggers during food reintroduction. The elemental formula can also be costly for many patients, and, currently, most insurance companies do not cover the cost of this intervention. In children, frequent use of a gastrostomy tube to administer the formula is also a shortcoming of this approach.

Allergy Testing–Directed Diet

Allergy testing–directed dietary therapy has the conceptual appeal of the identification of trigger foods, thereby streamlining the empiric elimination and reintroduction process. A large, retrospective study in children utilized a combination of skin prick and atopy patch testing of 23 different foods to formulate an elimination diet, and

demonstrated a 72% histologic remission rate.⁴⁸ Subsequent pediatric studies have reported response rates of 53% to 65% using allergy testing–directed diets.^{49,50} Adult studies have demonstrated substantially lower response rates; for example, a prospective trial utilizing a combination of skin prick and atopy patch testing in 22 adults with EoE achieved only a 26% remission rate.⁵¹ A prospective study of 50 adults with EoE found a positive predictive value of 13% for skin prick testing, suffering from both false-positive and false-negative test results.⁵² Based on these studies, the use of immunoglobulin E–based allergy testing in EoE for recognizing causative foods is not supported. Novel immunologic assays are needed to accurately classify food triggers in EoE.

Empiric Elimination Diet

Given the difficulties with following an elemental diet and the variable response rates to skin prick and atopy patch testing to detect specific food triggers in EoE, a number of studies have used an empiric elimination diet. This approach eliminates foods with the most common food allergens. The 6–food elimination diet (SFED) eliminates cow’s milk, egg, soy, wheat, peanut/tree nut, and fish/shellfish. First studied in children, the SFED has shown consistent effectiveness in the treatment of EoE, with a demonstrated histologic remission in 74% of children who were treated with it.⁵³ Similar histologic response rates were found in prospective, adult EoE studies from the United States and Spain.^{52,54} In the Spanish study, patients were followed for up to 3 years and remained in remission while avoiding their specific trigger foods.⁵⁴ In both adult and pediatric populations, milk, wheat, egg, and soy have been identified as the 4 most common food triggers for EoE. Empiric elimination of 1 food group (milk), 2 (milk and wheat), or 4 (milk, wheat, egg, and soy) is being actively investigated as an alternative to the SFED.⁵¹

The empiric elimination diet has demonstrated a consistently high degree of effectiveness while allowing for continued consumption of a restricted number of table foods that include fruits, vegetables, meat, poultry, rice, beans, and alternative grains, such as quinoa. In patients showing histologic response, the eliminated food groups are sequentially reintroduced while monitoring for disease recurrence using endoscopic biopsies. The requirement of repeated endoscopies during the reintroduction phase is a considerable drawback to this approach. Practically, the empiric elimination diet can be challenging to follow due to concerns with dietary contamination, psychosocial impact of restricted diets, and costs of allergen-free food products.⁵⁵ The incorporation of a dietitian in patient education and dietary monitoring improves the success of the empiric elimination diet

approach. A number of noninvasive methods to sample the esophagus, including the Esophageal String Test (EnteroTrack), Cytosponge (University of Cambridge), and unsedated transnasal endoscopy, are actively being investigated.^{56–58}

Considerations for Choosing a Therapeutic Approach

As there are no controlled studies comparing dietary therapy with corticosteroid therapy in patients with EoE, the choice of treatment approach is currently individualized and based on a discussion with the patient and on patient preference.² A dietary approach requires a highly motivated patient and physician as well as available dietary resources. Research across medical disciplines has demonstrated widespread patient acceptance for the use of dietary interventions to manage medical conditions. Many patients find the concept of treating their disease by eliminating an inciting food allergen more appealing than taking a drug to counteract the downstream inflammatory response. Furthermore, when discussing dietary approaches, it is important to emphasize that the strict elimination of multiple foods is for a limited time and that the goal is ultimately to reintroduce food to help liberalize the foods being eliminated. The long-term goal is the identification and continued elimination of 1 or 2 food groups. Once a food trigger has been identified, occasional dietary indiscretion is likely acceptable, in distinction to patients with food-associated anaphylaxis. For example, a small case series described tolerance to baked milk in patients with cow’s milk–mediated EoE.⁵⁹

Summary

A clinical approach to EoE begins with an increased awareness of the disease and its manifestations. The diagnosis should be considered in a child presenting with vomiting, food refusal, prolonged feeding times, family history of EoE, and abdominal pain, especially if the symptoms have not improved with empiric therapeutic trials of acid suppression. The diagnosis should be strongly entertained in both children and adults with dysphagia and food impactions, regardless of the presence or absence of heartburn. Other presentations include atypical chest pain and heartburn that do not respond to empiric PPI therapy.

Once the diagnosis is made, the decision to pursue either medical or dietary therapy should be discussed with the patient. If dietary therapy is chosen, options include elemental diet, allergy testing–directed diet, and empiric elimination diet. Empiric elimination diet has many advantages over the other methods and is the

favored approach to dietary therapy. The exact empiric elimination is often individualized per patient, but the most widely used diet is the SFED. Partnership with a skilled dietitian is crucial to the success of dietary therapy and reintroduction of trigger foods. Given that EoE is a chronic disease and that natural history studies have shown increased stricture formation in untreated disease, maintenance dietary therapy should be pursued to prevent EoE recurrence in both children and adults.

Dr Gonsalves serves on the scientific advisory board for Allakos.

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