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# Eosinophilic gastroenteritis: Pathogenesis, diagnosis, and treatment

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**Abstract**

Eosinophilic gastroenteritis (EGE) is a gastrointestinal disorder of unclear etiology that is characterized by eosinophilic infiltration of the stomach and small intestine, and consists of mucosal, muscular, and serosal subtypes. Eosinophilic infiltration of the gastrointestinal tract is a fundamental histopathological characteristic of EGE and is driven by several T-helper type 2 (Th2)-dependent cytokines and induced by food allergy. Due to the lack of a diagnostic gold standard, EGE has a high rate of delayed diagnosis or misdiagnosis. However, several new diagnostic strategies have been developed, such as novel genetic biomarkers and imaging tests. Although dietary therapy and corticosteroids remain the common choices for EGE treatment, recent decades have seen the emergence of novel treatment alternatives, such as biologics that target particular molecules involved in the pathogenic process. Preliminary investigations and clinical trials have demonstrated the efficacy of biologics and provided additional insights for the era of refractory or corticosteroid-dependent EGE biologics.

**Keywords:** Eosinophilic gastroenteritis; Pathogenesis; Diagnosis; Treatment

## Introduction

Eosinophilic gastrointestinal disorders (EGIDs) are a spectrum of rare and heterogeneous diseases that are characterized by the eosinophilic infiltration of the digestive tract and have been classified into eosinophilic esophagitis (EoE), eosinophilic gastritis, eosinophilic enteritis, and eosinophilic colitis, depending on the location of eosinophilic infiltration. Eosinophilic gastroenteritis (EGE) is a broadly defined disease that most commonly affects the stomach and/or small intestine.[1] Klein *et al*[2] classified EGE as mucosal, muscular, and serosal layer diseases depending on the depth of eosinophilic infiltration. This review systemically outlines our current knowledge of EGE, with special attention to its pathogenesis, potential diagnostic tests, and novel medications.

## Epidemiology and Etiology

Although EGE is ideally considered a rare disease, its incidence and prevalence are increasing. The exact prevalence of EGE is unknown due to variable reports from different studies and countries. For example, Spergel *et al*[3] performed a large survey in 2011 and suggested that the estimated prevalence of EGE in the United States of America (USA) was 28/100,000, with variable distribution across the different regions. Recent population-based studies in the USA have revealed that the overall prevalence of EGE is 5.1–8.4/100,000 persons.[4,5] Differences in study design, data collection, and selection bias might have contributed to the variability. The lack of golden diagnostic criteria and high risk of misdiagnosis are the main reasons that disease incidence and prevalence remain undetermined.

EGE can occur at any age (from infancy to adulthood), but has a peak onset between the third and fifth decades of life. Females are predisposed to EGE compared to males.[4] Ito *et al*[6] revealed the racial differences in the prevalence of EoE and EGE that Caucasian is dominant among EoE, while Asian is dominant among EGE. These differences probably due to the diversity in *Helicobacter pylori* infection, dietary habits, and other genetic and environment factors.

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To depict the prevalence more accurately, Licari *et al*[7] showed an overall prevalence among patients referred to clinics with gastrointestinal symptoms in non-EoE EGIDs to be 1.9%, which is higher than that of inflammatory bowel disease (IBD), indicating an increasingly important role of EGE in clinical practice.

Genetic and environmental factors are considered predisposing factors for EGE. Zadeh-Esmaeel *et al*[8] identified seven central genes (*TXN*, *PRDX2*, *NR3C1*, *GRB2*, *PIK3C3*, *AP2B1*, and *REPS1*) that were highly expressed in the gastric antrum of patients with EGE and which could be considered potential biomarkers. In 2020, Shoda *et al*[9] built a gastric tissue- and blood-diagnostic platform called EDGP18 by using 18 specific dysregulated genes and uncovered the robust association between these genes and histologic and endoscopic findings in patients with eosinophilic gastritis. Among the 18 genes, eight genes associated with cytokines/chemokines, eosinophilia, cell adhesion, antimicrobial defense, and the epithelium were upregulated, whereas 10 genes that were associated with antimicrobial defense, fibrosis, ion transport, neurosensory activity, and stomach-related processes were downregulated.

Bacterial infections and hygiene status may contribute to the etiology of EGE. Furuta *et al*[10] illustrated that the decreased rate of *H. pylori* infection may contribute to increased susceptibility to EGID. Individuals who are not exposed to bacterial infections during childhood may maintain the ability to mount T-helper type 2 (Th2)-dominant immune responses even in adulthood and, therefore, be at a greater risk of developing various types of allergies. EoE and EGE have a shared etiology. Dellon *et al*[11] reported that *H. pylori* infection was inversely associated with EoE. Familial clustering of EoE has been reported in Western countries, indicating the potential role of environmental factors. Allergic conditions are relatively common in patients with EGE. A study from the USA National Administrative Database showed that 45.6% of patients with EGE had allergic symptoms, such as rhinitis and asthma, which is significantly higher than that in the source population.[5]

How are these etiological factors driving EGE? This may be explained by the previously well-described and new pieces of evidence about the pathogenesis of EGE.

## Pathogenesis

Abnormally increased eosinophil infiltration in the stomach and bowel is a key histopathological characteristic of EGE. Eosinophils are tissue-dwelling cells that populate in the lamina propria of the gastrointestinal tract and which normally increase in numbers toward the distal segments of the gastrointestinal tract, with none in the esophagus and most in the cecum and appendix.[12] Consequently, it is easier to diagnose EoE than EGE. Eosinophil accumulation during inflammatory responses involves their maturation and release from the bone marrow (in approximately 8 days), adhesion, and transmigration from the post-capillary endothelium into peripheral circulation, followed by chemotaxis and activation in tissues.[13] Many cytokines and chemokines have been shown to mediate this process, most of which are associated with Th2-mediated immune responses. For example, interleukin-3 (IL-3), IL-5, and granulocyte–macrophage colony-stimulating factor (GM-CSF) modulate eosinophil production in the bone marrow, whereas IL-5 is involved in the expansion and release of eosinophils. The migration of eosinophils toward tissues is initiated by local chemoattractant molecules that are responsible for both physiological homing and recruitment to inflammatory loci. Some of the most crucial molecules belong to the eotaxin family, among which eotaxin-1 plays a key role in EGE and eotaxin-3 in EoE.[14] Here, it should be noted that there is a balance between IL-5 and the eotaxin family. Hogan and Rothenberg[15] proposed a new model to explain the dichotomy between peripheral blood and tissue eosinophilia, and claimed that eosinophils aggregate in tissues when the eotaxin-1 level is higher than the IL-5 level, whereas they accumulate in blood when the IL-5 level is higher than the eotaxin-1 level.

Upon recruitment to targeted loci, eosinophils are activated and undergo degranulation to release four major cationic proteins, namely, eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and major basic protein (MBP). MBP, EPO, EDN, and ECP have cytotoxic effects on the epithelium. The toxic hydrogen peroxide and halide acids generated by EPO can cause further injury to gastrointestinal tissue. Eosinophils can secrete other mediators, such as leukotrienes, which increase vascular permeability and promote mucus secretion; interleukins (IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, etc.), which enhance inflammatory responses; and transforming growth factor beta (TGF-β), which facilitates epithelium growth, tissue remodeling, and fibrosis. Prussin *et al*[16] divided Th2 cells into two subpopulations based on IL-5 expression: IL-5$^+$Th2 cells that correlate with allergic EGE and IL-5$^-$Th2 cells that correlate with peanut allergy. The presence of IL-5$^+$Th2 cells was linked to peripheral blood eosinophilia. Interestingly, the authors also showed that some patients with EGE displayed non-atopic-like responses, instead of Th2 responses to food, implying the existence of another T-cell-independent pathogenesis for EGE. Other Th2 cytokines, such as IL-4 and IL-13, are also involved in the pathogenetic process. IL-4 plays a dominant role in the differentiation of Th2 cells, whereas IL-4 and IL-13 are essential for immunoglobulin E (IgE) class switching and expression.[17] IL-13 can upregulate eotaxin-3 and vascular cell adhesion molecules (VCAM), thereby potentiating allergic inflammation.[17]

Other possible mediators of this process have also been identified. In 2016, using microarray, Sobh *et al*[18] first described a simultaneous increase in thymic stromal lymphopoietin (TSLP) and IL-33 in infants with EGE, which are key cytokines in allergic disorders. Produced mainly by epithelial cells and expressed in the skin, lungs, thymus, and intestinal mucosa, TSLP has two known isoforms, namely, long and short TSLP.[19] Short TSLP is the main isoform, which is expressed under steady state and has anti-inflammatory and antimicro-

bial properties. Long TSLP can activate mast cells, dendritic cells, and T cells by binding to the TSLP receptor (TSLPR), and has pro-inflammatory functions. In 2020, Guo *et al*[20] noted that the mRNA expression of long TSLP showed a significant and positive correlation with peak eosinophilic counts in the gastrointestinal mucosa of patients with EGE. Conversely, short TSLP showed a negative correlation. Sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) is an inhibitory receptor that is mainly expressed on the surface of mature eosinophils and mast cells. It has been demonstrated that Siglec-8 induces eosinophilic cell death *in vitro* when crossed-linked with anti-Siglec-8 mAbs.[21]

The schematic diagram showing the pathogenesis and potential targets of EGE was shown in Figure 1.

Together, these findings imply that EGE is generally accepted as a Th2-mediated allergic reaction. Based on the role of IgE, food allergic disorders can be classified as IgE-mediated, cell-mediated, and mixed IgE- and cell-mediated.[22] EGE follows a mixed mechanism, although the role of IgE in EGE is still unclear.

In addition to eosinophils, it was shown that mast cells also undergo an activation and degranulation process. The mast cells in tissues from patients with EGID displayed increased levels of cell surface markers associated with degranulation, such as CD107a and CD63.[23] Furthermore, this degranulation process can be induced by eosinophils releasing soluble mediators.

Findings associated with EoE might provide additional insights into the pathogenesis of EGE. Both the esophageal deposition of IgG4 and IgG4 sensitization to food have been observed in EoE, suggesting that EoE may be an IgG4-associated disease.[24] Similarly, IgG4 deposition has been observed in the stomach and small intestine of patients with EGE, where eosinophils infiltrate.[25] Besides, TGF-β has been found to play a role in long-term remodeling and fibrosis development in EoE. Further studies are required to understand the exact roles of IgG4 and TGF-β in EGE.

Overall, the pathogenesis of EGE is complex and still not fully understood. Many risk factors can lead to eosinophil infiltration and cause symptoms associated with the disease; however, a bulk of cells and cytokines are suggested to act mutually to mediate disease. Understanding the pathogenesis, especially acknowledging the role of cytokines and other molecules, may provide many potential therapeutic targets.

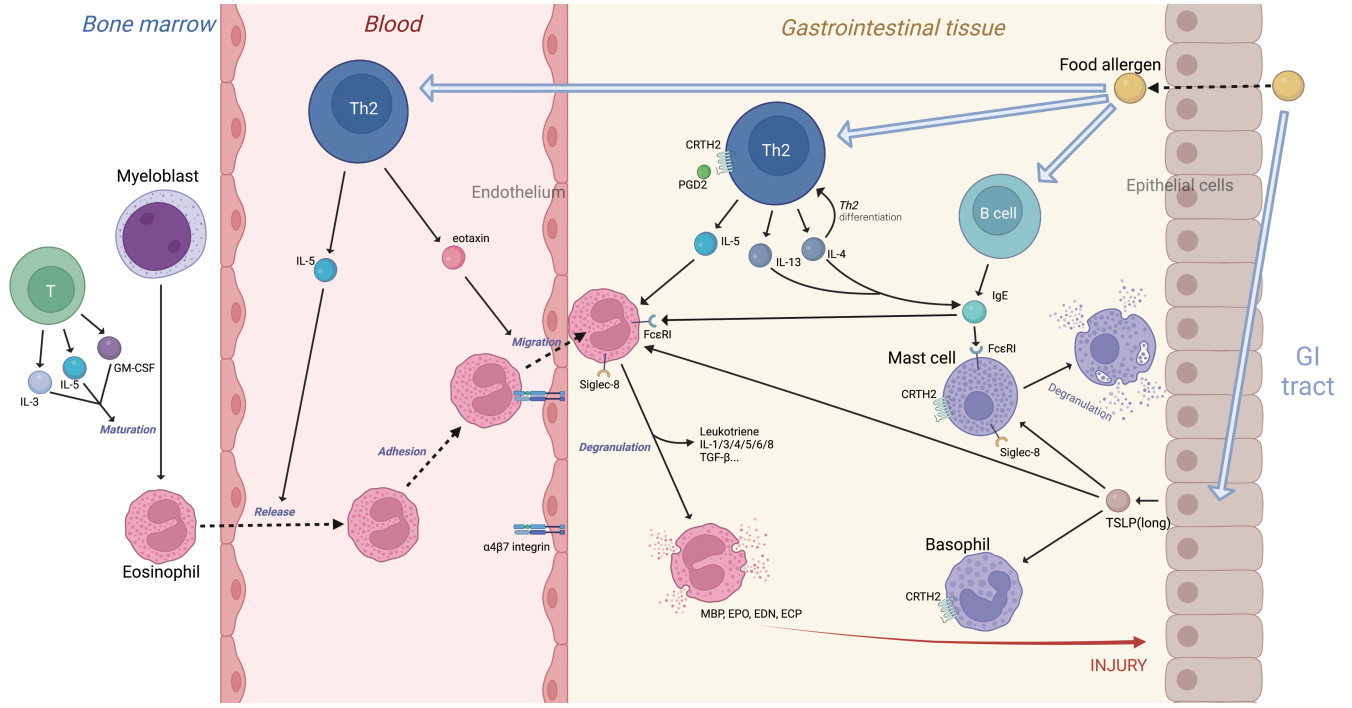


**Figure 1:** A schematic diagram showing the pathogenesis and potential targets of EGE. Exposure to food allergens in the gastrointestinal tract activates T and B cells in blood and tissue. Th2-mediated cytokines (IL-4, IL-5, IL-13, etc.) play important roles in the release, migration, and degranulation of eosinophils. In the bone marrow compartment, IL-3, IL-5, and GM-CSF stimulate the maturation of eosinophils. Further, IL-5 regulates the release of eosinophils from the bone marrow, while eotaxin promotes chemotaxis and migration toward tissue. After being recruited in the gut, eosinophils undergo a degranulation process, releasing four major cationic proteins (MBP, EPO, EDN, and ECP) that are cytotoxic to the epithelium and secrete cytokines that enhance the inflammatory responses. Activated B cells produce IgE, which binds to the FcεRI receptor on eosinophils and mast cells, inducing mast cell degranulation. Recently, it has been found that epithelial cells can secrete TSLP, the long isoform of which has pro-inflammatory functions. CRTH2 locates to the surface of eosinophils, mast cells, and basophils and mediates chemotaxis. Siglec-8 is an inhibitory receptor expressed on the surface of eosinophils and mast cells. Binding of Siglec-8 by its antibody can regulate cell death *in vitro*. CRTH2: Chemoattractant receptor expressed on Th2 cells; ECP: Eosinophil cationic protein; EDN: Eosinophil-derived neurotoxin; EGE: Eosinophilic gastroenteritis; EPO: Eosinophil peroxidase; FcεRIFc: Fc epsilon receptor I; GI tract: Gastrointestinal tract; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IgE: Immunoglobulin E; IL: Interleukin; MBP: Major basic protein; PGD2: Prostaglandin D2; Siglec: Sialic acid-binding immunoglobin-like lectin; TGF-β: Transforming growth factor beta; Th2: T-helper type 2; TSLP: Thymic stromal lymphopoietin.

## Clinical Manifestations

The clinical symptoms of EGE depend on the location and depth of the eosinophilic infiltration. The mucosal subtype is predominant in all three Klein classifications, partly due to the convenience of obtaining evidence for eosinophilic infiltration in the mucosa. Patients usually present with abdominal pain, vomiting, early satiety, bloating, diarrhea, and gastrointestinal bleeding.[1] Malabsorption and protein-losing enteropathy may occur in severe cases. The muscular subtype is characterized by eosinophil infiltration in the muscular layer, which results in wall thickening and impaired intestinal motility, and causes obstruction symptoms, such as nausea, vomiting, and abdominal distention. Perforation, intussusception, small bowel diverticulosis, and volvulus may also occur infrequently. The serosal subtype is the least reported form of EGE, presenting with eosinophilic abdominal ascites along with symptoms more characteristic of the mucosal and muscular type.[2] Patients may also have peritonitis and eosinophilic pleural effusions. Beyond the three subtypes, few patients have transmural eosinophilic infiltration and are categorized into the mixed subtype.

In addition, patients with EGE may present extraintestinal manifestations. More than 50% of the EGE patients have co-existing atopic diseases, such as asthma, defined food sensitivities, eczema, or rhinitis.[26] Eosinophilic infiltration may also affect the ampulla and peri-ampulla duodenum causing edema, fibrosis, and deformation, resulting in pancreatic duct obstruction and acute pancreatitis.[27] The spleen is the major site for eosinophil disposal. Di Sabatino *et al*[28] showed that 85% of the participants had splenic hypofunction, as indicated by the pitted red cells. Besides, eosinophilic cystitis and urinary bladder dysfunction were reported in several case reports.[29,30]

## Diagnosis and Disease Evaluation

In 1990, Talley *et al*[31][31] proposed the following diagnostic criteria: (1) the presence of gastrointestinal symptoms, (2) biopsies showing eosinophil infiltration in one or more areas of the gastrointestinal tract from the esophagus to the colon and characteristic radiologic findings with peripheral eosinophilia, and (3) no evidence of parasitic or extraintestinal disease. The diagnosis of EGE is often delayed and presumably missed altogether. A population-based study in the USA found that patients with EGE lost an average of 3.6 years between presentation of the initial symptom and diagnosis.[32] A workshop hosted by the Food and Drug Administration (FDA) in 2021 indicated a prolonged delay of 4–9 years.[1] Delay in referral and the endoscopy procedure, and the absence of biopsy and/or histopathology may be a few reasons underlying the delayed diagnosis.[32] To date, there is no gold standard for EGE diagnosis.

As shown in Figure 2, a diagnostic flowchart of EGE was suggested. Collecting patients' medical history is the first and most important measure. It is important to focus on the history of atopic diseases, such as bronchial asthma, allergic rhinitis, atopic dermatitis, and IgE-mediated food allergy.

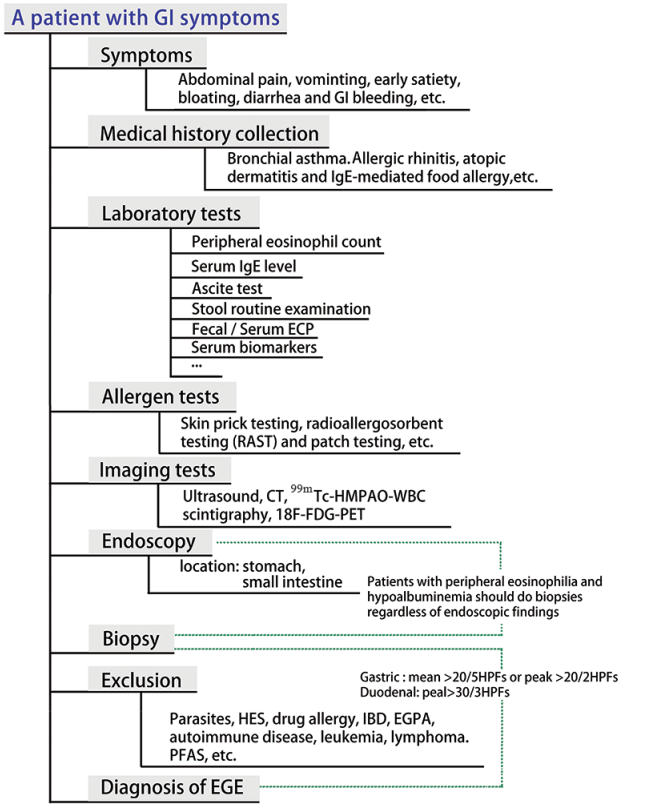


**Figure 2:** Diagnostic flowchart of EGE. 18F-FDG: $^{18}$F-fluorodeoxyglucose; $^{99m}$Tc-HMPAO: $^{99m}$Tc-hexamethylpropyleneamineoxime; CT: Computed tomography; ECP: Eosinophil cationic protein; EGE: Eosinophilic gastroenteritis; HES: Hypereosinophilic syndrome; EGPA: Eosinophilic granulomatous vasculitis; GI: Gastrointestinal; HPFs: High-power fields; IBD: Inflammatory bowel disease; IgE: Immunoglobulin E; PFAS: Pollen-food allergy syndrome; RAST: Radioallergosorbent testing.

## Laboratory findings

Non-invasive blood tests with high sensitivity and specificity are promising diagnostic alternatives. Peripheral blood eosinophilia is observed in >80% of patients with EGE. Absolute eosinophil count (AEC) has been used to categorize the disease as mild (600–1500 eosinophils/μL), moderate (1500–5000 eosinophils/μL), and severe (>5000 eosinophils/μL).[33] A decrease in the serum albumin level and an increase in the α1-antitrypsin level in 24-h feces samples indicate loss of proteins. Fecal examination also helps exclude the diagnosis of parasitic infections. In case of serosal EGE, ascitic eosinophil counts may also contribute to the disease diagnosis.

IL-5, IL-13, IL-33, eotaxin-3, and TSLP are known to have essential functions in the pathogenesis of EGE, but their serum levels are below the limit of detection. This may be attributed to the patchy and limited distribution of lesions in the gastrointestinal tract.[34] As mentioned earlier, Shoda *et al*[9] established a molecular diagnostic criterion for EGE (called the EGDP18 score) using the

gastric mRNA transcript and circulating protein levels and proved it to be a sufficient way for diagnosing EGE, with a sensitivity of 88–95% and a specificity of 100%. They also proved that the combined levels of plasma eotaxin-3, thymus and activation regulated chemokine (TARC), and IL-5 render the capacity to monitor EGE activity with high sensitivity and specificity (100% and 72%, respectively).[9]

Evaluation of atopy may help in understanding its etiology. Total serum IgE levels, skin prick testing, radioallergosorbent testing (RAST), and patch testing are commonly used to detect specific food and environmental allergens.

Imaging tests such as ultrasound and computed tomography (CT) help evaluate the involvement of the gastrointestinal tract and categorize EGE, although its diagnostic value is limited. Ultrasound can reveal the thickening of intestinal walls, ascites, and peritoneal nodules and could be one of the best measures for follow-up monitoring. CT shows ascites, thickened intestinal walls, occasionally localized lymphadenopathy, and signs of complications such as intussusception and perforation. $^{99m}$Tc-hexamethylpropyleneamineoxime ($^{99m}$Tc-HMPAO)-WBC scintigraphy has been shown to be a useful tool for detecting active eosinophilic infiltration. In 2011, Harris *et al*[35] provided evidence that the $^{18}$F-fluorodeoxyglucose (18F-FDG) uptake rate (Ki), as measured by positron emission tomography (PET), could precisely predict the degree of eosinophil-mediated inflammatory response in the lungs of patients with asthma. Importantly, this may be a potential approach to assess EGE as well.

Endoscopy and biopsies play key roles in the initial diagnosis of the disease. Fujiwara *et al*[36] demonstrated the associated endoscopic findings in a 287-patient cohort, among which erythema was most frequently observed (72%), followed by ulcers (39%), discolorations (33%), erosion (28%), nodules (28%), and polyps (28%). There were also several unique and rare observations, such as submucosal tumor-like deep large ulcers, antral *Penthorum*-like appearances, "muskmelon-like appearances," multiple white granular elevations, cracks, and antral rings.[36]

In several large prospective studies, normal endoscopic appearance was the most common finding, with the ratio ranging from 60% to 90%.[37,38] Therefore, biopsies are needed. A large retrospective study by Brenner *et al*[39] showed that the diagnostic rate of biopsy in EGE is low but substantially increases when combining with peripheral eosinophilia and hypoalbuminemia. Given its ability to affect different regions of the gastrointestinal tract and patchy distribution, full-range biopsies should be taken, regardless of where macroscopic lesions lie. The sampling loci should be considered when determining if a sample is normal as the number of eosinophils increases as one moves from the esophagus to the terminal ileum and cecum, and decreases from the terminal ileum and cecum to the rectum. Reed *et al*[40] studied 92 gastric and 94 duodenal biopsy specimens and identified the threshold for eosinophils to distinguish EGE patients with high specificity. A mean gastric count >20 in five high-power fields (HPFs) or a peak count of >20 in two HPFs provided a specificity of 100%, while a peak duodenal eosinophil count >30 in three HPFs provided a specificity of 94%.

Current histological diagnostic methods for EGE are time-consuming, and hematoxylin and eosin (H&E) staining usually only detects intact eosinophils and cannot fully capture the extent of eosinophil degranulation. Hasan *et al*[41] proposed a novel semi-automated detection method for assessing EPO staining: digital pixel quantification of EPO staining (EPO/mm$^2$) and proved it to be markedly elevated in biopsies that exceeded histologic thresholds for eosinophilic gastritis and/or eosinophilic duodenitis (EG/EoD). This also overcomes the inefficiencies of manual counting. Other degranulation products (EDN, MBP, and ECP) were not chosen because only EPO is eosinophil-specific.

## Differential Diagnosis

Other disorders that present with gastrointestinal symptoms and eosinophilia should be differentiated from EGE through careful examination. Diseases that require consideration include EoE, infection, hypereosinophilic syndrome (HES), drug allergy, IBD, autoimmune diseases, and malignant tumors.[42]

Intestinal parasites play a predominant role in infections that result in peripheral eosinophilia; thus, travel history should be provided, and stools should be evaluated for ova and parasites.

HES shows increased peripheral eosinophils (>1.5 × 10$^9$/L) for at least 6 months with tissue damage present. Multiple organ systems are involved in HES (e.g., heart, lungs, brain, and kidneys). Klion *et al*[43] introduced a classification system for HES and identified a category called "overlap HES," referring to eosinophilia restricted to a single organ or organ system, such as eosinophilic pneumonia and EGE. HES and EGE have clinical similarities, making them hard to distinguish, and in some circumstances, multi-system HES can present with isolated gastrointestinal involvement. Consequently, systematic evaluation of eosinophilia would be important for EGE diagnosis, in case other organ systems are involved.

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg–Strauss syndrome) is often misdiagnosed as EGE as vasculitis is often not seen in biopsies specimens.[44]

## Treatment

To date, there is no definitive consensus on the best treatment for EGE. Treatment is primarily empirical. Thus far, several therapeutic options have been suggested and proven to be efficient, such as dietary intervention, corticosteroids, mast cell stabilizers (cromolyn sodium, etc.), leukotriene receptor antagonists (montelukast, etc.), immunomodulators, biologics, and surgery.

### Diet therapy

EGE is strongly associated with food allergens. Diet therapy is often used as the initial treatment, but the recurrence rate is high. Patients are suggested to take rather a targeted/empirical elimination diet or an elemental diet.

An empirical diet called the "6-FED" excludes the six most common food allergens, namely, milk, soy, eggs, wheat, peanuts/tree nuts, and shellfish/fish. If 6-FED works, the number of foods that need to be eliminated and re-introduced later can be largely reduced.[46] Molina-Infante *et al*[47] used a step-up approach (two to four foods first and then four to six foods), which enabled early identification of a majority of responders with fewer food triggers and thus facilitated re-introduction. An elemental diet aims to avoid all protein antigen exposure because it utilizes a nutritionally complete amino acid-based formula that is free of any intact or hydrolyzed proteins.

Once remission is achieved, the optimal way to advance from FED and re-introduce a normal diet remains unclear. Food re-introduction can minimize unnecessary nutritional deficiencies and improve a patient's quality of life (QOL).[48] Currently, the common method follows the subsequent administration of lowest to highest risk foods.

### Corticosteroids

Corticosteroids remain the most common therapeutic alternative for all patients with EGE because these drugs suppress the transcription of chemokines and eosinophilic growth factors, such as IL-3, IL-5, and GM-CSF. Most patients are initially prescribed 20–40 mg prednisone per day for 2-6 weeks, followed by a gradual reduction in the dosage, from weeks to months.

Some patients may experience multiple recurrences and require reiterative therapy. With different follow-up times, the relapse rate was observed to vary between 25% and 60%.[49,50] Among the 20 patients receiving corticosteroid treatment at the time of diagnosis, 60% (12/20) had relapses and 15% (3/20) developed corticosteroid dependence because of the relapses.[50] Budesonide, a synthetic steroid that reduces side effects due to a high first-pass hepatic metabolism, can be used as an alternative to systemic steroids. Additionally, budesonide can act in a sustained-release enteric-soluble capsule, which can be applied to patients with jejunal and ileal disorders.

Whether every patient with EGE should initially be administered corticosteroids requires considerations, given that the spontaneous remission was observed in 40% of the patients with EGID.[50] A prospective study concluded that systemic steroids should be administered initially to individuals suffering from severe disease and an absolute increase in their peripheral eosinophils.[38]

### Leukotriene receptor antagonists

The leukotriene receptor antagonist montelukast and other antiallergic agents, such as mast cell stabilizers and antihistamine drugs, serve as second-line therapies for EGE. Frisen *et al*[51] demonstrated the efficacy of montelukast in patients with duodenal eosinophilia (ClinicalTrials. gov Identifier: NCT00148603) and reported that 83% of the patients had a positive clinical response in terms of pain relief but showed no significant changes in eosinophilic infiltration. There are case reports of patients with EGE who responded successfully when montelukast only was used as the first-line therapy.[49,52]

### Immunomodulatory therapy

Azathioprine (AZA), 6-mercaptopurine (6-MP), and calcineurin inhibitors are suitable alternatives for patients with steroid dependence. AZA can inhibit purine synthesis, thereby affecting DNA and RNA synthesis. AZA was shown to induce and maintain complete clinical and histological remission in patients who were not administered steroids.[53] Tacrolimus (FK506), a calcineurin inhibitor, is used against atopic dermatitis and can decrease tissue eosinophil counts via its inhibitory effects on mast cells, pruritus, and innate allergic response.[54] *In vivo* and *in vitro* studies showed that tacrolimus ameliorates eosinophil levels and associated pathogenesis in allergen-, IL-5-, and IL-13-induced EoE and EGE.[55]

### Biologics

Certain cells, cytokines, and chemokines mediate eosinophilic infiltration process. Biologics targeting these molecules can be considered effective and promising approaches against EGE. Actively studied or used biologics in clinical trials are listed in Table 1.

#### Anti-Siglec-8

In humans, Siglec-8 is expressed on the surface of eosinophils, mast cells, and basophils. Kano *et al*[55] demonstrated that in activated eosinophils, Siglec-8 ligation by its monoclonal antibody (mAb) leads to reactive oxygen species (ROS)-dependent enhancement of the IL-5-induced extracellular signal-regulated kinase (ERK) phosphorylation, resulting in regulated eosinophil cell death. A phase 2 trial showed that anti-Siglec-8 antibody AK002 reduced the number of gastrointestinal eosinophils and alleviated symptoms in EGE.[56] Additional phase 2 and 3 trials for AK002 are under way [Table 1].

#### Anti-IL-5

Mepolizumab treatment was showed to significantly reduce the use of oral corticosteroids in eosinophilic asthma.[57] However, large cohort studies or clinical trials are absent about its efficacy in EGE. However, in EoE, two randomized control trials (RCTs) revealed a significant decrease in esophageal eosinophils but limited improvement in symptoms.[58,59]

**Table 1: Current clinical status of biologics in EGE and EoE.**

| Targets | Drugs | Mechanisms | Current acquired results in EGE | Current acquired results in EoE | Completed trials in EGE* | Ongoing trials in EGE (NCT number, phase, last updated date)* |
|---|---|---|---|---|---|---|
| Siglec-8 | AK002 | Ligation of Siglec-8 to its mAb leads to a regulated eosinophil cell death | Reduce gastrointestinal eosinophils and release symptoms[56] | Ongoing: NCT04322708, phase2/3, 2021/7/30 | NCT03496571 (phase 2, 2020) | NCT03664960, phase 2, 2021/6/23<br>NCT04620811, phase 3, 2021/1/7<br>NCT05152563, phase 3, 2021/12/10<br>NCT04856891, phase 3, 2021/12/17 |
| IL-5 | Mepolizumab | Block IL-5 | Decrease corticosteroid dosage[78] | Reduce esophageal eosinophils,[58] but symptom improvement is limited[59] | NCT00266565 (phase 1/2, 2005) | — |
| | Reslizumab (SCH455700) | — | — | Reduce esophageal eosinophils, but symptom improvement is limited[61] | NCT00017862 (phase 2, 2003) | — |
| | Benralizumab | Block α subunit of IL-5 receptor | — | — | NCT03473977 (phase 2/3, 2022) | NCT05251909, phase 3, 2022/4/14 |
| IL-4 | Ptrainra | An IL-4-mutein binding to α subunit of IL-4 receptor | — | — | — | — |
| | Dupilumab | Block α-subunit of IL-4 receptor | — | — | — | NCT03678545, phase 2, 2022/2/23 |
| IL-13 | Dectrekumab (QAX576) | Block IL-13 | — | Reduce esophageal eosinophils without histological remission[63] | — | — |
| | Cendakimab (RPC4046) | | — | Reduce histologic and endoscopic features[64] (NCT02098473, phase 2) | — | — |
| IgE | OmAb | Block IgE binding to both, FcεRI and CD23 and downregulate surface FcεRI on mast cells and basophils | Decrease AEC and allergen specific Th2 responses[66] | Did not reduce the symptoms nor the eosinophil counts[79] | NCT00084097 (pilot study, 2017) | — |
| | Ligelizumab (QGE031) | Same as OmAb with higher affinity | — | — | — | — |
| | DARPin E2_79 | An engineered protein inhibits the binding of free IgE to FcεRI, and disrupts preformed IgE–FcεRI complexes *in vitro* | — | — | — | — |
| α4β7-integrin | Vedolizumab | Block α4β7-integrin | Induce clinical and histological improvements[73] | Reduce esophagus eosinophils with clinical remission and histologic improvement[80] | — | — |

AEC: Absolute eosinophil count; Ang-1: Angiotensin-1; CCR3: C-C chemokine receptor type 3; EGE: Eosinophilic gastroenteritis; EoE: Eosinophilic esophagitis; FcεRIFc: Fc epsilon receptor I; IgE: Immunoglobulin E; IL: Interleukin; mAb: Monoclonal antibody; OmAb: Omalizumab; Siglec: Sialic acid-binding immunoglobulin-like lectin 8; -: Not applicate. *For clinical trials in the table, a completed one is presented in the form of NCT number and its phase, while an ongoing one is presented in the form of NCT number, its phase, and the last updated date.

Reslizumab has been proven to improve disease progression in eosinophilic asthma.[60] Spergel *et al*[61] showed that reslizumab contributed to the decrease in esophageal eosinophil infiltration but not in symptom improvement.

A phase 2 trial for benralizumab aiming to assess its efficacy in EGE was completed (ClinicalTrials.gov Identifier: NCT03473977) recently. However, the result has not been revealed yet. Now, a phase 3 trial is in the recruitment stage (ClinicalTrials.gov Identifier: NCT05251909).

## Anti-IL-4 and Anti-IL-13

IL-4 and IL-13 are Th2 cytokines that regulate Th2 differentiation and IgE expression. Dupilumab (anti-IL-4) has been certified to reduce symptoms and eosinophilic infiltration in EoE.[62] Concerning EGE, a phase 2 trial to test its efficacy is currently underway (ClinicalTrials.gov Identifier: NCT03678545).

QAX576, an anti-IL-13 antibody, was reported to improve intraepithelial esophageal eosinophil counts and dysregulated esophageal disease-related transcripts in patients with EoE.[63] However, a phase 2 trial in EoE proved the therapeutic effect of another anti-IL-13 antibody called cendakimab (RPC4046), which significantly decreased esophageal eosinophil counts and improved endoscopic and histological scores.[64] Theoretically, all the aforementioned anti-IL-4 and -IL-13 antibodies may have a potential role in EGE treatment; however, none of them have been studied clinically.

## Anti-IgE

Omalizumab (OmAb) is an anti-IgE mAb widely recognized as an effective treatment for allergic disorders, such as asthma and rhinitis, by reducing the numbers of circulating eosinophils, blocking IgE binding to FcεRI and CD23, and downregulating surface FcεRI on mast cells and basophils.[65] Theoretically, OmAb should be effective for EGE. Three potential mechanisms were proposed to explain its functions: blocking IgE-facilitated antigen presentation, inhibiting mast cell and basophil activation, and blocking FcεRI-mediated inhibition of toll-like receptor (TLR) signaling in plasmacytoid dendritic cells (pDCs), thus increasing type 1 interferon expression to modify Th1/Th2 imbalances. However, the efficacy of OmAbs in EGE patients remains controversial. Foroughi *et al*[66] studied nine patients and demonstrated that OmAb was associated with a decrease in AECs and allergen-specific Th2 responses in patients with EGE. Conversely, in another clinical trial (ClinicalTrials. gov Identifier: NCT00084097), no enough evidence was presented to support Foroughi's results.[67] Therefore, it would be important to perform additional large RCTs to conclude the effect of OmAb.

Nevertheless, in the clinical use of OmAb, Pennington *et al*[68] discovered that after the OmAb treatment which neutralizes free serum IgE and gradually decreases the levels of surface IgE on effector cells, the effector cells may respond to maintain their own homeostasis, which may counteract OmAb treatment. This means that

excess OmAb is required during the process. Instead of removing IgE by classical OmAb, the authors tried to replace, not to remove, IgE by an IgE-R419N-$Fc_{3-4}$ variant, which introduces a novel glycosylation site, to avoid the IgE consumption by OmAb.

Other anti-IgE monoclonal antibodies are also being studied currently. Ligelizumab (QGE031) has a greater affinity and results in stronger inhibition of FcεRI expression on mast cells and basophils than OmAb.[69] Kim *et al*[70] reported an engineered protein inhibitor called DARPin E2_79, which can not only inhibit the binding of free IgE to FcεRI but also disrupt preformed IgE–FcεRI complexes *in vitro* through a facilitated dissociation mechanism. These antibodies still lack sufficient clinical data to be applied as a therapeutic alternative for EGE.

### Anti-α4β7-integrin

α4β7-integrin has been shown to play an important role in eosinophil localization in IBD. Vedolizumab may inhibit the recruitment of eosinophils to the intestinal mucosa.[71] Researchers reported that vedolizumab was effective in 40–75% patients with EG/EGE who were experiencing treatment refractoriness or steroid dependence.[72,73] However, current studies are limited by small sample sizes and lack regular follow-ups.

### Chemoattractant receptors expressed on Th2 cell (CRTH2) antagonist

CRTH2 mediate chemotaxis of eosinophils, basophils, and mast cells in response to prostaglandin D2 (PGD2). Straumann *et al*[74] demonstrated the beneficial effects of OC000459 in patients with EoE who were corticosteroid-dependent. However, its function in EGE remains unclear.

### Other targets

To the best of our knowledge, certain treatments for other eosinophilic diseases with similar pathology, such as asthma, may facilitate the identification of new approaches to treat EGID. The following targets have not been explored in the context of EGE or EoE:

### Anti-eotaxin

Cysteine- cysteine chemokine receptor-3 (CCR3) is a specific receptor for eotaxin-1, which is involved in eosinophil infiltration in tissues. Song *et al*[14] demonstrated that anti-CCR3 antibody can reduce eosinophil infiltration in the gastrointestinal mucosa and improve clinical symptoms in mouse models. However, there is no study addressing its effects in humans currently.

### Anti-TSLP

Tezepelumab, a mAb against TSLP, has been demonstrated to reduce exacerbations in allergic asthma in a phase 3 study.[75] TSLP is a possible target for EGID, but no clinical study has been conducted.

### Anti-TGF-β

TGF-β plays a role in the long-term remodeling and development of fibrosis. Clinical trials for losartan in EoE are ongoing, and no published result has been presented yet.

Clinical practice is limited in EGE owing to the fewer clinical trials for EGE than for EoE. Currently, six clinical trials of new biologics against EGE are underway, including those for benralizumab, dupilumab, and AK002. For EGE, attempts might be made by catching up the step of EoE.

## *Surgical therapy*

Surgical treatment should be avoided in case of great difficulties in diagnosis or severe complications. In serosal subtype EGE, endoscopy which mainly focuses on the mucosal layer, may fail to detect eosinophilic infiltration. Laparotomy or laparoscopic full-thickness biopsy will help. As is mentioned before, eosinophilic infiltration in the duodenum may lead to inflammation, edema, and fibrosis, sometimes involving the duodenal papilla, which may cause mechanical obstruction in the pancreatic duct.[76] In other circumstances, patients may present as acute bowel obstruction. In most cases, obstructions can be reversed by corticosteroid, avoiding unnecessary surgical treatment. However, for patients presenting with acute abdomen, such as perforation and intussusception, surgical treatment should be taken into account.[33]

However, there are not enough studies on postoperative outcomes in EGE because of its rarity and low incidence of complications.

## Prognosis

The disease course of EGE is associated with its histological pattern. According to the Klein classification, serosal disease presents with a majority of single flares and no continuous chronic course, mucosal disease mostly with a continuous course, and muscular disease with a recurring course.[2] Pineton de Chambrun *et al*[50] reported a large series of adult patients with EGE and eventually identified that the disease courses were different, with half the patients presenting with a more complex natural history characterized by unpredictable relapses and chronic courses. In another study, Havlichek *et al*[77] found that presence of weight loss, hypoalbuminemia, serosal disease involvement, or anemia at the time of diagnosis put the patients at a higher risk of developing a chronic course that may require long-term medication. During the initial inspection of patients, clinicians may need to pay attention to these factors to determine future medical therapy.

## Conclusions

EGE is an uncommon and heterogeneous gastrointestinal disease that has a complex pathogenesis and is often under-diagnosed. In recent years, the prevalence of EGE has increased gradually. Consequently, the field of EGE has expanded rapidly, achieving a deeper understanding of its pathogenesis, diagnosis, and treatment.

Diet therapy and corticosteroids are the two major treatments for EGE, and corticosteroids remain to be the initial medication for patients with severe symptoms. Our improved understandings of the disease pathogenesis are expected to pave the way for an era of biologics to treat refractory and corticosteroid-dependent EGE.


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## Conflicts of interest

None

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