

Diagnosis and Treatment of Eosinophilic Gastrointestinal Disorders

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Eosinophilic gastrointestinal disorders are a heterogeneous group of disorders defined primarily by an eosinophil-rich inflammatory infiltration of the gastrointestinal mucosa in the absence of other known causes for eosinophilia. In this review, the pathogenesis, clinical symptoms, diagnosis, and treatment of eosinophilic esophagitis (EE) are discussed. As the most common eosinophilic gastrointestinal disorder, EE is associated with food or inhalant hypersensitivity in up to 80% of EE patients. CD4 T cell production of Th2 cytokines interleukin-5 (IL-5) and IL-13 are important in the pathogenesis of these disorders. Clinical characteristics of patients with EE include nausea, vomiting, abdominal pain, dysphagia, food impaction, and feeding disorders. Diagnostic criteria include presence of symptoms consistent with esophageal dysfunction and peak eosinophil count of >15 eosinophils per one high powered field. Gastroesophageal reflux disease must be eliminated diagnostically by the absence of responsiveness to proton pump inhibitors or normal pH monitoring of the distal esophagus. The most common treatment modalities for EE include dietary elimination and oral or topical steroids to decrease esophageal inflammatory responses. Treatment interventions typically require 4–12 weeks to determine efficacy. Leukotriene inhibitors are not as efficacious as steroid therapy. Mepolizumab (anti-IL-5) and omalizumab (anti-IgE) are newer therapies currently under investigation. Future therapeutic agents may target the proinflammatory cytokines involved in the pathogenesis of disease, but more randomized controlled studies are needed to evaluate the benefits and harms of various therapeutic approaches.

Introduction

EOSINOPHILIC GASTROINTESTINAL DISORDERS (EGIDs) are a heterogeneous group of disorders defined primarily by an eosinophil-rich inflammatory infiltration of the gastrointestinal mucosa in the absence of other known causes for eosinophilia. A diverse set of symptoms occur in association with intestinal eosinophilia, which range from mild abdominal pain to severe weight loss and failure to thrive. The EGID most commonly associated with food allergies is eosinophilic esophagitis (EE). It has emerged in the past decade as the most common EGID. In this article, we will review the pathogenesis, clinical symptoms, diagnosis, and treatment of EE. We will also review potential future therapies currently under investigation.

Pathogenesis

The gastrointestinal tract is an immunologically active organ that is responsive to a variety of stimuli and is daily exposed to a diverse seemingly overwhelming load of antigens. It has the delicate task of creating tolerance to normal flora and nutritive products and responding to pathogens.

To accomplish this balance of controlled and protective immune responses, the mucosa of the intestine is comprised of an epithelial barrier on the surface and the underlying lamina propria with many immunologically active cells. Antigens can cross the epithelium through dendritic cells or M cell. The M cell is a specialized cell derived from enterocytes with the major function of transporting antigens from the lumen of the intestine to the subepithelial lymphoid tissue, also known as the gut-associated lymphoid tissue. The gut-associated lymphoid tissue includes peyer's patches and mesenteric lymph nodes. The lamina propria is home to intraepithelial lymphocytes that consistently contribute to immune responses in the mucosa.¹

In EGIDs, the antigen carrying dendritic cell stimulates CD4 T cells to produce key cytokines that stimulate an increase in eosinophil presence in the GI mucosa. Proinflammatory cytokines interleukin-5 (IL-5), IL-13, and tumor necrosis factor-alpha are increased in EE, which contributes to the increase in eosinophils and mast cells. Eotaxin 3, a cytokine critical for eosinophil migration, is also upregulated in these disorders.¹

Increased fibrosis has been shown in children with EE, and there is concern that remodeling may occur with prolonged

inflammation. However, it is unclear at this time if this fibrosis is irreversible because studies suggest corticosteroids may decrease this response.² The disorder is chronic, however, because the inflammation returns when corticosteroids are discontinued.^{1,3}

Immunologic Spectrum of Disease

EGIDs are frequently mediated by IgE and non-IgE immunologic reactions to food antigens. These disorders fall along a continuum and can be IgE mediated, non-IgE mediated, or be mediated by a combination of IgE and non-IgE immunologic mechanisms. The classic IgE-mediated gastrointestinal disorders involve gastrointestinal anaphylaxis where a rapid onset of nausea, vomiting, abdominal pain, and/or diarrhea follows ingestion of specific food allergens. These reactions typically occur within 20 minutes to 3–4 hours of ingestion. Non-IgE-mediated gastrointestinal responses to food typically occur within 2–3 days to weeks after ingestion and more typically involve vomiting or diarrhea. Cow's milk protein enterocolitis or food protein-induced enterocolitis fall into this category. The response to the food protein is specific but does not involve IgE-mediated mechanisms. T cell responses are thought to play a role. Because of the absence of IgE-mediated immune responses, typical immediate hypersensitivity allergy tests to detect food-specific IgE are negative in non-IgE-mediated disorders. EGIDs are mediated by both IgE and non-IgE-mediated mechanisms with EE having a strong association with IgE-mediated responses to food antigens.^{4,5}

Diagnosis

The First International Gastrointestinal Eosinophil Research Symposium determined as a consensus that the diagnostic criteria for EE should be a clinico-pathologic one. Since other disorders can have similar pathologic features and symptoms, severe gastroesophageal reflux disease (GERD), parasitic disease, and inflammatory bowel disease should be eliminated as diagnostic possibilities before diagnosis of EE. GERD is typically eliminated diagnostically through the presence of persistent symptoms on PPI therapy and an upper gastrointestinal series and upper endoscopy with biopsy while the patient is on a proton pump inhibitor therapy for 1–2 months. Alternatively, a pH probe can be used to eliminate this diagnostic confounder. Upper endoscopy is currently the gold standard, as other noninvasive tests have poor sensitivity and specificity for EE. Isolated esophageal eosinophilia typically involving >15–20 eosinophils in the most densely affected high powered field (hpf) is the pathologic criteria for diagnosis of EE⁶ (Table 1).

There are several distinguishing features that differentiate EE from GERD.³ Patients with EE are typically male, but patients with GERD are equally distributed between males and females. Although atopic disease is associated with EE,

patients with GERD have no higher prevalence of atopy than the general population. In contrast to reflux patients, familial clustering is very common in EE. Also, biopsies from patients with EE commonly show eosinophils in the proximal esophagus, but this is rare in patients with GERD. Esophageal eosinophilia can occur in patients with GERD, but typically it is not >15 cells/hpf.³

Eosinophils are found normally in all parts of the gastrointestinal tract besides the esophagus.⁷ Diagnosis of EE must include clear eosinophilia in the esophagus as noted above, but a minority of patients have eosinophils solely confined to the esophagus. More often, there are eosinophils in other parts of the gastrointestinal tract along with the esophagus. Eosinophils have been shown in the stomach, duodenum, and colon in EE patients.⁸

Since aeroallergen and food hypersensitivity can play a role in EE, other tests that are utilized to diagnose coexisting sensitization include serum IgE, peripheral eosinophil count, and specific IgE testing by immediate hypersensitivity skin prick testing or serum testing. Atopy patch testing is used in some centers as an adjunctive way to determine non-IgE-mediated sensitivity to foods.⁶

Clinical characteristics of patients with EE include nausea, vomiting, abdominal pain, dysphagia, food impaction, and feeding disorders. Younger patients present with nausea and vomiting, whereas older patients present with dysphagia and food impaction. Early studies have shown up to half of patients with rhinoconjunctivitis, one-half with possible food allergy (defined as at least one positive prick skin test or specific IgE test or an anaphylactic reaction to a food), and one-third with wheezing. Family history of atopic disease has been noted in up to three-fourths of EE pediatric patients.⁹

The frequency of the disorder was estimated to be increasing until recently when biopsy specimens were retrospectively analyzed using histopathologic criteria for diagnosis of 15 eosinophils/hpf or greater. From 1992 to 1999, when the number of diagnoses were corrected for the number of increased endoscopies, the proportion of biopsy specimens meeting the criteria for EE did not change during this period. Therefore, it is likely that EE existed >20 years ago but was unrecognized.¹⁰

Natural History

EE appears to be a chronic relapsing disease in adults. Thirty-two out of 51 (62%) of adults with treatment with fluticasone 220 mEq/puff, 4 puffs swallowed twice daily, for 6 weeks replied to a one page phone questionnaire regarding symptoms of EE. With a mean follow-up of 3 years, 91% of these patients reported recurrent symptoms at a mean of 8.8 months after treatment was completed. Sixty-nine percent needed to repeat the topical steroid treatment at least one time.¹¹

TABLE 1. DIAGNOSTIC CRITERIA FOR THE DIAGNOSIS OF EOSINOPHILIC ESOPHAGITIS

Clinical symptoms of esophageal dysfunction
Peak count of >15 eosinophils in 1 high-power field
Lack of responsiveness to high-dose proton pump inhibition (up to 2 mg/kg/day) or normal pH monitoring of the distal esophagus

Pediatric patients also seem to have persistent disease. In a follow-up study of 620 patients over 14 years with a mean follow-up time of 3.2 years, of 330 EE patients (53%), <10% had remission of disease, defined by tolerance to food allergens and discontinuation of all medical therapy. The patients who developed tolerance had allergies to fewer foods (2.4 foods) than the general EE population (6.9 foods). In a small cohort of patients who received no medical or dietary therapy for EE and returned for follow-up 6 years after initial evaluation, endoscopies were unchanged from the initial evaluation. Therefore, the natural history of disease appears to be persistent and chronic in children.¹²

Endoscopic Features

Gross findings upon endoscopy can reveal mucosal pallor, linear furrowing with vertical lines of the esophageal mucosa, concentric rings, white exudates, white specks, nodules or granularity, and strictures in the proximal, middle, or distal esophagus.^{13,14} None of these findings are pathognomonic for EE, however.⁶ Histopathologic review of biopsies of patients with EE include the following characteristics: eosinophil degranulation, eosinophilic microabscesses, superficial layering of eosinophils in the upper one-third to half of the squamous epithelium, basal layer hyperplasia occupying >20% of the epithelium, lamina propria fibrosis, increased T cells, and increased mast cells.^{3,6} A consensus statement for the diagnosis and treatment of EE recommends that gastroenterologists treating adults and children with symptoms of esophageal dysfunction and numerous intraepithelial eosinophils in esophageal biopsy specimens ensure that the disease cannot be attributed solely to GERD before making a diagnosis of EE.⁶

Environmental and Food Allergies

A seasonal variation in diagnosis and clinical symptoms of EE has been observed in both adults and children. Aeroallergen hypersensitivity can be very prominent in the clinical expression of disease in EE. One report of a 21-year-old woman with a history of asthma and allergic rhinoconjunctivitis revealed esophageal biopsy specimens obtained in the spring and winter showing numerous eosinophils and hyperplasia of the basal layer in May, but by February, the inflammation had entirely subsided and the squamous epithelium had a normal appearance.¹⁵ Allergic rhinitis can coexist with EE or precede the development of EE,¹⁶ and, more recently, Moawad et al. showed that there is a correlation between the diagnosis of EE and aeroallergen pollen counts.¹⁷

Cockroach, mold, and dust mite hypersensitivity also play a role in EE. Cockroach and dust mite allergen given intranasally caused a significant increase in the levels of esophageal eosinophils and mast cells compared with saline-challenged mice. Mice deficient in eotaxin-1/2, CCR3, and IL-5 showed ablated esophageal eosinophilia after cockroach or dust mite allergen exposure.¹⁸ House dust mite and mold has been shown to induce cytokine production of Th2 cytokines by peripheral blood mononuclear cells in adult patients with EE.¹⁹ There is a clear role of aeroallergen hypersensitivity in EE and immediate hypersensitivity skin prick testing can be used to identify these in EE patients. Immunotherapy may modulate disease, but a determination of the effect of immunotherapy on EE has not yet been elucidated.

Food allergies play a significant role in the development of EE. The first report to demonstrate this was performed in 1995. Ten patients (age 8 months–12.5 years) with EE were given amino acid based formula for >6 weeks, and endoscopy was performed pre- and post-trial. The maximal intraepithelial eosinophil counts decreased significantly from a median of 41/hpf to 0.5/hpf after treatment.²⁰ Liacouras et al. subsequently treated 172 EE patients with an elemental amino acid formula and saw significant improvement in biopsies similar to the first report.²¹ Selective 6 food elimination diet (milk, soy, wheat, egg, peanut, and seafood) has also been compared to an elemental diet followed by endoscopy after 6 weeks of therapy. Seventy-four percent of the patients on the 6 food diet had <10 eosinophils/hpf after dietary intervention, and 88% of patients on the elemental diet had <10 eosinophils/hpf.²² Therefore, a selective diet has been considered almost equally efficacious to complete food allergen avoidance in EE.

Spergel et al. have used a combination of skin prick and atopy patch testing to guide dietary therapy in 146 EE patients. After 6 weeks, esophagogastrroduodenoscopy (EGD) with biopsy showed 78% resolution (<5 eosinophils/hpf).²³ Patch testing and skin prick testing have been used with variable results to determine food sensitivities in patients with EE.²⁴ Sampson determined 95% positive predictive cut off values for IgE-mediated food allergy²⁵ and, in the context of EE, food-specific IgE may be useful in determining relevant food hypersensitivities. In a cross-sectional study of 53 patients with EE, the overall prevalence of food and inhalant sensitization was 80%. For foods, serum IgE measurement detected more allergic sensitization than did skin prick testing.²⁶ Therefore, skin prick, serum-specific IgE, and patch testing have all been utilized to determine the role of immunologic responses to foods in EE.

Medical Treatment

Medical therapy in EE currently consists of systemic or topical corticosteroids, but leukotriene receptor antagonists have been studied as a potential treatment. There is currently no universal therapeutic approach in EE. Only approximately one-third of members of American College of Gastroenterology, American Academy of Allergy, Asthma, and Immunology, and North American Society Pediatric Gastroenterology, Hepatology, and Nutrition, when surveyed, reported using diagnostic criteria proposed in a 2007 consensus document.^{6,27} Seventy-one percent and 35% of 1,836 physicians reported treating some patients with EE with a food elimination or elemental diet, respectively.²⁷

Swallowed fluticasone was the first topical steroid used in clinical trials found to be effective in EE. In 36 patients receiving 880 µg of fluticasone propionate for 3 months, 50% of patients achieved histologic remission compared to 9% in placebo-treated patients. However, allergic patients were less responsive to this therapy.²⁸ Oral steroid therapy was determined subsequently to be just as effective as topical fluticasone in EE. Prednisone at 1 mg/kg twice daily was compared to topical fluticasone (110 mcg/puff in patients 1–10 years old or 220 mcg/puff in patients who were >11 years old). The majority of patients were symptom free after 4 months of therapy, and only 0%–2.8% had persistent or recurrent symptoms. There were no significant differences between the 2 groups. After steroid discontinuation, at

week 24 in both groups, about 44%–45% had recurrence of symptomatology. Systemic adverse effects were noted in 40% of the prednisone-treated patients, whereas esophageal candidal overgrowth was seen in 15% of the fluticasone-treated patients.²⁹

The risks of corticosteroid therapy must be balanced with the potential consequences of persistent esophageal inflammation (ie, stricture formation and dysphagia). The efficacy and the ease of administration of topical fluticasone have made this a treatment option for practitioners. However, the long-term efficacy of this treatment is unknown and there are clear nonresponders to topical steroid alone.^{27,30}

Fluticasone is dispensed in a metered dose inhaler, which requires the coordination of manual pressure of the inhaler followed by a swallow. This is not feasible for many young children, so an alternative therapy was determined to be effective. Oral budesonide was studied in 20 young children. Children <10 years old received 1 mg daily, and those >10 years received 2 mg/day. Each 0.5 mg Pulmicort Respule™ was mixed with 5 g (5 packets) of sucralose (Splenda™) to create a volume of 8–12 mL. Three to 4 months after treatment was started, 80% were determined to be responders, 5% partial responders, and 15% nonresponders.³¹ A 15-day course of budesonide has also been shown to be effective in adolescents and adults with EE.³² This form of therapy can be utilized in young children, adolescents, and adults with EE.

Montelukast, a leukotriene receptor antagonist, was studied in a very small group of patients and did not perform as well as systemic corticosteroids. Treatment with montelukast for a median period of 14 months in 8 out of 12 patients did not change the density of tissue eosinophils. However, subjective clinical improvement was noted in 3 patients on montelukast who were not on steroids simultaneously.³³ There have been no randomized controlled clinical trials assessing the efficacy of montelukast in EE.³⁴

New Investigational Therapies

Newer therapies for EE are targeted against pathogenic Th2 cytokines or adaptive immunologic cellular markers known to contribute to the inflammatory response. Anti-IL-5 therapy has also been investigated as a therapy for EE. A phase I/II study in 4 adult patients showed a marked decrease in peripheral blood and esophageal eosinophilia.³⁵ In another adult, that mepolizumab has been determined to decrease tissue eosinophils, but its efficacy is poorer for resolution of clinical symptoms. There was a marked reduction of mean esophageal eosinophilia in the mepolizumab group compared with the placebo group 4 weeks after initiation of treatment. No further reduction of eosinophil numbers was observed in response to the 2 additional infusions at 5 and 9 weeks after initiation of therapy in either group.³⁶ Mepolizumab is not yet U.S. Food and Drug Administration approved so it is not currently available for use in EE.

Since allergen sensitization and IgE-mediated mechanisms are seen in up to around 80% of children and adults with EE,³⁷ it is plausible that anti-IgE antibody therapy would be therapeutic. FcεRI is expressed in human intestinal epithelial cells,³⁸ may play a role in EGID and is down-regulated by anti-IgE therapy.³⁹ Omalizumab is a humanized therapeutic monoclonal antibody that binds to IgE, preventing it from activating mast cells and basophils and

decreasing the concentration of high-affinity IgE receptors on these cells. At present, omalizumab is the only clinically available anti-IgE therapeutic.⁴⁰

Adult patients with EGID and a history of atopic disease have been shown to benefit from this therapy. In 9 adult patients, treatment with omalizumab every 2 weeks for 16 weeks significantly decreased the symptom scores, serum IgE levels, and allergen skin test wheal and erythema responses compared to baseline. Absolute blood eosinophil counts, tissue eosinophil counts in the duodenum and gastric antrum, and basophil and dendritic cell FcεRI expression all declined too.⁴¹

Future Potential Therapies

IL-13 is both necessary and sufficient to produce experimental EE in mice.³ Overexpression of pulmonary IL-13 in mice induces evidence of esophageal remodeling,⁴² and IL-13 gene expression is upregulated in the esophagus of patients with EE.³ IL-13 is also capable of directly stimulating esophageal tissue to produce eosinophil-attracting chemokines and drive eosinophil migration.⁴³

Therefore, future treatment modalities designed to decrease expression of IL-13 may be useful in EE. Indeed, recently humanization of a potent mouse anti-human IL-13 monoclonal antibody has been achieved.⁴⁴ The use of these agents may be effective in EE treatment in the future.

The mean expression levels of eotaxins 1, 2, and 3 and CCR-3 in biopsy tissue samples have been shown to be markedly elevated in patients with EE as compared with GERD and healthy control groups. Eotaxin 3 was the most highly expressed.⁴⁵ Eotaxin-3 tissue expression in pediatric EE patients positively correlated with esophageal eosinophil numbers and peripheral blood eosinophil CCR3. These parameters seemed to be lower in patients in disease remission than those with active disease.⁴⁶ Therefore, there is some evidence that eotaxin-3 and CCR3 are involved in disease pathogenesis in EE. Hence, chemokine and chemokine receptor antagonists may also be a future treatment modality for EE patients.

Future Studies

The diagnostic criteria for EE include endoscopic biopsy and pathologic examination to identify eosinophil counts. There is no serologic biomarker yet identified or a noninvasive marker for the diagnosis of EE. Since symptoms have not been shown to correlate with esophageal eosinophil counts, a serologic or noninvasive marker for disease would decrease the need for endoscopy in these patients, an invasive procedure that carries risk. Future investigation to identify noninvasive diagnostic markers is desired. Eosinophil-derived neurotoxin,⁴⁷ and eotaxin-3⁴⁵ are potential markers, and a symptom score questionnaire has been proposed as an alternative to endoscopy in pediatric patients,⁴⁸ but there is no diagnostic test that is robust to identify EE without endoscopy at this time. Proteomic analysis may be useful in the future to identify currently unknown serologic biomarkers.

A Cochrane review of nonsurgical interventions for EE has identified several areas for study in the future of EE. Only 3 randomized controlled trials were identified; therefore, there is a limited ability to determine the benefits and risks of different medical interventions currently used in EE. There have been no randomized controlled trials of

hypoallergenic diets, mast cell inhibitors, leukotriene receptor antagonists, or immune modulators. More randomized controlled studies are needed to determine effective therapies.³⁴

In summary, the EE is a chronic, relapsing disease that is diagnosed best by the combination of clinical and pathologic features. Aeroallergen and food hypersensitivity are important triggers and can be identified through skin prick and serum-specific IgE testing. Oral and topical steroids and dietary elimination are all effective in controlling inflammation in EE. Treatment interventions typically require 4–12 weeks to determine efficacy. Newer investigated therapies include anti-IL-5 and omalizumab, but more randomized controlled studies are needed to evaluate the benefits and harms of therapeutic approaches.

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