Eosinophilic gastroenteritis: diagnosis and clinical perspectives

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Abstract: Eosinophilic gastroenteritis (EGE) is a digestive disorder in children and adults that is characterized by eosinophilic infiltration in the stomach and intestine. The underlying molecular mechanisms predisposing to this disease are unknown, but it seems that hypersensitivity response plays a major role in its pathogenesis, as many patients have a history of seasonal allergies, food sensitivities, asthma, and eczema. Symptoms and clinical presentations vary, depending on the site and layer of the gastrointestinal wall infiltrated by eosinophils. Laboratory results, radiological findings, and endoscopy can provide important diagnostic evidence for EGE; however, the cornerstone of the diagnosis remains the histological examination of gastric and duodenal specimens for evidence of eosinophilic infiltration (>20 eosinophils per high-power field), and finally clinicians make the diagnosis in correlation with and by exclusion of other disorders associated with eosinophilic infiltration. Although spontaneous remission is reported in around 30%–40% of EGE cases, most patients require ongoing treatment. The management options for this disorder include both dietary and pharmacological approaches, with corticosteroids being the mainstay of therapy. The subsequent course is quite variable. Some patients have no recurrences, while a few experience recurrent symptoms during or immediately after corticosteroid interruption. An alternative therapeutic armamentarium includes mast-cell stabilizers, leukotriene antagonists, antihistamines, immunomodulators, and biological agents. In this review, we provide a summary of the different diagnostic tools utilized in practice, as well as the different therapeutic approaches available for EGE management.

Keywords: eosinophilic gastroenteritis, eosinophils, abdominal pain, steroids

Introduction

Eosinophilic gastroenteritis (EGE) is an inflammatory disorder of the gastrointestinal (GI) tract characterized by eosinophilic infiltration of the bowel wall, with the stomach and small intestine being the most commonly affected areas.1 Because the symptoms are very similar to other GI disorders, EGE has been often underdiagnosed and thus considered a rare disorder. However, as our understanding of the disease is evolving, its prevalence is expected to increase.2

Kajiser first described EGE in 1937,3 and since then about 300 cases have been reported in the literature. Its prevalence in the US is estimated to range from 8.4 to 28 cases per 100,000 people4,5 and it can occur at any age from infancy to the seventh decade, but it typically peaks between the third and fifth decade of life.6,7 In 1970, Klein et al5 classified the disease according to the anatomical location of eosinophilic infiltration in the different layers of the intestinal wall into three subtypes: mucosal, muscular and serosal.
Mucosal EGE is the most common variety, seen in about 57% to 100% of cases, and presents with features of abdominal pain, nausea, vomiting, dyspepsia, diarrhea, malabsorption, or protein-losing enteropathy, which in turn may cause hypoaalbuminemia, anemia, and weight loss. Additionally, the occurrence of lower-GI bleeding may imply colonic involvement. Involvement of the muscular layer occurs in 30%–70% of all EGE cases, and may cause bowel-wall thickening and intestinal obstruction. Also, it can present as an obstructing cecal mass or intussusception. Patients with muscular EGE often have cramps and abdominal pain associated with nausea and vomiting. The serosal type is the least common, with an estimated prevalence of 4.5%–9% in Japan and 13% in the US, and causes peritoneal irritation that leads to eosinophilic ascites and abundant peripheral eosinophilia, peritonitis, and perforation in more severe cases. Intestinal intussusceptions may occur in the serosal type too. Furthermore, Chang et al observed that the muscular and serosal types are associated with concomitant mucosal eosinophilic infiltration, suggesting centrifugal disease progression from the mucosa toward muscular and serosal layers.

What triggers such dense infiltration in EGE is not fully elucidated yet. It is possible that different pathogenetic mechanisms are involved, such as hypersensitivity to allergens. Some studies have reported that about 45%–63% of patients diagnosed with EGE had a history of allergies, such as asthma, rhinitis, drug or food allergies, and eczema, while others have found an association with other autoimmune conditions, such as ulcerative colitis, celiac disease, and systemic lupus erythematosus. However, the latter are quite questionable, because the definition of EGE requires the exclusion of secondary causes of gut eosinophilic inflammation (inflammatory bowel disease, autoimmune disease, and malignancies). Altogether, these data suggest that EGE may result from immunodysregulation in response to an allergic reaction. Furthermore, 64% of reported cases include a family history of atopic diseases, suggesting a possible hereditary component (genetic factors) as a risk factor. Finally, other environmental factors, such as parasitic infestation or drugs, have been suggested to act as predisposing factors too. In the allergic subtype of the disease, it is thought that food allergens cross the intestinal mucosa and trigger an inflammatory response, which includes mast-cell degranulation and recruitment of eosinophils.

New recent evidence suggests that mucosal eosinophilia is relatively common in patients with functional dyspepsia (FD), in both adults and children. Du et al conducted a pilot study demonstrating that FD is directly correlated with increased infiltration of degranulated eosinophils, supporting early clinical evidence of a role of eosinophils in FD pathogenesis. Aro et al also found evidence of duodenal eosinophilia associated with dyspepsia among other factors that are commonly associated to EGE as well. A case series of patients with FD in whom EGE was established to be the correct diagnosis after further investigation was reported by Australian researchers. Interestingly, patients with FD show low-grade GI eosinophilia. All these studies together suggest that FD may either be another eosinophil-mediated disease or a mild form of EGE, especially if we consider that drugs used for the treatment of EGE have also been found to be therapeutic in this population.

Pathogenesis
Eosinophilic recruitment into inflammatory tissue is a complex process regulated by a number of inflammatory cytokines. IL3, IL5, and granulocyte–macrophage colony-stimulating factors (GM-CSFs) modulate bone-marrow production of eosinophils, with IL5 and GM-CSF additionally regulating eosinophil activation and survival. In association with a chemokine named eotaxin, IL5 seems to regulate eosinophilic recruitment and accumulation. Interestingly, Desreumaux et al detected IL3, IL5, and GM-CSF in duodenal and colonic tissue in 90% of patients with EGE. In the same study, they also showed that eotaxin 1 and α4β7 integrin regulate eosinophil homing into the lamina propria of the stomach and small intestine. The importance of eotaxin in EGE was shown by Hogan et al in an animal model of food allergen–induced EGE, in which they demonstrated that lack of eotaxin blunted eosinophilic accumulation in the gut. Other mediators like IL4, IL13, IL1β, leukotrienes (LTs), and TNFα that are involved in induction of cell-adhesion molecules leading to selective eosinophil recruitment have been proposed to help in prolonging lymphocytic and eosinophilic activity, as they were detected in diseased intestinal walls by immunostaining. Jaffe et al showed enhanced expression of IL4, IL5, and IFNγ in peripheral T cells of patients with allergic EGE. In the case of allergens, IgE is involved in mast-cell degranulation. In 1985, Oyaizu et al presented evidence for the hypothetical IgE-induced, mast-cell–mediated mechanism of eosinophilic chemotaxis in patients with EGE. Years later, a case report by Inamura et al demonstrated accumulation of mast cells in the interstitium of the colon wall after immunohistochemical staining for the
 mast-cell enzyme tryptase, suggesting the pathogenic role of IgE.

Furthermore, it has been demonstrated that eosinophils have the potential to regulate the enteric nervous system by releasing granule proteins, particularly eosinophil-granule MBP, and other soluble mediators that directly activate mast cells. This is known as the eosinophil–mast cell axis,

Interestingly, mast cells and eosinophils have been found to be codependent. Mast cells induce eosinophils in the gastric mucosa, and eosinophils in turn can activate mast cells by producing and releasing factors for their growth, proliferation, maturation, degranulation, and survival.

Of note, animal studies have shown that acute stress activates mast cells, inducing FI-function disturbances, which are also activated in stress and may have a role in the visceral hypersensitivity of irritable bowel–syndrome patients, without allergic degranulation. This finding may provide an all-important link with stress-related symptoms of FGIDs and EGE.

Eosinophils play an important role in the host defense of the GI system. Indeed, increased numbers of eosinophils in the GI mucosa are triggered by helminths and bacterial infections. Eosinophil-mediated inflammatory responses triggered by helminth infection induce the activation of lymphocyte $T_{H2}$, overexpression of eosinophil-activating cytokines, and generation of antigen-specific IgE antibodies. On the other hand, antibacterial properties of eosinophils are exerted against Gram-negative bacteria, which express a lipopolysaccharide on their walls that triggers rapid release of mitochondrial DNA from eosinophils, as well as granule proteins that form a toxic extracellular structure that kills bacteria.

In conclusion, the pathogenesis of EGE is complex, as many factors can trigger eosinophil load in the GI tract, consequently leading to a difficult diagnosis and to an empirical and unsystematic therapeutic approach to treat it.

**Diagnosis**

In 1990, Talley et al suggested three criteria for the diagnosis of EGE, which are still used widely: presence of GI symptoms, histological demonstration of eosinophil infiltration into the GI tract or presence of high eosinophil count in ascetic liquid (serosal disease), and exclusion of other causes of tissue eosinophilia (differential diagnosis). Interestingly, peripheral count is an insensitive marker for mucosal eosinophilia in FGIDs.

**History and clinical exams**

Because there is no gold standard for this disease, a wide variety of diagnostic criteria are presented. After a detailed history of patients, including history of food or drug allergies, concomitant atopic diseases, and family history of allergies, and physical examination, thorough evaluation of the patient is necessary, starting with laboratory evaluation.

A complete blood count plays an important role in raising suspicion of EGE. Peripheral blood eosinophilia is present in about 70% of cases, with higher levels in patients with mucosa-predominant pattern and at greater risk of relapse. The absolute eosinophil count (AEC) is used to categorize the disease in mild (AEC, 600–1,500 eosinophils/μL), moderate (AEC, 1,500–5,000 eosinophils/μL), and severe (>5,000 eosinophils/μL). Iron-deficiency anemia may be evident and hypoalbuminemia present, especially in patients with mucosal involvement. Total serum IgE ≥100 IU/mL is reportedly present in about two-thirds of EGE cases. Erythrocyte-sedimentation rate has been reported elevated in a few cases.

To identify the inability to digest and adsorb proteins in the GI tract, fecal protein loss is assessed by measuring the levels of α1-antitrypsin in a 24-hour feces collection. Normal α1-antitrypsin level is 0–54 mg/dL, and is highly increased in the feces of patients with EGE. Protein loss can also result in low levels of immunoglobulins, but serum IgE may stay elevated. Furthermore, stool examination should be performed to rule out parasitic infections (ie, Strongyloides, Ascaris, Ancylostoma, Anisakis, Capillaria, Toxicara, Trichiura, and Trichinella spp.). Mild–moderate steatorrhea is present in about 30% of patients, and can be detected by qualitative and quantitative stool tests. Finally, some reports of EGE cases have demonstrated the presence of exudative fluid with net eosinophilic predominance reaching about 90% of white blood cells in the peritoneal fluid.

**Endoscopic and imaging studies**

The next step toward diagnosis requires either endoscopy or imaging studies.

The gross endoscopic appearance of EGE includes normal aspect, erythematous, nodular, friable, and often ulcerated mucosa, pseudopolyps, and polyps. Sometimes,
diffuse inflammation with complete loss of villi, infiltration of the GI wall, submucosal edema, and fibrosis may be present. 

Although findings from endoscopic biopsies can play an important role in diagnosis, endoscopy remains not sensitive or specific for diagnosis of the disease. Furthermore, the patchy distribution of eosinophilic infiltrates requires multiple biopsy specimens, at least five or six, from normal and abnormal mucosa to avoid the possibility of sampling error and missing a diagnosis. In patients with esophageal or colonic symptoms, additional biopsy specimens may be obtained from relevant sites to aid in the diagnosis. Endoscopic ultrasound is useful for the assessment of muscular and subserosal types, as it utilizes a fine aspiration needle that facilitates access to these tissue sites. Patients with serosal involvement also present with ascites.

Radiographic changes are specific, variable, and/or absent in about 40% of patients. It is possible to observe enlarged gastric folds with or without nodular filling defects. In extensive disease strictures, ulceration or polypoid lesions may be present, and valvulae conniventes may be thickened and flattened. In muscular EGE, localized involvement of the antrum and pylorus may occur, causing narrowing of the distal antrum and gastric retention. The small intestine may be dilated, with an increase in thickness of the mucosal folds, while in the colon prominent mucosal folds may be observed. Ultrasound and computed tomography (CT) may show ascites, thickened intestinal walls, and occasionally localized lymphadenopathy. However, similar changes are also observed in Crohn’s disease, lymphoma, and granulomatous disease. A “halo sign” and “araneid limb–like sign” can be observed on CT as secondary to bowel-wall layering, and both can help in differentiating between an inflammatory and neoplastic lesion. Radioisotope scan with technetium (99mTc) hexamethylpropyleneamineoxime–labeled white blood cells provides a useful tool in assessing the extent of the disease and monitoring therapeutic response, but has little diagnostic value, as this method does not differentiate EGE from other causes of intestinal inflammation.

Biopsy and histopathological analysis
Histopathological examination of gastric and duodenal biopsies has a crucial role in diagnosing EGE. Despite many tools being able to aid in the obtainment of biopsies, the most accurate method is surgery, which provides a full-thickness specimen for comprehensive pathology and facilitates diagnosis of muscular and serosal EGE. Biopsies from both normally and abnormally appearing mucosa should be taken, because even normal areas can harbor a diagnostic microscopic appearance. Normal eosinophil count varies based on the anatomic site of the GI tract. In the duodenum, it is set at <10 eosinophils per high-power field (HPF) in pediatric patients and <19 eosinophils/HPF in adults. Therefore, a microscopic examination that reveals >10 eosinophils/HPF in children and >20 eosinophils/HPF in adults has been set in most reports as the threshold for fulfilling the second diagnostic criterion for mucosal EGE. However, in the cecum the threshold must be set at higher values, as up to 40 eosinophils/HPF has been suggested to be normal at this site and up to 16 in the colons of pediatric patients and up to 50 in adults. Furthermore, when evaluating the number of eosinophils, environmental factors need to be considered: eosinophil counts are higher during peak allergy seasons and among populations living in southern regions of the US.

It has been noted that the presence of intraepithelial eosinophils and eosinophils in Peyer’s patches, as well as extracellular deposition of eosinophil MBPs, favor the development of EGE. Particularly, the latter finding reflects the degree of degranulation in activated eosinophils, which is linked to greater structural damage. Observations of crypt hyperplasia, epithelial cell necrosis, villous atrophy, or abscesses are also common in EGE. Mast-cell infiltrates and hyperplastic mesenteric lymph nodes infiltrated with eosinophils may be present.

Interestingly, evidence exists suggesting that the degranulation observed on histology may be affected by the method of tissue procurement during biopsy. Increased eosinophil degranulation is observed in tissue obtained by endoscopic forceps compared to a scalpel.

Differential diagnosis
Following confirmation of eosinophilic infiltration into the GI tract, diseases in which GI symptoms are associated with peripheral eosinophilia must be differentiated from EGE. The main differential diagnoses are intestinal parasites, eosinophilic esophagitis, eosinophilic ascites, celiac disease, protein-losing enteropathy from intolerance to cow-milk protein, infantile formula–protein intolerance, and idiopathic hypereosinophilic syndrome.

Intestinal parasites, such as Ascaris, Anisakis, Ancylostoma, Strongyloides, Capillaria, Toxocara, Trichiura, and Trichinella, all cause eosinophilia and can
be excluded with careful examination of the stool for ova and parasites.\(^{80-84}\) In eosinophilic esophagitis, only the esophagus is involved and not the whole bowel. Typically, eosinophils can be found in superficial clusters near the surface of the epithelium, and an expansion of the basal layer is also seen in response to inflammatory epithelium damage. Ridges or furrows may be seen in the esophageal mucosa via endoscopy.\(^{85,86}\) Celiac disease is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in other grains. It is characterized by blunting of the villi and crypt hyperplasia in the small bowel, and predominant lymphocyte infiltration of crypts.\(^{87}\) Finally, hypereosinophilic syndrome is an idiopathic condition associated with a myeloproliferative disorder, characterized by marked peripheral eosinophilia exceeding 1,500 eosinophils per HPF that persists for more than 6 consecutive months. In addition to the GI tract, the targets of hypereosinophilic syndrome are the heart, central nervous system, lungs, liver, skin, and kidneys,\(^{88,89}\) with >55% of patients having severe complications in one or more of these sites.\(^{90}\) Idiopathic hypereosinophilic syndrome can be ruled out when there is an absence of eosinophilic infiltration in all other organs except the bowel.\(^{91}\)

Additionally, vasculitis (ie, Churg–Strauss syndrome, polyarteritis nodosa), connective-tissue diseases, inflammatory bowel diseases, lymphoma, leukemia, and mastocytosis are also associated with peripheral eosinophilia, and must be differentiated from EGE.

Management
Several therapeutic options have been suggested for EGE management: dietary modifications, steroids, LT inhibitors, mast-cell stabilizers, immunomodulators, and biological agents. All these treatment approaches have been described in small case series or single reports, and to our knowledge only a double-blind randomized, crossover trial has evaluated the efficacy of a LT inhibitor, montelukast, in pediatric patients.\(^{92}\) However, more randomized prospective clinical trials to describe the efficacies of different treatments or predictors of response to one or another option have not been reported in the literature yet, and thus are warranted so that the effectiveness of the various treatments can be more robustly established and provide guidance to clinicians.

Thus far, treatment for EGE has been empirical and based on the severity of the clinical manifestations, as well as on clinicians’ experience. Patients with mild disease can be treated symptomatically,\(^{68}\) while more symptomatic patients and those with evidence of malabsorption need more aggressive therapy.

Dietary therapy
The strong association of EGE with food allergies has prompted the introduction of many dietary strategies based on results from food-allergy tests. When a low number of food allergens are identified, patients should be maintained on a targeted elimination diet, while when more or no allergens are detected, the “empiric elimination diet” or elemental diet might be used, which consist of the elimination of a single food or a combination of them. The empirical elimination of the six most common food antigens from the diet (also called six-food elimination diet or 6-FED) and 7-FED (excluding red meats also) have been frequently assessed in recent years.\(^{93}\)

However, the role of dietary therapy as an approach is controversial. A systematic review by Lucendo et al\(^{94}\) investigated the efficacy of dietary treatment in EGE and found significant improvement in most cases, with clinical remission in >75% of patients who undertook the elemental diet. Interestingly, the efficacy of dietary restrictions has mainly been reported in the setting of mucosal EGE,\(^{94}\) which is well known to be associated with food allergy, while efficacy in muscular and serosal diseases, less linked to food allergies,\(^{7}\) was has been only rarely reported. However, the findings reported in the review by Lucendo et al were not supported by histopathological exams, which makes the validity of the dietary approach questionable. Most importantly, the authors concluded that unequivocal use of dietary treatment cannot be supported, due to the lack of well-designed, high-quality studies.\(^{94}\)

On the contrary, a retrospective study of Chen et al\(^{14}\) indicated that an elimination diet can lead to clinical and histological improvement; however, in this study the dietary therapy was used in combination with other pharmacological interventions. More recently, a retrospective study by Wong et al\(^{9}\) reported that one in 18 patients with EGE tested positive for a food allergy and had clinical improvement with an elimination diet, and follow-up endoscopy showed resolution of eosinophilic infiltration. Conversely, Yamada et al\(^{95}\) showed that the elemental diet caused rapid improvement in symptoms, but duodenal eosinophilic infiltration persisted. However, Katz et al\(^{96}\) reported that an elimination diet might fail to prevent recurrence.
The most solid evidence of the efficacy of the dietary approach to treat EGE has been provided in pediatric patients (<3 years of age). However, no randomized studies exist to assess their efficacy accurately, but only single or small case series (up to 12 patients) have been reported, in which the conclusions are considered weak because histological assessment is rarely reported. Notably, a retrospective study by Ko et al trialed different dietary therapies (elemental diet, 7-FED, and empirical avoidance of one to three foods) in 30 children with EGE. Despite 82% of patients having a positive clinical response, histological assessment was not available for most of them, making it difficult to extrapolate these data to larger populations.

Recently, trials have been conducted in adults to evaluate the effectiveness of dietary therapy in EGE treatment. In 2009, a prospective trial was conducted in adults with histological diagnosis of EGE and treated for 6 weeks with the 6-FED or elemental diet. The results were encouraging, as clinical and histological remission was observed in both groups. However, the number of patients involved was small and the placebo-control group was missing, and thus further trials are needed. Finally, a prospective interventional study is ongoing to evaluate the effect of a 6-week elemental diet in adult patients (18–65 years of age) with EGE, and complete histological remission (<30 eosinophils/HPF) and improvement are set as primary and secondary outcomes, respectively.

The overall data in the literature is insufficient to recommend empirical and total-elimination diets in routine management; however, an elemental diet may be considered initially as an adjunct treatment for severe cases. Additionally, from the literature it appears clear that the later EGE appears during childhood, the worse it responds to dietary modification. Finally, patient tolerability and adherence to such strategies are difficult to track, especially when empirical elimination or elemental diets are used. Therefore, future randomized controlled studies are required, and must include assessment of histological remission to better characterize the phenotype of patients with EGE who respond to dietary therapy.

Corticosteroids

Corticosteroid therapy is the mainstay of EGE treatment in both adults and children. Corticosteroids suppress the gene transcription of IL3, IL4, IL5, GM-CSF, and various chemokines. In many studies, it has been proven that corticosteroids decreased both the number of eosinophils and the effects of their toxic products. The appropriate duration of steroid therapy is unknown, and relapse often necessitates long-term treatment. Unfortunately, this may cause serious adverse effects in some patients, and there is also the risk that resistance to corticosteroids may develop, as it is already known to occur in asthma with patients maintaining eosinophilia despite high doses of steroids. These patients will require alternative approaches.

Although evidence to date demonstrates that corticosteroids are the most effective therapy for EGE, no randomized controlled studies are available to guide treatment. Reasons for that may be attributed to the fact that the low prevalence of EGE can make difficult to enroll a big number of patients that can go to trial.

Prednisolone

Prednisolone acts by inducing eosinophil apoptosis and inhibiting chemotaxis. It is the first-choice corticosteroid for induction of remission of EGE, and has been reported to be effective in >90% of cases. Prednisolone is orally administered at an initial dose of 30–40 mg/day for 6–8 weeks with various schemes of dose tapering. It induces complete remission of symptoms within 2 or 3 weeks of treatment, reducing eosinophil tissue infiltration, blood hypereosinophilia, and controlling ascites. Notably, Zhang et al showed that the highest response rate to prednisolone was among patients with the serosal type. Because of the long-term side effects, prednisolone is suspended after remission has been achieved. However, relapses can occur, and require low maintenance doses (1–10 mg/day) of prednisolone for a longer time or substitution of prednisolone with budesonide. In cases of initial unresponsiveness, either reevaluation of EGE diagnosis and type or switching to a different pharmacological agent (budesonide or steroid-sparing agents) must be considered. Additionally, long-term steroid treatments can predispose patients to adverse effects that may not be tolerated well, and in such cases steroid-sparing agents can be beneficial.

Budesonide

Budesonide is commonly used for Crohn’s disease and ulcerative colitis. It reduces inflammation and capillary permeability by binding to steroid receptors with high affinity. The advantage of budesonide is that it can be administered as a topically active corticosteroid, thanks to slow-release enteric-coated capsules (budesonide CIR [controlled ileal release]) and has high (90%) first-pass
metabolism, which together produce fewer side effects, due to its lower systemic impact. There has been only one case\textsuperscript{115} in which the patient could not be treated with budesonide CIR because of gastric involvement, and thus the patient was treated with regular budesonide oral tablets for 2 weeks and showed remission \(>2\) years.

Many studies have demonstrated that budesonide is effective for induction and maintenance of remission\textsuperscript{19,98,115–118} accompanied by histological improvement in inflammatory alterations.\textsuperscript{9,112,119,120} Reed et al\textsuperscript{19} showed that treatment with budesonide, administered either as viscous slurry or enteral release, induced remission in 61% of patients. However, the results were not analyzed based on the specific formulation of budesonide, and thus we are most likely missing a piece of information about the real effectiveness of budesonide in those cases analyzed. The usual dose is 9 mg/day, and can be tapered to 6 mg/day for prolonged use, as well as for maintenance therapy. Collectively, the efficacy and better safety profile of budesonide compared to other corticosteroids are of particular benefit for the long-term management of certain EGE cases.

**Leukotriene-receptor antagonists**

LT-receptor antagonists are a class of drugs commonly used to treat asthma that prevent or reverse some of the pathological features associated with the inflammatory process mediated by LTs (LTs) C\textsubscript{4}, D\textsubscript{4}, and E\textsubscript{4}. It has demonstrated efficacy for various eosinophilic disorders, including EGE.

**Montelukast sodium**

Montelukast sodium is a potent and selective LTD\textsubscript{4} inhibitor at the cysteinyl LT receptor CysLT\textsubscript{1}.\textsuperscript{121} The usual dose is 5–10 mg/day, shown to be effective either alone\textsuperscript{122} or in combination with a low dose of steroids\textsuperscript{9,116} for induction and maintenance of remission in steroid-dependent or -refractory disease in both adults and children.\textsuperscript{55} The majority of reports in the literature concerning its use in EGE have shown exciting results. Indeed, positive clinical and histological responses were achieved in a majority of patients within 2–4 weeks from the beginning of treatment,\textsuperscript{56,92,122,123} with remission of at least 12 months.\textsuperscript{55} Moreover, three case reports have displayed successful steroid tapering of steroid-dependent patients with EGE once montelukast sodium had begun.\textsuperscript{54,121,124} Daikh et al\textsuperscript{125} commented on the reduction of eosinophilia with montelukast, but the absence of any symptomatic relief, in a patient with EGE. Tien et al\textsuperscript{54} observed that three patients treated with an LT antagonist alone had a good outcome without relapse during follow-up. On the other hand, only two studies have shown a lack of montelukast efficacy in patients.\textsuperscript{16,124} More randomized trials are required to assess the long-term benefits and side effects of LT antagonists in EGE.

**Mast-cell stabilizers**

Mast-cell stabilizers block mast-cell degranulation, stabilizing the cells and thereby preventing the release of histamine and related mediators, which are hypothesized to be involved in the pathogenesis of EGE.

**Sodium cromoglycate or cromolyn**

Oral sodium cromoglycate (SCG) or cromolyn blocks the release of such mediators as histamine, LTs, and others from mast cells that attract inflammatory cells, including eosinophils. The dose used has been different among different reports, ranging from 100 mg to 300 mg three or four times daily and the duration of treatment may vary from 10 weeks to over a year.\textsuperscript{55} These differences can be imputable to the severity of the disease at the moment of diagnosis. Studies on SCG efficacy are controversial, as it has been found effective in many cases, with complete clinical and histological remission\textsuperscript{7,126–132} but not in others.\textsuperscript{7,119,132} Considering that in these studies, both responsive and unresponsive patients to SCG had similar features in terms of the intestinal layer (~90% vs muscular EGE) and site involved (~64% stomach and duodenum), we can hypothesize that the underlying pathogenic mechanism of EGE in unresponsive patients does not involve mast-cell degranulation. However, altogether the results provide evidence of SCG efficacy in the treatment of EGE and suggest its employment as an alternative to the steroids commonly used.

**Antihistamines**

**Ketotifen**

Ketotifen is a first-generation H\textsubscript{1} antihistamine\textsuperscript{133} and mast-cell stabilizer,\textsuperscript{134} as it also modulates the release of mast-cell mediators. It is used at a dose of 1–2 mg twice daily bid. Thus far, there have been few studies on the use of ketotifen, and with contrasting results. Melamed et al\textsuperscript{135} described six patients with EGE who responded clinically and histologically to ketotifen. The same result was achieved in the single case report described by Bolukbas et al.\textsuperscript{136} On the other hand, Freeman et al\textsuperscript{137} reported a single case in which the drug provided only symptomatic benefits, with prompt clinical relapse when the treatment
was interrupted. Furthermore, despite the use of ketotifen, endoscopic abnormalities persisted and appeared to progress. This agent has also been proposed as an adjunct to steroids and montelukast for treating refractory EGE in pediatric patients.\textsuperscript{54} In that study, one patient had a good prognosis, while another did not improve in any symptoms. Finally, it is hard to make conclusions about the use of ketotifen in EGE, as it has never been used as monotherapy.

Overall, given the natural history of EGE, it is not clear if the remissions described in individual case reports were due to medications or spontaneous remission. Studies to date do not support use of LT-receptor antagonists, cromolyn, proton-pump inhibitors (PPIs), or ketotifen as monotherapy for EGE. However, if patients have comorbid conditions for which they are indicated, evidence demonstrates they are unlikely to be harmful.

Other therapies

Considering that some patients are unresponsive or do not tolerate well the side effects well, especially associated with the use of corticosteroids, additional therapies have been proposed.

Immunomodulators

Alternatives for patients who are dependent on steroids or resistant to them include myelosuppressive drugs such as azathioprine (Aza) and 6-mercaptopurine (6MP). They act by inhibiting purine synthesis, which ultimately affects DNA/RNA synthesis. These drugs also inhibit the proliferation of T and B lymphocytes, which leads to decreased production of cytotoxic T lymphocytes and plasma cells.\textsuperscript{138}

6-Mercaptopurine

6MP is a ribonucleotide that has an immunosuppressive effect by inhibiting an enzyme called phosphoribosyl pyrophosphate amidotransferase, (PRPP amidotransferase) involved in the synthesis and metabolism of purine nucleotide RNA and DNA.

To date, there has been only one published study using 6MP in eosinophilic oesophagitis,\textsuperscript{138} in which the patient achieved clinical and histological remission that was maintained for >3 years.

Azathioprine

Aza is a thiopurine analogue that is incorporated into DNA structure, causing chain termination and cytotoxicity. It is commonly used as an immunosuppressive agent in organ transplants and patients with autoimmune diseases, including inflammatory bowel diseases.

Aza’s efficacy has been observed in patients with steroid-dependent and -refractory EGE disease at a dose of 50 mg/day usually. Some studies showed that patients treated with Aza alone had complete clinical and histological remission\textsuperscript{139} that was maintained for >3 years.\textsuperscript{138} On the other hand, another study showed that the combination of Aza and prednisolone 2 mg/day was more effective than Aza alone.\textsuperscript{16} Interestingly, in this same study, the patient was treated for >1 year with Aza without any relevant side effects, suggesting that it is well tolerated for long-term treatment. However, controlled randomized trials with a larger number of patients and comparing immunomodulators to other EGE therapies are needed to drive more solid conclusions.

Proton-pump inhibitors\textsuperscript{79}

Even if gastroesophageal reflux is absent, neutralization of gastric acidity with a PPI is thought to be effective in improving symptoms and the degree of pathology. However, a study showed that PPI treatment with lansoprazole (10 mg/day) improved the extent of duodenal eosinophilic infiltration in a pediatric patient with EGE, and the mechanism has been hypothesized to involve blockade of IL4 and IL13 activity, as well as acid suppression, which may shorten eosinophil viability by increasing pH.\textsuperscript{95} Therefore, utilization of PPIs should not be underestimated.

Novel therapies: biological agents

Considering that both IgE-dependent and delayed T\textsubscript{H}2 cell-mediated allergic mechanisms, with production of different cytokines that promote eosinophil migration, activation, and survival, were demonstrated to be involved in the pathogenesis of EGE, recently monoclonal antibodies against IL5, TNF\textalpha, and IgE were adopted in clinical trials to treat EGE.

Reslizumab

It is well known that IL5, a cytokine produced by T\textsubscript{H}2 cells and mast cells, is a key mediator in eosinophil activation, and it has been demonstrated to regulate various processes associated with eosinophils.\textsuperscript{140} Based on these properties, neutralizing antibodies against IL5 have been generated to lower eosinophil blood and tissue levels with the goal of impacting diseases characterized by T\textsubscript{H}2 environments and eosinophilia, such as EGE.
Prussin et al\textsuperscript{141} reported the results of a pilot study with reslizumab (previously SCH55700) administered in a single intravenous dose (1 mg/kg intravenously, equivalent to a 750 mg dose) in four patients with EGE. Reslizumab was effective in three patients and reduced both tissue and peripheral blood eosinophilia, with a peak at 48 hours postadministration. However, reslizumab failed to relieve the symptoms, confirming that several inflammatory mediators are involved in the pathogenesis of EGE whose blockade may be required to control the clinical manifestations of the disease completely. On the contrary, Kim et al\textsuperscript{142} showed that reslizumab treatment induced improvement of eosinophilia and clinical symptoms in six of eight patients with hypereosinophilic syndrome or EGE. However, in both studies, its use was associated with rebound hypereosinophilia, which the authors attributed to a serum factor that enhances eosinophil survival by using an in vitro approach in cultured eosinophils isolated from patients or normal donors. Because the effect was reversed by the addition of reslizumab, they suggested that this factor may be IL5 itself.

\subsection*{Infliximab}

In addition to IL5, TNF\textalpha has been found to be upregulated in EGE and involved in the induction of cell-adhesion molecules, leading to selective eosinophil recruitment. There is only one multiple case report describing the use of an anti-TNF\textalpha, infliximab, in EGE.\textsuperscript{100} In this study, infliximab was reported to be highly effective in inducing remission in refractory EGE in pediatric patients, but its use is limited by the development of resistance and secondary loss of response, both of which can be managed by switching to adalimumab, which allows sustained remission and endoscopic improvement.

\subsection*{Omalizumab}

Omalizumab, a humanized therapeutic anti-IgE monoclonal antibody that reduces free IgE levels, is widely recognized as an effective treatment for allergic asthma and seasonal allergic rhinitis,\textsuperscript{143} with the reported capability to reduce peripheral blood,\textsuperscript{144} bronchial,\textsuperscript{145} and skin\textsuperscript{146} eosinophilia. Therefore, it is possible that omalizumab may be effective in the treatment of EGE. Foroughi et al\textsuperscript{147} reported success in an open-label study of nine patients treated with omalizumab at a maximum dose of 375 mg subcutaneously every 2 weeks for a total of eight doses. At the end of the study, omalizumab was well tolerated by the patients, and able to block IgE effectively in patients with EGE, as demonstrated by a significant decrease in allergen-specific basophil activation. Omalizumab was also associated with a drop in AEC and increase in EGE symptoms, suggesting that IgE-mediated processes play a major role in the generation of eosinophilic inflammation in EGE and that anti-IgE therapy alone as an adjunct with other targeted therapies, may be an effective treatment for EGE.

\subsection*{Suplatast tosilate}

Suplatast tosilate is a selective T\textsubscript{H}2 cytokine inhibitor that suppresses the effects of allergen-induced eosinophil infiltration and IgE production.\textsuperscript{148,149} It was shown to be effective in the management of severe refractory and steroid-dependent EGE, with beneficial effects on symptoms and histological appearance on follow-up study.\textsuperscript{150}

\subsection*{Intravenous immunoglobulin}

Intravenous immunoglobulin treatment for EGE has been successful in two reported cases: one in a patient with steroid-refractory EGE and concomitant systemic lupus erythematosus,\textsuperscript{18} and the other in a patient in whom prolonged steroid treatment caused osteopenia and who was unresponsive to montelukast as an alternative approach.\textsuperscript{124}

\subsection*{Interferon-\alpha}

IFN\textalpha seems promising too, because of its inhibitory effect on the degranulation of eosinophils or the expression of active eosinophilic cytokines by T cells and mast cells.\textsuperscript{151,152} It has been successfully used to treat a patient with EGE and concomitant food allergy.\textsuperscript{124} Indeed, he became asymptomatic and able to come off steroid treatment; however, he had to be discontinued, due to weight loss with a recurrence of eosinophilia.

\subsection*{Fecal microbiota transplantation}

Recently, a study on the efficacy of fecal microbiota transplantation (FMT) in a patient with severe EGE presenting as frequent bowel obstruction and diarrhea was reported in the literature.\textsuperscript{153} FMT was able to reduce the frequency of diarrhea markedly, even before prednisone had been added as an adjunct therapy. This indicated the active therapeutic role of FMT in EGE cases presenting as long-term diarrhea, but it raises the question whether FMT alone could cure EGE or maintain long-term clinical remission if prednisone were not given.

\subsection*{Surgical care}

Surgical treatment is avoided as far as possible; however, it is necessary in cases of severe EGE that are complicated
by perforation, intussusception, or intestinal occlusion or when performing a full-thickness intestinal biopsy to establish the diagnosis. It has been reported that about 40% of EGE patients may need surgery during the course of their disease, and about half of those may experience recurrence, even after surgical excision.\textsuperscript{154}

**Prognosis**

Although EGE is reported to wax and wane, no changes in survival rate have been observed, whereas growth alterations were seen in children and adolescents.\textsuperscript{155} However, when the disease manifests in infancy and specific food sensitization can be identified, the likelihood of disease remission by late childhood is high.

Mild and sporadic symptoms can be managed with reassurance and observation, whereas oral corticosteroids can control disabling GI symptoms and reduce blood and tissue eosinophil levels, but in certain cases they can reappear if the treatment is stopped. Dietary management and steroid-sparing agents are necessary to lower the collateral effects of steroid use and maintain an adequate quality of life. Altogether, follow-up studies in small case series and retrospective studies have demonstrated that EGE has a good prognosis and is not associated with malignancy.

**Discussion and conclusion**

EGE is a chronic GI disease characterized by eosinophilic infiltration and degranulation that in turn causes damage to the GI wall.\textsuperscript{7}

The presence of peripheral eosinophilia, abundant eosinophils in the GI tract, and dramatic response to steroids provide some support that the disease is mediated by a hypersensitivity reaction.\textsuperscript{12,156} Both IgE-dependent and delayed T\textsubscript{H}2 cell–mediated hypersensitivity mechanisms have been demonstrated to be involved in the pathogenesis of EGE.\textsuperscript{38,157}

EGE is a disease that requires broad knowledge from a gastroenterologist. Due to the aspecific nature of the GI symptoms of EGE, especially in those patients with mild symptoms, many clinicians rarely think of EGE, unless these symptoms are refractory or elevated peripheral blood eosinophils are found. However, it is known that not all EGE patients have an elevated level of peripheral blood eosinophils,\textsuperscript{53,88,111} which may result in the missed diagnosis of those with normal counts of peripheral blood eosinophils. Therefore, EGE diagnosis is problematic, as it is necessary for clinicians to have a high index of clinical suspicion. EGE should be considered when a patient presents with unexplained GI symptoms that cannot be defined by parasitic or other GI diseases characterized by eosinophilic infiltration. Other evidence, such as laboratory results, radiological findings, and endoscopy provide important pieces of information that together with histological results will lead to a definitive diagnosis of EGE.

Of note, the low prevalence of EGE has meant that most of our knowledge about this disorder comes from individual case reports and short case series, making it difficult to elucidate the definitive features of its epidemiology. Therefore, this disease has been classically defined as a rare disturbance of the GI tract. However, there is now growing evidence suggesting that mucosal eosinophilia is relatively common in patients with FD, and thus EGE prevalence is expected to rise.

Many therapeutic options are available for the management of EGE, including both nonpharmacological (diet) and pharmacological approaches, which have been reported in single and case series, showing variable efficacy. The dietary approach is usually considered an initial strategy before drug treatment, especially when a food allergy is highly suspected. For patients with moderate–severe disease, corticosteroids represent the mainstay of therapy. Since prolonged corticosteroid treatment carries the risk of serious adverse effects, other options with better safety profiles have been proposed. These include budesonide and steroid-sparing agents, such as LT inhibitors, immunomodulators, antihistamines, and mast-cell stabilizers. Furthermore, the disease is recognized as a chronic disorder, and very frequently, due also to relapse, requires a maintenance regimen by taking into consideration the safety profile of the drug in use.\textsuperscript{53} High AEC at diagnosis was found to be an independent predictor of relapses, as was extensive intestinal involvement. Some case series have found higher relapsing rates of 60%–80%,\textsuperscript{53} while others have noted a possible association between younger age (<20 years) and disease recurrence.\textsuperscript{155} However, research has not identified any other predictors of EGE disease evolution; therefore, the duration of such maintenance therapy cannot be predicted at this point.

In the last decade, biological therapy with a monoclonal antibody against inflammatory cytokines (IL\textsubscript{5}, IFN\textsubscript{\gamma}, TNF\textsubscript{α}) and IgE,\textsuperscript{53} was adopted in clinical trials or reported in single studies for the management of EGE, showing promising results in terms of efficacy and safety. Of note, recently other biological therapies have been in clinical development for the treatment of eosinophilic disorders,
especially asthma. Interestingly, some of these therapies, such as benralizumab (against IL5 receptor) and QAX576 (against IL13) are also in ongoing clinical trials for hyper-eosinophilic syndrome and eosinophilic oesophagitis, respectively, suggesting that in the near future new therapeutic tools may be available for the management of EGE as well.

In conclusion, because EGE is a rare disease, it is commonly underdiagnosed (or underreported). However, good communication among clinicians, endoscopists, and pathologists may help decrease the rate of missed diagnosis. Prospective and randomized clinical trials to evaluate the best treatment available are still lacking. Therefore, nosystematic and practical strategy has been put forth yet for health-care teams to follow in their management of EGE cases. Further studies are needed to compare the efficacy and safety profiles of the various treatments available, as well as to select predictors of relapses, which in turn will guide decision-making for the initial phase of treatment and maintenance therapy in a more consistent fashion.

Disclosure
The authors report no conflicts of interest in this work.

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