



Review

Eosinophilic gastrointestinal diseases beyond eosinophilic esophagitis

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Key Messages

- The eosinophilic gastrointestinal diseases (EGIDs) are a rare group of diseases that can affect each part of the gastrointestinal (GI) tract. The diagnosis of an EGID is made when clinical symptoms match the part of the intestinal tract affected by eosinophilia.
- The EGIDs are diagnoses of exclusion and can be made only after other causes of GI eosinophilia have been ruled out.
- Except for EoE, consensus diagnostic criteria for the remaining EGIDs that include eosinophilic gastritis, eosinophilic gastroenteritis, and eosinophilic colitis are lacking.
- Corticosteroids are a mainstay of treatment for EGIDs.
- Dietary treatment for EGIDs other than EoE is supported in only small clinical series.

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ABSTRACT

Objective: Eosinophilic gastrointestinal diseases (EGIDs) are a rare group of disorders that can have varied clinical presentations dependent on the involved segment within the gastrointestinal tract. Eosinophilic gastritis presents with abdominal pain or vomiting, eosinophilic gastroenteritis presents with diarrhea and anemia or hypoalbuminemia, and eosinophilic colitis can present with diarrhea or bloody stools. These nonspecific symptoms remain poorly understood in their relation to the underlying pathogenesis, but a significant percentage of patients have atopy. In this review, we discuss the current literature on EGIDs to promote a practical approach to diagnosis and care.

Data Sources: Review of published literature.

Study Selections: Clinically relevant literature from 1900 through 2018 was obtained from a PubMed search. Those that addressed prevalence, diagnosis, clinical manifestations, natural history, and treatment of EGIDs were reviewed and are summarized in this article.

Results: Of the 485 articles found in the search, most of which were case reports, 71 were selected for review. The natural history of EGIDs is based primarily on case series and small numbers of patients, making therapeutic decisions difficult. Treatment remains limited to dietary restriction that is not effective in many patients and topical or systemic corticosteroids whose long-term use is to be avoided if possible.

Conclusions: With the seeming increase in all types of EGIDs, phenotypic descriptions are emerging that will likely promote better understanding of the pathogenesis and identification of novel therapeutic targets.

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Introduction

In the early 1990s an emerging body of clinical experiences by gastroenterologists and allergists identified features of a new disease,

eosinophilic esophagitis (EoE).^{1,2} Descriptions identified children who presented with nonspecific symptoms such as abdominal pain and vomiting and adults who presented with stereotypical features of dysphagia and food impactions.^{2,3} Common to the 2 groups were that a large percentage of patients had atopy, all had dense esophageal eosinophilia, and most responded to diet restriction of specific foods or topical steroids.^{4,5} Rapid progress was made in this field because of robust collaborations between allergists and

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Table 1
Clinical Symptoms of Eosinophilic Gastrointestinal Diseases

Mucosal	diarrhea, malabsorption, gastrointestinal bleeding, protein losing enteropathy, vomiting, abdominal pain
Muscular	vomiting, abdominal distention, abdominal pain, vomiting
Serosal	abdominal distention, ascites, peritonitis

gastroenterologists in identifying key clinical features, impactful therapeutic approaches, and novel therapeutic targets.

During the past decade, a similar trend has appeared with respect to an emerging group of children and adults with and without atopy who are presenting with nonspecific symptoms and who are subsequently found to have dense gastrointestinal (GI) eosinophilia. Because of the engagement between allergists and gastroenterologists concerning EoE, a template is in place for considering approaches to clinical evaluation and therapeutic endeavors of these patients. Even more importantly, the pathophysiology of these conditions will undergo more rapid and targeted evaluation because of these collaborations.

Eosinophilic GI diseases (EGIDs) are a group of disorders characterized by symptoms of GI dysfunction seen in combination with eosinophilic inflammation most commonly of the GI mucosa but often of the muscular or serosal layers; other etiologies of these findings need to have been ruled out.⁶⁻⁸ In 1970 a classification system by Klein et al⁹ delineated involvement of eosinophilic gastroenteritis (EGE) based on the depth of eosinophilic inflammation within the GI tract, specifically the mucosal, muscular, and/or serosal layers (Table 1). Among EGIDs, those with mucosal inflammation tend to present with diarrhea and potentially malabsorption and bleeding; those with muscular inflammation can present with obstruction, and those with serosal disease can present with eosinophilic ascites.⁶ Although studies suggest that the mucosal form, particularly in eosinophilic gastritis (EG), is the most common,¹⁰ not all layers are routinely examined by biopsy, so the exact prevalence of each subtype is unknown. Similarly, although the stomach and duodenum are the most frequently segments reported to be involved, they also are the most frequently examined by biopsy at endoscopy, making firm conclusions difficult.¹¹ In patients who present with any grouping of these symptoms, referral to a gastroenterologist for evaluation and likely esophagogastroduodenoscopy or colonoscopy is warranted.

The more recent literature categorizes EGIDs as a group of diseases that affect different organs within the GI tract, such as EoE, EG, EGE, and eosinophilic colitis (EC), in which the eosinophilic inflammation is limited to the esophagus, stomach, small intestine, and colon, respectively.^{6,8} In some circumstances, multiple parts of the GI tract can be involved. The benefit of this more recent categorization is that it lets clinicians not only interpret symptoms and laboratory values based on which part of the GI tract is affected but also target treatments as in other diseases such as inflammatory bowel disease.

The clinical presentation varies and is dependent on the location in which the inflammation arises.^{6,8,11} Except for EoE, the literature is currently lacking consensus diagnostic criteria and accepted therapeutic approaches for other EGIDs.^{8,11} This review focuses on the state of the art with respect to treatments and future research regarding EGIDs except for EoE, which has been extensively reviewed elsewhere.⁴ For this review, EGID refers to EG, EGE, and EC unless otherwise specified.

Epidemiology

Given the rarity of EGIDs, epidemiologic data are limited and primarily from case series; thus, the exact prevalence is unknown. A single-center gastroenterology group diagnosed 30 patients with EGE over an 8-year period, indicating a frequency of 0.67% of upper

endoscopies performed.¹² However, prevalence among patients undergoing endoscopies cannot be extrapolated to indicate prevalence in an unselected patient population. To address this, Spergel et al¹³ administered an electronic survey to 10,874 US physicians, including pediatric and adult allergists, immunologists, and gastroenterologists. A total of 1,836 responses (17%) identified a prevalence of EGE or EC in 28 of 100,000 based on patients seen by gastroenterologists and in 2 of 100,000 based on patients seen by allergists and immunologists. More recently, Mansoor et al¹⁴ established a population-based database to investigate the epidemiology of EGIDs in the United States through extracting data from electronic health records from 26 major health care systems from 1999 through 2017. Results from their study estimated a prevalence of EGE in 5.1 of 100,000 persons and of EC in 2.1 of 100,000 persons. Similarly, Jensen et al¹⁵ performed a retrospective analysis of the IMS Health LifeLink (IMS Health, Alexandria, Virginia) and PharMetrics Plus (DGI, LLC, Fairfax, Virginia) claims databases to estimate the prevalence of EGIDs in patients 0 to 64 years old by *International Classification of Diseases, Ninth Revision* codes, with an estimated prevalence of 6.3, 8.4, and 3.3 of 100,000 for EG, EGE, and EC, respectively. Although studies relying on surveys and review of electronic medical records are likely to have inaccuracies and might not reflect true prevalence, one can conclude from the available literature that EGIDs are rare, with an estimate of fewer than 50,000 total patients affected in the United States.¹⁵

The EGIDs are often associated with other atopic conditions such as food allergies, asthma, and atopic dermatitis.¹³⁻¹⁸ More specifically, comorbid atopic conditions have been noted in 38.5% of patients with EG, 45.6% of those with EGE, and 41.8% of those with EC, with a larger proportion of concomitant atopic disease in pediatric patients.¹⁵ EGIDs have a peak age of diagnosis in the third decade of life,¹⁵ although they have been reported in pediatric patients.¹⁹ More specifically, Jensen et al¹⁵ reported the highest prevalence of EGE among children younger than 5 years, with EG being more prevalent in older groups and no age difference noted for EC. Although EoE has a clear male predominance,⁴ the literature regarding sex predilection for other EGIDs has been mixed. Jensen et al¹⁵ noted a female predominance for EG but no significant sex difference for EGE and EC. Mark et al²⁰ noted an increased prevalence of all non-EoE EGIDs in female patients, whereas Durieu et al²¹ noted a strong male predilection in patients with EC. It also has been noted that the serosal form is more common in women at least 40 years old. Therefore, demographics can vary among EGIDs and future studies are needed to better characterize these differences.

Clinical Presentation

The clinical presentation of EGIDs varies based on the affected area of the GI tract.^{6,8,11} For instance, the stomach typically acts as a reservoir for food as the digestive process is started. Thus, patients with EG can present with symptoms primarily of nausea, vomiting, and early satiety.⁸ In some circumstances, patients, especially teenage girls, can present with an isolated ulcer that might perforate and is not responsive to proton pump inhibitors.²² In the study by Jensen et al,¹⁵ the most common symptoms noted by the 774 patients with EG were abdominal pain, chest pain and throat pain, and nausea and vomiting. Of note, 10.2% of patients with EG were noted to have concurrent EoE, which could explain the prominence of throat pain.¹⁵ The small intestine is where nutrients are absorbed and fluid is secreted, and thus presenting symptoms of EGE are nonspecific and include diarrhea, vomiting, and abdominal pain.¹¹ Because of its massive surface area, disruptions in the small intestinal barrier can lead to malnutrition, anemia, and protein-losing enteropathy.^{6,8,17,23} A study by Reed et al,¹⁷ which described 44 patients with EGE, noted that vomiting and abdominal pain were the most common symptoms, occurring in 71% and 62% of the

cohort, respectively. Similarly, Jensen et al¹⁵ reported abdominal pain, diarrhea, and nausea and vomiting as the most common symptoms among 954 patients with EGE. The colon participates in fluid absorption, and thus patients with EC can present with diarrhea, abdominal pain, and hematochezia.^{8,15,20} Although patients with non-EoE EGIDs can have obstruction,²⁴ stricture is not commonly seen, which differs from EoE.^{22,25}

Pathogenesis

Eosinophils are present in all regions of the GI tract with the exception of the esophagus and can participate in immune homeostasis.²⁶ In support of this are mouse-based studies that associated the absence of eosinophils with dysregulation of the mucosal barrier.^{27,28} Eosinophils increase owing to specific immune responses, such as to helminth infections and allergic disease, with interleukin (IL)-5 being key in enhancing eosinophilopoiesis and activation.²⁶ When eosinophils are present in increased numbers, their effector functions, primarily because of their ability to release cationic proteins stored in cytoplasmic granules and to release different cytokines, contribute to host defense.^{26,29}

Despite these findings, large numbers of mucosal eosinophils, especially when they are associated with architectural changes, likely indicate a pathologic process. Given the prevalence of atopic disease in patients with EGIDs, it has been suggested that exposure to a food or other antigen could be driving eosinophils to accumulate.³⁰ Although exact mechanisms have yet to be elucidated, a T-helper cell type 2 (T_H2) immune response is likely central.¹¹ Demonstrating the dominance of T_H2 impact in EGIDs, Jaffe et al³¹ reported an increase in T_H2 cytokines IL-4 and IL-5 after mitogenic stimulation in adult patients with EGE. Interestingly, when comparing food allergen-specific CD4 T-cell responses among patients with EGE, patients with peanut allergy mediated by immunoglobulin E (IgE), and healthy controls, Prussin et al³² noted 2 T_H2 subpopulations. Specifically, patients with EGE had a unique association with an IL-5⁺ response to foods (IL-5⁺, IL-4⁺) that differed from those with IgE-mediated peanut allergy, which was mostly IL-5⁻ (IL-5⁻, IL-4⁺).³² This suggests different T_H2 cytokine responses that might explain the different clinical presentations of IgE-mediated or eosinophilic rich pathology. Further supporting this, Upadhyaya et al³³ demonstrated the T_H2 heterogeneity of these 2 subpopulations by showing that multiple rounds of antigen exposure were required to generate IL-5⁺ T_H2 subpopulations seen in EGE.

Although a T_H2 response is key in EoE,⁴ it is not clear whether EoE and other EGIDs share a common pathogenesis. Features that are common include atopy in many patients and many patients demonstrate sensitization to food allergens and eosinophilic or T_H2 inflammation.^{8,31,34-36} However, as discussed in further detail below, response to dietary therapy is less effective in EGIDs than in EoE.³⁷ In addition, Caldwell et al³⁸ demonstrated that the transcriptome in EG differs from that in EoE, arguing that differences in underlying mechanisms could exist that need further study.

Diagnosis

Diagnosis of EGIDs requires (1) presence of recurrent GI symptoms, (2) demonstration of GI eosinophilic infiltrate, and (3) absence of other causes of both.^{6,9,23,39} Although consensus diagnostic criteria exist for EoE,^{4,5} they are lacking for other EGIDs because of the rarity of these conditions and knowledge on the threshold of eosinophil numbers and/or other histopathologic findings that indicate GI pathology.^{7,40,41} To address this, DeBrosse et al⁴⁰ evaluated the quantity and location of eosinophils in the GI tract of healthy pediatric patients and noted a gradient, with none present in the healthy esophagus, a maximum of 26 eosinophils per high-powered field (eos/hpf) in the healthy duodenum, and 50 eos/hpf noted in the ascending

colon with numbers decreasing to the 30s more distally. Different definitions of pathologic eosinophilic inflammation have been used in various studies, ranging from 20 to 80 eos/hpf, depending on what part of the intestine was sampled.⁴²⁻⁴⁵ Additional factors such as the location and depth of biopsy samples obtained, analyses used for histologic examinations, experience of the pathologist, and the knowledge that geographic variation in the normal number of eosinophils in a healthy GI tract likely exists can affect reliable interpretation.⁶ Salmon-colored patch lesions rich with an eosinophilic infiltrate can be located throughout the small bowel mucosae and can aid in diagnosis.⁴⁶ Overall, based on prior studies on healthy controls, peak eosinophil counts higher than 30 eos/hpf in the stomach, 50 eos/hpf in the duodenum, and 30 eos/hpf in the large bowel (dependent on location) in an affected segment are commonly used to aid in diagnosis.^{11,25,40,44,47} Assessment for associated cellular findings and architectural changes seen in EGIDs, such as degranulated eosinophils, intraepithelial eosinophils, crypt abscesses, and epithelial degenerative and regenerative changes, would assist in an accurate diagnosis.⁴⁵ A recent meta-analysis by Kiss et al⁴¹ analyzed data on eosinophil density in healthy patients. They noted the cumulative mean eosinophil cell numbers per high-powered field were 8.25 (95% confidence interval 4.71–11.8), 11.52 (95% confidence interval 7.21–15.83), and 11.10 (95% confidence interval 9.11–13.09) for the duodenum, terminal ileum, and large intestine and rectum, respectively.⁴¹ However, they concluded that based on current literature there is no normal cutoff for eosinophil density because many studies included patients with irritable bowel syndrome and functional GI disorders as control subjects and suggested that prospective multicenter studies are needed to establish normal values.⁴¹

The EGIDs can be diagnosed only after other etiologies of GI eosinophilia have been ruled out.⁶ Therefore, one of the essential functions of allergists, immunologists, and gastroenterologists is to evaluate for possible diseases that could be contributing to GI eosinophilia (Table 2). The differential diagnosis includes infection, hypereosinophilic syndrome (HES), drug allergy, chronic inflammatory conditions such as inflammatory bowel disease, autoimmune diseases, chronic graft-vs-host disease, malignancy such as leukemia and lymphoma, and immuno-dysregulation polyendocrinopathy enteropathy X-linked syndrome.^{8,11,25,45} Among infectious causes, parasitic infections are a prominent cause; therefore, a travel history and a stool sample for ova and parasites are recommended to obtain serology for *Strongyloides stercoralis* and/or *Toxocara canis*.⁸ In general, history or physical examination permits rapid exclusion of other causes.

Although up to 90% of patients with an EGID can have peripheral eosinophilia,¹⁸ the underlying etiology is not always certain, and when blood eosinophilia with an eosinophil count higher than 1,500/mm³ on at least 2 occasions is seen, patients should be evaluated for HES. HES is defined as blood eosinophilia with an eosinophil count higher than 1,500/mm³ on at least 2 occasions or when there is evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia after secondary causes of eosinophilia have been ruled out.⁴⁸ Therefore, EGIDs are not considered a form of HES.²⁵ HES can affect many organ systems including, but not limited to, the heart, lungs, skin, GI tract, and

Table 2
Differential Diagnosis of Eosinophilic Gastrointestinal Disorders

Infection
Hypereosinophilic syndrome
Drug allergy
Chronic inflammatory conditions
Autoimmune disease
Chronic graft-vs-host disease
Malignancy
Immuno-dysregulation polyendocrinopathy enteropathy X-linked syndrome

nervous system. Prussin²⁵ recently published a list of suggested studies to perform in the evaluation of HES in patients with GI eosinophilia and an absolute eosinophil count higher than 1,500/mm². Evaluations should seek pertinent drug and travel histories and testing for ova and parasites, *S. stercoralis* serology, T-cell receptor clonality studies (to evaluate for lymphocytic HES), FIP1-like-1 and platelet-derived growth factor receptor- α fusion gene studies (to evaluate for myeloid HES), and a cardiac echocardiogram (to assess for target organ damage).²⁵

In addition, allergists and immunologists should consider, particularly in adult patients, eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome). EGPA is a vasculitis with multisystem involvement most commonly associated with asthma, chronic sinus disease, nasal polyps, and peripheral eosinophilia.⁴⁹ Although the lung is the most commonly involved organ, additional systems can be involved including the GI tract producing symptoms such as abdominal pain, diarrhea, and bleeding with mucosal evidence of ulcers and colitis; thus, it should be considered in the differential of EGIDs if other characteristic clinical symptoms are present.⁵⁰ Antineutrophil cytoplasmic antibodies are often obtained as part of the diagnostic workup but are noted in only 30% to 60% of patients with EGPA.⁵¹ The American College of Rheumatology has established diagnostic criteria for EGPA in patients with vasculitis, which include asthma, more than 10% eosinophils, mononeuropathy or polyneuropathy, migratory transient pulmonary opacities detected radiographically, paranasal sinus abnormality, and a biopsy sample containing a blood vessel showing the accumulation of eosinophils in extravascular areas.⁵² The presence of at least 4 of these criteria is noted to have a sensitivity of 85% and a specificity of greater than 99%.⁵²

Another consideration for causes of GI eosinophilia is inflammatory bowel diseases. The 2 most common are Crohn disease and ulcerative colitis. Either of these chronic diseases can present with symptoms of bloody diarrhea, abdominal pain, or growth failure and laboratory parameters including anemia and increased erythrocyte sedimentation rate or C-reactive protein. In general, patients with inflammatory bowel disease appear sicker than those with EGIDs who will not have increased erythrocyte sedimentation rate or C-reactive protein.

Natural History

Although EoE is typically considered chronic with few exceptions,⁵³ the literature thus far demonstrates that natural history can vary among patients with other EGIDs. Pineton et al⁴² evaluated long-term outcomes of 43 patients diagnosed with EGE and noted 3 different courses of disease progression. Specifically, 18 had an initial flare without a relapse (42%), 17 (37%) had recurring diseases, described as multiple flares separated by periods of full remission, and 9 (21%) had chronic disease. For those with recurring disease, the interval between flares was highly variable and ranged from months to years.⁴² Notably, the peripheral eosinophil count was increased in all patients with recurrence of disease in whom it was available, indicating that evaluation of serum eosinophils could be of clinical utility in assessing for recurrence. Similarly, Reed et al¹⁷ noted that one third of their pediatric and adult EGE cohort also underwent long-term remission. Although the true prevalence of each disease course among patients with EGIDs is unknown, understanding the variance in natural history is essential for patient education and for analyzing treatment outcomes because a portion of patients will have an initial flare without relapse.

Treatment

Given the rarity of EGIDs, no randomized controlled studies are available to guide treatment. In some circumstances, EGIDs can be

difficult to control⁸ and require long-term courses of corticosteroids.^{17,42,54} Reed et al¹⁷ evaluated the efficacy of various therapies including corticosteroids, dietary therapy, mast cell inhibitors, H₂ antagonists, and leukotriene receptor antagonists in 44 patients with EGEs, including pediatric patients, for an average of 26.2 months, with 76% of patients needing more than 1 treatment modality. When including all treatment modalities, 60% had symptom resolution and 51% had histologic resolution. The most effective therapy was corticosteroids, with 22 of 36 patients placed on corticosteroids (61%) having symptomatic resolution. Although 12 of 21 patients (57%) treated with dietary therapy reported symptomatic improvement, most of those patients (71%) also were treated with corticosteroids, complicating reliable interpretation. Of the 28 patients in whom assessment for histologic remission was available, 19 demonstrated remission after therapy, of which 9 were treated with corticosteroids, 6 were treated with a combination of dietary therapy and steroids, and 4 were treated with dietary therapy. Formulations of corticosteroids in this study included oral corticosteroids, budesonide as a viscous slurry or enteral release, or swallowed fluticasone; however, results were not analyzed based on what formulation of corticosteroid or specific dietary therapy was used.¹⁷ No patient treated with mast cell inhibitors, H₂ antagonists, or leukotriene receptor antagonists alone had symptomatic or histologic resolution.¹⁷ Other studies have similarly noted the efficacy of corticosteroids in treatment. Pineton et al⁴² noted that of their 43 patients with EGE, oral corticosteroids followed by a rapid taper was the most effective treatment because it induced remission in 95% of patients (18 of 19) in whom it was used. Chen et al⁵⁴ similarly noted that of their 15 patients with EGE, the 13 patients treated with oral corticosteroids followed by a taper had symptom remission within 2 weeks, with 5 patients having relapses in the 12 months after discontinuation. There also are reports of success with topical steroids in the form of budesonide, typically as a budesonide capsule.⁵⁵⁻⁵⁸ For usage of budesonide capsules for treatment of EG, patients are often instructed to open the capsule and swallow the granules mixed with applesauce for optimal delivery.²⁵ For patients with jejunal or ileal disease, an intact capsule might be preferred.²⁵ Because fluticasone is not available in a form that easily targets the GI tract beyond the esophagus, its use in EGIDs is currently limited. However, there are reports of patients in whom fluticasone was noted to relieve gastric eosinophilia when used primarily for treatment of EoE.⁵⁹

Given the effectiveness of dietary therapy as a treatment option for EoE,⁵³ a common question posed to allergists and immunologists concerns the role of dietary therapy in treatment of EGIDs. Like corticosteroids, no randomized studies exist to accurately answer this question, but case reports and case series have reported successful treatment with elemental diets in children with EGIDs, indicating it could be beneficial in certain patients.^{60,61} In addition, Ko et al³⁴ retrospectively evaluated response to dietary therapy in 30 children with EG, defined as at least 70 gastric eos/hpf, with 43% of patients having concurrent EoE and 21% having concurrent EGE. Dietary therapies trialed included an elemental diet, a 7-food elimination diet (milk, egg, wheat, soy, peanut and tree nuts, fish and shellfish, and red meat), and empiric avoidance of 1 to 3 foods. Overall, 82% of patients had a clinical response and 78% had a histologic response to dietary therapy; however, the maximum number of children in whom histologic remission was assessed in each dietary treatment group was only 5, making it difficult extrapolate these results to larger populations.³⁴ Interestingly, patients with concurrent EoE were more resistant to therapy, with 6 of 16 patients having persistent esophageal eosinophilia despite remission of gastric inflammation. Although 86% of patients were noted to be sensitized to several foods by positive skin prick test reaction or serum analyses, response to dietary therapy did not correlate with their food sensitization.³⁴

In the cohort described by Reed et al,¹⁷ 21 of 44 patients with EGE (47%) were treated with dietary therapy, with 13 being placed on an elemental formula, 7 on a testing-directed diet, and 1 on a diet not specified. Twelve of the 21 patients (57%) reported symptom resolution; however, 15 of them also received corticosteroids during their treatment course, complicating accurate interpretation.¹⁷ Further complicating reliable interpretation is the lack of assessment for histologic remission in all patients.¹⁷ Because of the absence of randomized controlled studies on dietary therapy for EGIDs, Lucendo et al³⁷ systematically reviewed the literature to assess the efficacy, symptomatic and histologic, of dietary interventions in children and adults with EGE and EC. Included were 30 studies, most of which were judged to be low quality because these were case reports or case series, with the study by Ko et al³⁴ being the only medium- to high-quality study identified. Elemental diets in children were noted to lead to clinical remission in 75.8% of cases. Histologic remission was noted in 5 of only 6 individuals in total, most of whom were patients with EG from the cohort of Ko et al.^{34,37} Empiric elimination diets also were evaluated. Of 16 patients on single-food elimination of cow's milk only (all children), 62% had symptomatic improvement, but no histologic assessments were available. Thirty-four patients underwent empiric a 6-food elimination diet (cow's milk, egg, wheat, soy, fish and shellfish, and peanut and tree nuts) or a 7-food elimination diet (addition of red meat avoidance), with 29 patients (85.3%) having symptomatic improvement; similarly, assessment of histologic remission was rarely obtained.³⁷ Allergy testing-directed elimination diets were rarely used across studies, with only 4 patients in total being treated with this method and only 1 patient having assessment for histologic remission.⁴ Overall, because of the lack of high-quality studies, which often lacked assessment for histologic remission, the conclusion of this systematic review was that unequivocal use of dietary treatment for patients with EGE and EC cannot be supported based on currently available research.³⁷

Although evidence to date demonstrates that corticosteroids are the most effective therapy for EGIDs, it is possible that phenotypes exist in EGID as has been suggested in EoE,⁶² indicating there could be a subset of patients in whom dietary therapy would be effective. Certain EGIDs, or phenotypes within them, could be more amenable to dietary therapy, as has been suggested in EG by Ko et al.³⁴ Demonstrating this, Katz et al⁶³ reported on 12 children with EGID and separated them into 2 cohorts. One group presented at younger than 1 year and responded to dietary therapy in the form of cow's milk avoidance, which was typically transient. A second group that presented later in childhood had a stronger atopic history and did not respond to dietary therapy, often requiring corticosteroid therapy.⁶³ Dependent on the clinical circumstances, with attention to severity of symptoms, it might be reasonable to offer an empiric elimination diet to motivated patients with the knowledge that overall efficacy is unknown. Future randomized controlled studies are needed that include assessment of histologic remission to better characterize the phenotype of patients with EGIDs who respond to dietary therapy and an elemental diet.

Additional therapies other than corticosteroids and dietary therapy have been trialed in small numbers of patients.⁶⁴ Because EGIDs often occur in patients with an atopic history, a trial of omalizumab, an anti-IgE monoclonal antibody, was trialed for treatment in 9 patients with EGE, with a statically significant decrease in peripheral eosinophil count noted but no significant change in tissue eosinophils.⁶⁵ Therefore, omalizumab is not currently recommended for treatment of EGIDs.²⁵ Similarly, because IL-5 is a central cytokine in eosinophil biology, monoclonal anti-IL-5 antibodies have been trialed in a small number of patients⁶⁶; however, larger studies are needed in EGID populations before conclusions can be made and it is not currently in the mainstay of therapy.

Thiopurines, such as azathioprine, which is more commonly used in inflammatory bowel disease, have demonstrated success in refractory cases.⁶⁷ In addition, although there have been case reports demonstrating success of leukotriene receptor antagonists in the treatment of EGE,^{68–70} treatment with montelukast in EoE has not been shown to be effective and is not currently standard for EGID treatment.⁷¹ Case reports have demonstrated conflicting results for oral cromolyn, with some cases reporting benefit^{72,73} vs studies of larger groups of patients with EoE not noting similar success.⁷⁴ Case reports also have noted the benefit of ketotifen, an H₁ receptor antagonist with mast cell stabilizing effects,⁷⁵ and proton pump inhibitors.³⁴ Overall, given the natural history of EGIDs, it is not clear if the remissions described in individual case reports were due to the medications or spontaneous remission. Studies to date do not support use of leukotriene receptor antagonists, cromolyn, proton pump inhibitors, or ketotifen as monotherapy for EGIDs. However, if patients have comorbid conditions for which they are indicated, evidence demonstrates they are unlikely to be harmful.

Conclusion

The EGIDs are uncommon conditions; however, because most patients with EGIDs have other atopic conditions, allergists and immunologists need to be aware of the clinical manifestations, evaluation, and treatment options for these patients. The key roles of allergists and immunologists include referral to a gastroenterologist for esophagogastroduodenoscopy or colonoscopy in patients with consistent clinical history and evaluation. When GI eosinophilia is identified, allergists and immunologists can provide an evaluation for other conditions that might explain this finding. They also might often be asked to assist in dietary therapy; therefore, an understanding of the evidence and limitations in dietary therapy is essential because the currently available literature demonstrates that corticosteroids are the most effective therapy option. Future high-quality studies with robust collaboration between allergists and gastroenterologists, as is seen in EoE, are needed to more adequately evaluate the prevalence, natural history, and efficacy of treatment options for patients with EGIDs.

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