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 and highly effective. 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 people^{4,5} 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 al⁶ 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.

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Mucosal EGE is the most common variety, seen in about 57%⁷ to 100%^{8,9} of cases, and presents with features of abdominal pain, nausea, vomiting, dyspepsia, diarrhea, malabsorption, or protein-losing enteropathy, which in turn may cause hypoalbuminemia, anemia, and weight loss. Additionally, the occurrence of lower-GI bleeding may imply colonic involvement.^{10,11} 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.¹² The serosal type is the least common, with an estimated prevalence of 4.5%–9% in Japan and 13% in the US,¹³ and causes peritoneal irritation that leads to eosinophilic ascites and abundant peripheral eosinophilia, peritonitis, and perforation in more severe cases.¹⁴ Intestinal intussusceptions may occur in the serosal type too.¹⁵ Furthermore, Chang et al⁸ observed that the muscular and serosal types are associated with concomitant mucosal eosinophilic infiltration,⁸ 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,^{5,8,12} while others have found an association with other autoimmune conditions, such as ulcerative colitis,¹⁶ celiac disease,¹⁷ and systemic lupus erythematosus.¹⁸ 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.¹⁹ Finally, other environmental factors, such as parasitic infestation or drugs, have been suggested to act as predisposing factors too.²⁰ 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.²¹

New recent evidence suggests that mucosal eosinophilia is relatively common in patients with functional

dyspepsia (FD),² in both adults²² and children.²³ Du et al conducted a pilot study demonstrating that FD is directly correlated with increased infiltration of degranulated eosinophils,² supporting early clinical evidence of a role of eosinophils in FD pathogenesis.²³ Aro et al also found evidence of duodenal eosinophilia associated with dyspepsia among other factors that are commonly associated to EGE as well.²⁴ 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.²⁵ Interestingly, patients with FD show low-grade GI eosinophilia.²⁶ 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.^{25,27,28}

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.^{29–32} Interestingly, Desreumaux et al³³ 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 $\alpha_4\beta_7$ integrin regulate eosinophilic homing into the lamina propria of the stomach and small intestine. The importance of eotaxin in EGE was shown by Hogan et al³⁴ 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, IL1 β , leukotrienes (LTs), and TNF α 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,^{20,35} as they were detected in diseased intestinal walls by immunostaining.³⁶ Jaffe et al³⁷ showed enhanced expression of IL4, IL5, and IFN γ 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 al³⁸ 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 al³⁹ 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,^{40–43} which seems to be involved in functional GI disorders (FGIDs), associated with increased visceral sensitivity⁴⁴ and disordered motility.⁴⁵

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.⁴⁶

Of note, animal studies have shown that acute stress activates mast cells, inducing FI-function disturbances, which are also activated in stress⁴⁷ and may have a role in the visceral hypersensitivity of irritable bowel–syndrome patients,⁴⁸ without allergic degranulation.⁴⁹ 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.⁵⁰

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 al⁷ suggested three criteria for the diagnosis of EGE, which are still used widely: presence of GI symptoms, histological demonstration of eosinophilic 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).⁵¹

Interestingly, peripheral count is an insensitive marker for mucosal eosinophilia in FGIDs.⁵²

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.^{7,53} The absolute eosinophil count (AEC) is used to categorize the disease in mild (AEC, 600–1,500 eosinophils (eos)/ μ L), moderate (AEC, 1,500–5,000 eosinophils/ μ L), and severe ($>5,000$ eosinophils/ μ L). 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.⁵⁴ Erythrocyte-sedimentation rate has been reported elevated in a few cases.¹²

To identify the inability to digest and adsorb proteins in the GI tract, fecal protein loss is assessed by measuring the levels of α_1 -antitrypsin in a 24-hour feces collection. Normal α_1 -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.).⁵⁵ 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.⁵⁶

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,¹⁴ pseudopolyps, and polyps.^{57,58} Sometimes,

diffuse inflammation with complete loss of villi, infiltration of the GI wall, submucosal edema, and fibrosis may be present.^{59,60} Although findings from endoscopic biopsies can play an important role in diagnosis,¹⁴ 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.⁹ 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.⁶¹ Patients with serosal involvement also present with ascites.¹⁴

Radiographic changes are aspecific, 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.¹² Ultrasound and computed tomography (CT) may show ascites, thickened intestinal walls, and occasionally localized lymphadenopathy.⁶² However, similar changes are also observed in Crohn's disease, lymphoma, and granulomatous disease.⁶³ 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.^{64,65} Radioisotope scan with technetium (^{99m}Tc) 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.^{66,67}

Biopsy and histopathological analysis

Histopathological examination of gastric and duodenal biopsies has a crucial role in diagnosing EGE.^{7,10,68} 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.⁶⁹ Biopsies from both normally and abnormally appearing mucosa should be taken, because even normal areas can harbor a diagnostic microscopic appearance.⁶⁸ 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.^{22,23} 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.^{19,52,58} 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,⁷⁰ and up to 16 in the colons of pediatric patients⁷¹ and up to 50 in adults.⁷² Furthermore, when evaluating the number of eosinophils, environmental factors need to be considered: eosinophil counts are higher during peak allergy seasons⁷³ and among populations living in southern regions of the US.⁷⁴

It has been noted that the presence of intraepithelial eosinophils and eosinophils in Peyer's patches,⁷⁵ as well as extracellular deposition of eosinophil MBPs,⁷⁶ favor the development of EGE. Particularly, the latter finding reflects the degree of degranulation in activated eosinophils, which is linked to greater structural damage.⁷⁷ 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.^{10,60,78}

Interestingly, evidence exists suggesting that the degranulation observed on histology may be affected by the method of tissue procurement during biopsy.⁷⁹ Particularly, 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*, *Toxicara*, *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 prolamins (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 al⁹⁴ 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 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 al¹⁴ 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 al⁹ 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 al⁹⁵ showed that the elemental diet caused rapid improvement in symptoms, but duodenal eosinophilic infiltration persisted. However, Katz et al⁹⁶ 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).^{57,97–104} 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 al¹⁰² 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.¹⁰²

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.¹⁰⁵ 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.¹⁰⁶

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.⁵³ 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.¹⁰⁷ In many studies, it has been proven that corticosteroids decreased both the number of eosinophils

and the effects of their toxic products.^{8,16} 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.^{7,108} 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.^{8,109} Prednisolone is orally administered at an initial dose of 30–40 mg/day for 6–8 weeks with various schemes of dose tapering.¹¹⁰ It induces complete remission of symptoms within 2¹⁴ or 3 weeks of treatment,¹ reducing eosinophilic tissue infiltration, blood hypereosinophilia, and controlling ascitis.⁸ Notably, Zhang et al¹¹¹ 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^{9,14} or substitution of prednisolone with budesonide.^{98,112} In cases of initial unresponsiveness, either reevaluation of EGE diagnosis and type¹¹³ 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.¹¹⁴ 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 case¹¹⁵ 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,^{19,98,115–118} accompanied by histological improvement in inflammatory alterations.^{9,112,119,120} Reed et al¹⁹ 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) C₄, D₄, and E₄. It has demonstrated efficacy for various eosinophilic disorders, including EGE.

Montelukast sodium

Montelukast sodium is a potent and selective LTD₄ inhibitor at the cysteinyl LT receptor CysLT₁.¹²¹ The usual dose is 5–10 mg/day, shown to be effective either alone¹²² or in combination with a low dose of steroids^{9,116} for induction and maintenance of remission in steroid-dependent or -refractory disease in both adults and children.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,^{56,92,122,123} with remission of at least 12 months.⁵⁵ Moreover, three case reports have displayed successful steroid tapering of steroid-dependent patients with EGE once montelukast sodium had begun.^{54,121,124} Daikh et al¹²⁵ commented on the reduction of eosinophilia with montelukast, but the absence of any symptomatic relief, in a patient with EGE. Tien et al⁵⁴ 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.^{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.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,^{7,126–132} but not in others.^{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 H₁ antihistamine¹³³ and mast-cell stabilizer,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 al¹³⁵ 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.¹³⁶ On the other hand, Freeman et al¹³⁷ 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.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.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,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 remission¹³⁹ that was maintained for >3 years.¹³⁸ On the other hand, another study showed that the combination of Aza and prednisolone 2 mg/day was more effective than Aza alone.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 inhibitors⁷⁹

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.⁹⁵ Therefore, utilization of PPIs should not be underestimated.

Novel therapies: biological agents

Considering that both IgE-dependent and delayed T_H2 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,⁵⁵ recently monoclonal antibodies against IL5, TNF α , and IgE were adopted in clinical trials to treat EGE.

Reslizumab

It is well known that IL5, a cytokine produced by T_H2 cells and mast cells, is a key mediator in eosinophil activation, and it has been demonstrated to regulate various processes associated with eosinophils.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_H2 environments and eosinophilia, such as EGE.

Prussin et al¹⁴¹ 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 al¹⁴² 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.

Infliximab

In addition to IL5, TNF α 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 α , infliximab, in EGE.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.

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,¹⁴³ with the reported capability to reduce peripheral blood,¹⁴⁴ bronchial,¹⁴⁵ and skin¹⁴⁶ eosinophilia. Therefore, it is possible that omalizumab may be effective in the treatment of EGE. Foroughi et al¹⁴⁷ 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 decrease 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.

Suplatast tosilate

Suplatast tosilate is a selective T_H2 cytokine inhibitor that suppresses the effects of allergen-induced eosinophilic infiltration and IgE production.^{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.¹⁵⁰

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,¹⁸ and the other in a patient in whom prolonged steroid treatment caused osteopenia and who was unresponsive to montelukast as an alternative approach.¹²⁴

Interferon- α

IFN α 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.^{151,152} It has been successfully used to treat a patient with EGE and concomitant food allergy.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.

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.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.

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.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.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.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.^{12,156} Both IgE-dependent and delayed T_H2 cell-mediated hypersensitivity mechanisms have been demonstrated to be involved in the pathogenesis of EGE.^{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,^{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.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%,⁵³ while others have noted a possible association between younger age (<20 years) and disease recurrence.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 (IL5, IFN α , TNF α) and IgE,³³ 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,¹⁵⁸ 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.

References

- Mori A, Enwelu C, Grier D, Badireddy M. Eosinophilic gastroenteritis: review of a rare and treatable disease of the gastrointestinal tract. *Case Rep Gastroenterol*. 2013;7(2):293–298. doi:10.1159/000354147
- Du L, Shen J, Kim JJ, Yu Y, Ma L, Dai N. Increased duodenal eosinophil degranulation in patients with functional dyspepsia: a prospective study. *Sci Rep*. 2016;6:34305. doi:10.1038/srep34305
- Kaijser R. Zur Kenntnis der allergischen Affektionen des Verdauungskanaals vom Standpunkt des Chirurgen aus. *Arch Klin Chir*. 1937;188:36–64.
- Spergel JM, Book WM, Mays E, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. *J Pediatr Gastroenterol Nutr*. 2011;52(3):300–306. doi:10.1097/MPG.0b013e3181eb5a9f
- Jensen ET, Martin CF, Kappelman MD, Dellon ES. Prevalence of eosinophilic gastritis, gastroenteritis, and colitis: estimates from a national administrative database. *J Pediatr Gastroenterol Nutr*. 2016;62(1):36–42. doi:10.1097/MPG.0000000000000865
- Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. *Medicine (Baltimore)*. 1970;49(4):299–319.
- Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut*. 1990;31(1):54–58.
- Chang JY, Choung RS, Lee RM, et al. A shift in the clinical spectrum of eosinophilic gastroenteritis toward the mucosal disease type. *Clin Gastroenterol Hepatol*. 2010;8(8):669–675; quiz e688. doi:10.1016/j.cgh.2010.04.022
- Wong GW, Lim KH, Wan WK, Low SC, Kong SC. Eosinophilic gastroenteritis: clinical profiles and treatment outcomes, a retrospective study of 18 adult patients in a Singapore Tertiary Hospital. *Med J Malaysia*. 2015;70(4):232–237.
- Lee CM, Changchien CS, Chen PC, et al. Eosinophilic gastroenteritis: 10 years experience. *Am J Gastroenterol*. 1993;88(1):70–74.
- Baig MA, Qadir A, Rasheed J. A review of eosinophilic gastroenteritis. *J Natl Med Assoc*. 2006;98(10):1616–1619.
- Ingle SB, Hinge Ingle CR. Eosinophilic gastroenteritis: an unusual type of gastroenteritis. *World J Gastroenterol*. 2013;19(31):5061–5066. doi:10.3748/wjg.v19.i31.5061
- Miyamoto T, Shibata T, Matsuura S, Kagesawa M, Ishizawa Y, Tamiya K. Eosinophilic gastroenteritis with ileus and ascites. *Intern Med*. 1996;35(10):779–782.
- Chen MJ, Chu CH, Lin SC, Shih SC, Wang TE. Eosinophilic gastroenteritis: clinical experience with 15 patients. *World J Gastroenterol*. 2003;9(12):2813–2816.
- Shin WG, Park CH, Lee YS, et al. Eosinophilic enteritis presenting as intussusception in adult. *Korean J Intern Med*. 2007;22(1):13–17.
- Copeland BH, Aramide OO, Wehbe SA, Fitzgerald SM, Krishnaswamy G. Eosinophilia in a patient with cyclical vomiting: a case report. *Clin Mol Allergy*. 2004;2(1):7. doi:10.1186/1476-7961-2-7
- Butterfield JH, Murray JA. Eosinophilic gastroenteritis and gluten-sensitive enteropathy in the same patient. *J Clin Gastroenterol*. 2002;34(5):552–553.
- Ciccio F, Giardina AR, Alessi N, et al. Successful intravenous immunoglobulin treatment for steroid-resistant eosinophilic enteritis in a patient with systemic lupus erythematosus. *Clin Exp Rheumatol*. 2011;29(6):1018–1020.
- Reed C, Woosley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. *Dig Liver Dis*. 2015;47(3):197–201. doi:10.1016/j.dld.2014.11.009
- Daneshjoo R. Eosinophilic gastroenteritis. *Curr Gastroenterol Rep*. 2002;4(5):366–372.
- Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest*. 2001;107(1):83–90. doi:10.1172/JCI10224
- Talley NJ, Walker MM, Aro P, et al. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. *Clin Gastroenterol Hepatol*. 2007;5(10):1175–1183. doi:10.1016/j.cgh.2007.05.015
- Friesen CA, Sandridge L, Andre L, Roberts CC, Abdel-Rahman SM. Mucosal eosinophilia and response to H1/H2 antagonist and cromolyn therapy in pediatric dyspepsia. *Clin Pediatr (Phila)*. 2006;45(2):143–147. doi:10.1177/000992280604500205
- Aro P, Ronkainen J, Storskrubb T, et al. Valid symptom reporting at upper endoscopy in a random sample of the Swedish adult general population: the Kalixanda study. *Scand J Gastroenterol*. 2004;39(12):1280–1288.
- Kalantar SJ, Marks R, Lambert JR, Badov D, Talley NJ. Dyspepsia due to eosinophilic gastroenteritis. *Dig Dis Sci*. 1997;42(11):2327–2332.
- Talley NJ, Ford AC. Functional dyspepsia. *N Engl J Med*. 2015;373(19):1853–1863. doi:10.1056/NEJMra1501505
- Friesen CA, Neilan NA, Schurman JV, Taylor DL, Kearns GL, Abdel-Rahman SM. Montelukast in the treatment of duodenal eosinophilia in children with dyspepsia: effect on eosinophil density and activation in relation to pharmacokinetics. *BMC Gastroenterol*. 2009;9:32. doi:10.1186/1471-230X-9-32
- Powell N, Walker MM, Talley NJ. Gastrointestinal eosinophils in health, disease and functional disorders. *Nat Rev Gastroenterol Hepatol*. 2010;7:146–156. doi:10.1038/nrgastro.2010.5
- Jose PJ, Griffiths-Johnson DA, Collins PD, et al. Eotaxin: a potent eosinophil chemoattractant cytokine detected in a guinea pig model of allergic airways inflammation. *J Exp Med*. 1994;179(3):881–887.
- Collins PD, Marleau S, Griffiths-Johnson DA, Jose PJ, Williams TJ. Cooperation between interleukin-5 and the chemokine eotaxin to induce eosinophil accumulation in vivo. *J Exp Med*. 1995;182:1169–1174.

31. Rothenberg ME, Ownbey R, Mehlhop PD, et al. Eotaxin triggers eosinophil-selective chemotaxis and calcium flux via a distinct receptor and induces pulmonary eosinophilia in the presence of interleukin 5 in mice. *Mol Med*. 1996;2(3):334–348.
32. Forssmann U, Ugucioni M, Loetscher P, et al. Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes. *J Exp Med*. 1997;185(12):2171–2176.
33. Desreumaux P, Bloget F, Seguy D, et al. Interleukin 3, granulocyte-macrophage colony-stimulating factor, and interleukin 5 in eosinophilic gastroenteritis. *Gastroenterology*. 1996;110(3):768–774.
34. Hogan SP, Mishra A, Brandt EB, Foster PS, Rothenberg ME. A critical role for eotaxin in experimental oral antigen-induced eosinophilic gastrointestinal allergy. *Proc Natl Acad Sci U S A*. 2000;97(12):6681–6686.
35. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol*. 2004;113(1):11–28. quiz 29. DOI:10.1016/j.jaci.2003.10.047
36. Blackshaw AJ, Levison DA. Eosinophilic infiltrates of the gastrointestinal tract. *J Clin Pathol*. 1986;39(1):1–7.
37. Jaffe JS, James SP, Mullins GE, Braun-Elwert L, Lubensky I, Metcalfe DD. Evidence for an abnormal profile of interleukin-4 (IL-4), IL-5, and gamma-interferon (gamma-IFN) in peripheral blood T cells from patients with allergic eosinophilic gastroenteritis. *J Clin Immunol*. 1994;14(5):299–309.
38. Oyaizu N, Uemura Y, Izumi H, Morii S, Nishi M, Hioki K. Eosinophilic gastroenteritis. Immunohistochemical evidence for IgE mast cell-mediated allergy. *Acta Pathol Jpn*. 1985;35(3):759–766.
39. Inamura H, Kashiwase Y, Morioka J, Suzuki K, Igarashi Y, Kurosawa M. Accumulation of mast cells in the interstitium of eosinophilic colitis. *Allergol Immunopathol (Madr)*. 2006;34(5):228–230.
40. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol*. 2006;24:147–174. doi:10.1146/annurev.immunol.24.021605.090720
41. O'Donnell MC, Ackerman SJ, Gleich GJ, Thomas LL. Activation of basophil and mast cell histamine release by eosinophil granule major basic protein. *J Exp Med*. 1983;157:1981–1991.
42. Piliponsky AM, Gleich GJ, Nagler A, Bar I, Levi-Schaffer F. Non-IgE-dependent activation of human lung- and cord blood-derived mast cells is induced by eosinophil major basic protein and modulated by the membrane form of stem cell factor. *Blood*. 2003;101(5):1898–1904. doi:10.1182/blood-2002-05-1488
43. Patella V, de Crescenzo G, Marino I, et al. Eosinophil granule proteins activate human heart mast cells. *J Immunol*. 1996;157(3):1219–1225.
44. Camilleri M, Coulie B, Tack JF. Visceral hypersensitivity: facts, speculations, and challenges. *Gut*. 2001;48(1):125–131.
45. Quigley EM. Disturbances of motility and visceral hypersensitivity in irritable bowel syndrome: biological markers or epiphenomenon. *Gastroenterol Clin North Am*. 2005;34(2):221–233. vi. doi:10.1016/j.gtc.2005.02.010
46. Piliponsky A, Daigle I, Simon H-U, Levi-Schaffer F. Expression and functionally of death receptors on the human mast cell line HMC-1. *J Allergy Clin Immunol*. 2000;105:1. doi:10.1016/S0091-6749(00)90623-7
47. Eutamene H, Theodorou V, Fioramonti J, Bueno L. Acute stress modulates the histamine content of mast cells in the gastrointestinal tract through interleukin-1 and corticotropin-releasing factor release in rats. *J Physiol*. 2003;553(Pt 3):959–966. doi:10.1113/jphysiol.2003.052274
48. Santos J, Guilarte M, Alonso C, Malagelada JR. Pathogenesis of irritable bowel syndrome: the mast cell connection. *Scand J Gastroenterol*. 2005;40(2):129–140. doi:10.1080/00365520410009410
49. Theoharides TC, Cochrane DE. Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J Neuroimmunol*. 2004;146:1–12. doi:10.1016/j.jneuroim.2003.10.041
50. Yousefi S, Gold JA, Andina N, et al. Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. *Nat Med*. 2008;14(9):949–953. doi:10.1038/nm.1855
51. Cello JP. Eosinophilic gastroenteritis—a complex disease entity. *Am J Med*. 1979;67(6):1097–1104. doi:10.1016/0002-9343(79)90652-1
52. Walker MM, Talley NJ. Functional gastrointestinal disorders and the potential role of eosinophils. *Gastroenterol Clin North Am*. 2008;37(2):383–395. vi. doi:10.1016/j.gtc.2008.02.007
53. Pineton de Chambrun G, Gonzalez F, Canva JY, et al. Natural history of eosinophilic gastroenteritis. *Clin Gastroenterol Hepatol*. 2011;9(11):950–956 e951. doi:10.1016/j.cgh.2011.07.017
54. Tien FM, Wu JF, Jeng YM, et al. Clinical features and treatment responses of children with eosinophilic gastroenteritis. *Pediatr Neonatol*. 2011;52(5):272–278. doi:10.1016/j.pedneo.2011.06.006
55. Abou Rached A, El Hajj W. Eosinophilic gastroenteritis: approach to diagnosis and management. *World J Gastrointest Pharmacol Ther*. 2016;7(4):513–523. doi:10.4292/wjgpt.v7.i4.513
56. Urek MC, Kujundzic M, Banic M, Urek R, Veic TS, Kardum D. Leukotriene receptor antagonists as potential steroid sparing agents in a patient with serosal eosinophilic gastroenteritis. *Gut*. 2006;55(9):1363–1364. doi:10.1136/gut.2006.099465
57. Chehade M, Sicherer SH, Magid MS, Rosenberg HK, Morotti RA. Multiple exudative ulcers and pseudopolyps in allergic eosinophilic gastroenteritis that responded to dietary therapy. *J Pediatr Gastroenterol Nutr*. 2007;45(3):354–357. doi:10.1097/MPG.0b013e31803219d5
58. Manatsathit W, Sermasathanasawadi R, Pongpaiboon A, Pongprasobchai S. Mucosal-type eosinophilic gastroenteritis in Thailand: 12-year retrospective study. *J Med Assoc Thai*. 2013;96(Suppl 2):S194–S202.
59. Johnstone JM, Morson BC. Eosinophilic gastroenteritis. *Histopathology*. 1978;2(5):335–348.
60. Katz AJ, Goldman H, Grand RJ. Gastric mucosal biopsy in eosinophilic (allergic) gastroenteritis. *Gastroenterology*. 1977;73(4 Pt 1):705–709.
61. Alnaser S, Aljebreen AM. Endoscopic ultrasound and histopathologic correlates in eosinophilic gastroenteritis. *Saudi J Gastroenterol*. 2007;13(2):91–94. doi:10.4103/1319-3767.32185
62. Marco-Domenech SF, Gil-Sanchez S, Jornet-Fayos J, Ambit-Capdevila S, Gonzalez-Anon M. Eosinophilic gastroenteritis: percutaneous biopsy under ultrasound guidance. *Abdom Imaging*. 1998;23(3):286–288.
63. Horton KM, Corl FM, Fishman EK. CT of nonneoplastic diseases of the small bowel: spectrum of disease. *J Comput Assist Tomogr*. 1999;23(3):417–428.
64. Anuradha C, Mittal R, Yacob M, Manipadam MT, Kurian S, Eapen A. Eosinophilic disorders of the gastrointestinal tract: imaging features. *Diagn Interv Radiol*. 2012;18(2):183–188. doi:10.4261/1305-3825.DIR.4490-11.1
65. Zheng X, Cheng J, Pan K, Yang K, Wang H, Wu E. Eosinophilic enteritis: CT features. *Abdom Imaging*. 2008;33(2):191–195. doi:10.1007/s00261-007-9209-1
66. Lee KJ, Hahn KB, Kim YS, et al. The usefulness of Tc-99m HMPAO labeled WBC SPECT in eosinophilic gastroenteritis. *Clin Nucl Med*. 1997;22(8):536–541.
67. Imai E, Kaminaga T, Kawasugi K, Yokokawa T, Furui S. The usefulness of 99mTc-hexamethylpropyleneamineoxime white blood cell scintigraphy in a patient with eosinophilic gastroenteritis. *Ann Nucl Med*. 2003;17(7):601–603.
68. Lee M, Hodges WG, Huggins TL, Lee EL. Eosinophilic gastroenteritis. *South Med J*. 1996;89(2):189–194. doi:10.1097/00007611-199602000-00006

69. Solis-Herruzo JA, de Cuenca B, Munoz-Yague MT. Laparoscopic findings in serosal eosinophilic gastroenteritis. Report of two cases. *Endoscopy*. 1988;20(4):152–153. doi:10.1055/s-2007-1018162
70. Lowichik A, Weinberg AG. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol*. 1996;9(2):110–114.
71. DeBrosse CW, Case JW, Putnam PE, Collins MH, Rothenberg ME. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol*. 2006;9(3):210–218. doi:10.2350/11-05-0130.1
72. Matsushita T, Maruyama R, Ishikawa N, et al. The number and distribution of eosinophils in the adult human gastrointestinal tract: a study and comparison of racial and environmental factors. *Am J Surg Pathol*. 2015;39(4):521–527. doi:10.1097/PAS.0000000000000370
73. Polydorides AD, Banner BF, Hannaway PJ, Yantiss RK. Evaluation of site-specific and seasonal variation in colonic mucosal eosinophils. *Hum Pathol*. 2008;39(6):832–836. doi:10.1016/j.humphath.2007.10.012
74. Pascal RR, Gramlich TL, Parker KM, Gansler TS. Geographic variations in eosinophil concentration in normal colonic mucosa. *Mod Pathol*. 1997;10(4):363–365.
75. Rothenberg ME, Mishra A, Brandt EB, Hogan SP. Gastrointestinal eosinophils. *Immunol Rev*. 2001;179:139–155.
76. Torpier G, Colombel JF, Mathieu-Chandelier C, et al. Eosinophilic gastroenteritis: ultrastructural evidence for a selective release of eosinophil major basic protein. *Clin Exp Immunol*. 1988;74(3):404–408.
77. Keshavarzian A, Saverymuttu SH, Tai PC, et al. Activated eosinophils in familial eosinophilic gastroenteritis. *Gastroenterology*. 1985;88(4):1041–1049. doi:10.1016/S0016-5085(85)80026-3
78. Ingle SB, Patle YG, Murdeshwar HG, Pujari GP. A case of early eosinophilic gastroenteritis with dramatic response to steroids. *J Crohns Colitis*. 2011;5(1):71–72. doi:10.1016/j.crohns.2010.10.002
79. Kato M, Kephart GM, Talley NJ, et al. Eosinophil infiltration and degranulation in normal human tissue. *Anat Rec*. 1998;252(3):418–425. doi:10.1002/(SICI)1097-0185(199811)252:3<418::AID-AR10>3.0.CO;2-1
80. Macedo T, MacCarty RL. Eosinophilic ileocolitis secondary to *Enterobius vermicularis*: case report. *Abdom Imaging*. 2000;25(5):530–532.
81. Esteve C, Resano A, Diaz-Tejeiro P, Fernandez-Benitez M. Eosinophilic gastritis due to Anisakis: a case report. *Allergol Immunopathol*. 2000;28:21–23.
82. Takeyama Y, Kamimura S, Suzumiya J, et al. Case report: eosinophilic colitis with high antibody titre against *Ascaris suum*. *J Gastroenterol Hepatol*. 1997;12(3):204–206.
83. Hong ST, Lim HS, Kim DH, Kim SJ. A case of gastroenteritis associated with gastric trichuriasis. *J Korean Med Sci*. 2003;18(3):429–432. doi:10.3346/jkms.2003.18.3.429
84. Saba R, Korkmaz M, Inan D, et al. Human fascioliasis. *Clin Microbiol Infect*. 2004;10(5):385–387. doi:10.1111/j.1469-0691.2004.00820.x
85. Zimmerman SL, Levine MS, Rubesin SE, et al. Idiopathic eosinophilic esophagitis in adults: the ringed esophagus. *Radiology*. 2005;236(1):159–165. doi:10.1148/radiol.2361041100
86. Samadi F, Levine MS, Rubesin SE, Katzka DA, Laufer I. Feline esophagus and gastroesophageal reflux. *AJR Am J Roentgenol*. 2010;194(4):972–976. doi:10.2214/AJR.09.3352
87. Di Sabatino A, Corazza GR. Coeliac disease. *Lancet*. 2009;373(9673):1480–1493. doi:10.1016/S0140-6736(09)60254-3
88. Hurrell JM, Genta RM, Melton SD. Histopathologic diagnosis of eosinophilic conditions in the gastrointestinal tract. *Adv Anat Pathol*. 2011;18(5):335–348. doi:10.1097/PAP.0b013e318229bfe2
89. Prussin C. Eosinophilic gastroenteritis and related eosinophilic disorders. *Gastroenterol Clin North Am*. 2014;43(2):317–327. doi:10.1016/j.gtc.2014.02.013
90. Roufosse F, Cogan E, Goldman M. Recent advances in pathogenesis and management of hypereosinophilic syndromes. *Allergy*. 2004;59(7):673–689. doi:10.1111/j.1398-9995.2004.00465.x
91. Matsushita M, Hajiro K, Morita Y, Takakuwa H, Suzuki T. Eosinophilic gastroenteritis involving the entire digestive tract. *Am J Gastroenterol*. 1995;90(10):1868–1870.
92. Friesen CA, Kearns GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. *J Pediatr Gastroenterol Nutr*. 2004;38(3):343–351.
93. Lucendo AJ. Eosinophilic gastroenteropathy. In: Guandalini S, Dhawan A, Branski D, editors. *Textbook of Pediatric Gastroenterology, Hepatology and Nutrition: A Comprehensive Guide to Practice*. Heidelberg: Springer; 2016:307–321.
94. Lucendo AJ, Serrano-Montalban B, Arias A, Redondo O, Tenias JM. Efficacy of dietary treatment for inducing disease remission in eosinophilic gastroenteritis. *J Pediatr Gastroenterol Nutr*. 2015;61(1):56–64. doi:10.1097/MPG.0000000000000766
95. Yamada Y, Toki F, Yamamoto H, Nishi A, Kato M. Proton pump inhibitor treatment decreased duodenal and esophageal eosinophilia in a case of eosinophilic gastroenteritis. *Allergol Int*. 2015;64(Suppl):S83–S85. doi:10.1016/j.alit.2015.06.002
96. Katz AJ, Twarog FJ, Zeiger RS, Falchuk ZM. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol*. 1984;74(1):72–78.
97. Khan S, Orenstein SR. Eosinophilic gastroenteritis masquerading as pyloric stenosis. *Clin Pediatr (Phila)*. 2000;39(1):55–57. doi:10.1177/000992280003900109
98. Busoni VB, Lifschitz C, Christiansen S, GdMT, Orsi M. [Eosinophilic gastroenteropathy: a pediatric series]. *Arch Argent Pediatr*. 2011;109(1):68–73. doi:10.1590/S0325-00752011000100019
99. Ko J, Magid MS, Benkov KJ, Chehade M, Nowak-Wegrzyn A. A 17-month-old boy with periorbital swelling. *Ann Allergy Asthma Immunol*. 2004;93(3):220–226. doi:10.1016/S1081-1206(10)61491-3
100. Turner D, Wolters VM, Russell RK, et al. Anti-TNF, infliximab, and adalimumab can be effective in eosinophilic bowel disease. *J Pediatr Gastroenterol Nutr*. 2013;56(5):492–497. doi:10.1097/MPG.0b013e3182801e60
101. Watanabe T, Fukuie T, Tajima I, Nomura I. [Allergic enterocolitis with protein-losing enteropathy in a 5-month-old girl: a case report]. *Arerugi*. 2013;62(11):1541–1547.
102. Ko HM, Morotti RA, Yershov O, Chehade M. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. *Am J Gastroenterol*. 2014;109(8):1277–1285. doi:10.1038/ajg.2014.166
103. Nelson TH, Klein GL, Galant SP. Severe eosinophilic gastroenteritis successfully treated with an elemental diet (Vivonex). *J Allergy Clin Immunol*. 1979;63:198.
104. Chehade M, Magid MS, Mofidi S, Nowak-Wegrzyn A, Sampson HA, Sicherer SH. Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up. *J Pediatr Gastroenterol Nutr*. 2006;42(5):516–521. doi:10.1097/01.mpg.0000221903.61157.4e
105. Gonsalves N, Doerfler B, Yang GY, Hirano. A prospective clinical trial of six food elimination diet or elemental diet in the treatment of adults with eosinophilic gastroenteritis. *Gastroenterology*. 2009;136(5):A–280. doi:10.1016/S0016-5085(09)61276-2
106. CEGIR 7809: effect of elemental diet on adult patients with eosinophilic gastroenteritis. <https://www.clinicaltrials.gov/ct2/show/NCT03320369?recrs=abdf&cond=Eosinophilic+Gastritis&draw=2&rank=35>. Accessed May 14, 2019.
107. Rothenberg ME. Eosinophilia. *N Engl J Med*. 1998;338(22):1592–1600. doi:10.1056/NEJM199805283382206
108. Barnes PJ, Adcock IM. Steroid resistance in asthma. *QJM*. 1995;88(7):455–468.

109. Khan S. Eosinophilic gastroenteritis. *Best Pract Res Clin Gastroenterol.* 2005;19(2):177–198. doi:10.1016/j.bpg.2005.01.009
110. Oh HE, Chetty R. Eosinophilic gastroenteritis: a review. *J Gastroenterol.* 2008;43(10):741–750. doi:10.1007/s00535-008-2230-5
111. Zhang L, Duan L, Ding S, et al. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics, a retrospective study of 42 patients. *Scand J Gastroenterol.* 2011;46(9):1074–1080. doi:10.3109/00365521.2011.579998
112. Lombardi C, Salmi A, Passalacqua G. An adult case of eosinophilic pyloric stenosis maintained on remission with oral budesonide. *Eur Ann Allergy Clin Immunol.* 2011;43(1):29–30.
113. Stone KD, Prussin C. Immunomodulatory therapy of eosinophil-associated gastrointestinal diseases. *Clin Exp Allergy.* 2008;38(12):1858–1865. doi:10.1111/j.1365-2222.2008.03122.x
114. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol.* 2007;102(10):2271–2279. quiz 2280. DOI:10.1111/j.1572-0241.2007.01379.x
115. Tan AC, Kruijmel JW, Naber TH. Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets. *Eur J Gastroenterol Hepatol.* 2001;13(4):425–427.
116. Müller M, Keller K, Stallmann S, Eckardt AJ. Clinicopathologic findings in eosinophilic gastroenteritis: a German case series. *J Genet Syndr Gene Ther.* 2014;5:1. doi:10.4172/2157-7412.1000230
117. Lombardi C, Salmi A, Savio A, Passalacqua G. Localized eosinophilic ileitis with mastocytosis successfully treated with oral budesonide. *Allergy.* 2007;62(11):1343–1345. doi:10.1111/j.1398-9995.2007.01461.x
118. Shahzad G, Moise D, Lipka S, Rizvon K, Mustacchia PJ. Eosinophilic enterocolitis diagnosed by means of upper endoscopy and colonoscopy with random biopsies treated with budesonide: a case report and review of the literature. *ISRN Gastroenterol.* 2011;2011:608901. doi:10.5402/2011/608901
119. Russel MG, Zeijen RN, Brummer RJ, de Bruine AP, van Kroonenburgh MJ, Stockbrugger RW. Eosinophilic enterocolitis diagnosed by means of technetium-99m albumin scintigraphy and treated with budesonide (CIR). *Gut.* 1994;35(10):1490–1492.
120. Siewert E, Lammert F, Koppitz P, Schmidt T, Matern S. Eosinophilic gastroenteritis with severe protein-losing enteropathy: successful treatment with budesonide. *Dig Liver Dis.* 2006;38(1):55–59. doi:10.1016/j.dld.2005.06.013
121. Neustrom MR, Friesen C. Treatment of eosinophilic gastroenteritis with montelukast. *J Allergy Clin Immunol.* 1999;104(2 Pt 1):506. doi:10.1016/S0091-6749(99)70404-5
122. Schwartz DA, Pardi DS, Murray JA. Use of montelukast as steroid-sparing agent for recurrent eosinophilic gastroenteritis. *Dig Dis Sci.* 2001;46(8):1787–1790.
123. Vanderhoof JA, Young RJ, Hanner TL, Kettlehut B. Montelukast: use in pediatric patients with eosinophilic gastrointestinal disease. *J Pediatr Gastroenterol Nutr.* 2003;36(2):293–294. doi:10.1097/00005176-200302000-00027
124. Lu E, Ballas ZK. Immuno-modulation in the treatment of eosinophilic gastroenteritis. *J Allergy Clin Immunol.* 2003;111:S262. doi:10.1016/S0091-6749(03)80936-3
125. Daikh BE, Ryan CK, Schwartz RH. Montelukast reduces peripheral blood eosinophilia but not tissue eosinophilia or symptoms in a patient with eosinophilic gastroenteritis and esophageal stricture. *Ann Allergy Asthma Immunol.* 2003;90(1):23–27. doi:10.1016/S1081-1206(10)63609-5
126. Moots RJ, Prouse P, Gumpel JM. Near fatal eosinophilic gastroenteritis responding to oral sodium cromoglycate. *Gut.* 1988;29(9):1282–1285.
127. Di Gioacchino M, Pizzicannella G, Fini N, et al. Sodium cromoglycate in the treatment of eosinophilic gastroenteritis. *Allergy.* 1990;45(3):161–166.
128. Beishuizen A, van Bodegraven AA, Bronsveld W, Sindram JW. Eosinophilic gastroenteritis—a disease with a wide clinical spectrum. *Neth J Med.* 1993;42(5–6):212–217.
129. Van Dellen RG, Lewis JC. Oral administration of cromolyn in a patient with protein-losing enteropathy, food allergy, and eosinophilic gastroenteritis. *Mayo Clin Proc.* 1994;69(5):441–444.
130. Perez-Millan A, Martin-Lorente JL, Lopez-Morante A, Yuguero L, Saez-Royuela F. Suberosal eosinophilic gastroenteritis treated efficaciously with sodium cromoglycate. *Dig Dis Sci.* 1997;42(2):342–344.
131. Suzuki J, Kawasaki Y, Nozawa R, et al. Oral disodium cromoglycate and ketotifen for a patient with eosinophilic gastroenteritis, food allergy and protein-losing enteropathy. *Asian Pac J Allergy Immunol.* 2003;21(3):193–197.
132. Sheikh RA, Prindiville TP, Pecha RE, Ruebner BH. Unusual presentations of eosinophilic gastroenteritis: case series and review of literature. *World J Gastroenterol.* 2009;15(17):2156–2161.
133. Kakiuchi M, Ohashi T, Musoh K, Kawamura K, Morikawa K, Kato H. Studies on the novel antiallergic agent HSR-609: its penetration into the central nervous system in mice and guinea pigs and its selectivity for the histamine H1-receptor. *Jpn J Pharmacol.* 1997;73(4):291–298.
134. Lemke TL, Williams DA. *Foye's Principles of Medicinal Chemistry*. Philadelphia: Lippincott Williams & Wilkins; 2008.
135. Melamed I, Feanny SJ, Sherman PM, Roifman CM. Benefit of ketotifen in patients with eosinophilic gastroenteritis. *Am J Med.* 1991;90(3):310–314.
136. Bolukbas FF, Bolukbas C, Uzunkoy A, Baba F, Horoz M, Ozturk E. A dramatic response to ketotifen in a case of eosinophilic gastroenteritis mimicking abdominal emergency. *Dig Dis Sci.* 2004;49(11–12):1782–1785.
137. Freeman HJ. Longstanding eosinophilic gastroenteritis of more than 20 years. *Can J Gastroenterol.* 2009;23(9):632–634.
138. Netzer P, Gschossmann JM, Straumann A, Sendensky A, Weimann R, Schoepfer AM. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol.* 2007;19(10):865–869. doi:10.1097/MEG.0b013e32825a6ab4
139. Redondo-Cerezo E, Cabello MJ, Gonzalez Y, Gomez M, Garcia-Montero M, de Teresa J. Eosinophilic gastroenteritis: our recent experience: one-year experience of atypical onset of an uncommon disease. *Scand J Gastroenterol.* 2001;36(12):1358–1360.
140. Simon D, Braathen LR, Simon HU. Anti-interleukin-5 antibody therapy in eosinophilic diseases. *Pathobiology.* 2005;72(6):287–292. doi:10.1159/000091326
141. Prussin C, James SP, Huber MM, Klion AD, Metcalfe DD. Pilot study of anti-IL-5 in eosinophilic gastroenteritis. *J Allergy Clin Immunol.* 2003;111(2):S275.
142. Kim YJ, Prussin C, Martin B, et al. Rebound eosinophilia after treatment of hypereosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700. *J Allergy Clin Immunol.* 2004;114(6):1449–1455. doi:10.1016/j.jaci.2004.08.027
143. Holgate S, Casale T, Wenzel S, Bosquel J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol.* 2005;115:459–465. doi:10.1016/j.jaci.2004.11.053
144. Noga O, Hanf G, Kunkel G. Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. *Int Arch Allergy Immunol.* 2003;131(1):46–52. doi:10.1159/000070434
145. Djukanovic R, Wilson SJ, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med.* 2004;170(6):583–593. doi:10.1164/rccm.200312-1651OC
146. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεR1 expression and function. *J Allergy Clin Immunol.* 2004;114(3):527–530. doi:10.1016/j.jaci.2004.06.032

147. Foroughi S, Foster B, Kim N, et al. Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J Allergy Clin Immunol.* **2007**;120(3):594–601. doi:10.1016/j.jaci.2007.06.015
148. Yamaya H, Basaki Y, Togawa M, Kojima M, Kiniwa M, Matsuura N. Down-regulation of Th2 cell-mediated murine peritoneal eosinophilia by antiallergic agents. *Life Sci.* **1995**;56(19):1647–1654.
149. Zhao GD, Yokoyama A, Kohno N, Sakai K, Hamada H, Hiwada K. Effect of suplatast tosilate (IPD-1151T) on a mouse model of asthma: inhibition of eosinophilic inflammation and bronchial hyperresponsiveness. *Int Arch Allergy Immunol.* **2000**;121(2):116–122. doi:10.1159/000024306
150. Shirai T, Hashimoto D, Suzuki K, et al. Successful treatment of eosinophilic gastroenteritis with suplatast tosilate. *J Allergy Clin Immunol.* **2001**;107(5):924–925.
151. Krishnaswamy G, Smith JK, Srikanth S, Chi DS, Kalbfleisch JH, Huang SK. Lymphoblastoid interferon-alpha inhibits T cell proliferation and expression of eosinophil-activating cytokines. *J Interferon Cytokine Res.* **1996**;16(10):819–827. doi:10.1089/jir.1996.16.819
152. Essayan DM, Krishnaswamy G, Oriente A, Lichtenstein LM, Huang SK. Differential regulation of antigen-induced IL-4 and IL-13 generation from T lymphocytes by IFN-alpha. *J Allergy Clin Immunol.* **1999**;103(3 Pt 1):451–457.
153. Dai YX, Shi CB, Cui BT, Wang M, Ji GZ, Zhang FM. Fecal microbiota transplantation and prednisone for severe eosinophilic gastroenteritis. *World J Gastroenterol.* **2014**;20(43):16368–16371. doi:10.3748/wjg.v20.i43.16368
154. Naylor AR. Eosinophilic gastroenteritis. *Scott Med J.* **1990**;35(6):163–165. doi:10.1177/003693309003500601
155. Al-Herz W, Mehta D, McGeady S. Eosinophilic gastroenteritis in children and adolescents. *J Allergy Clin Immunol.* **2001**;107:S193.
156. Dobbins JW, Sheahan DG, Behar J. Eosinophilic gastroenteritis with esophageal involvement. *Gastroenterology.* **1977**;72(6):1312–1316.
157. Rothenberg ME, Mishra A, Brandt EB, Hogan SP. Gastrointestinal eosinophils in health and disease. *Adv Immunol.* **2001**;78:291–328.
158. Legrand F, Klion AD. Biologic therapies targeting eosinophils: current status and future prospects. *J Allergy Clin Immunol Pract.* **2015**;3(2):167–174. doi:10.1016/j.jaip.2015.01.013

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