Eosinophilic Gastrointestinal Diseases Beyond the Esophagus: An Evolving Field and Nomenclature

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Abstract: The eosinophilic gastrointestinal diseases (EGIDs) are a group of chronic, immune-mediated gastrointestinal (GI) diseases characterized by GI symptoms and pathologic eosinophilic infiltration of specific areas within the GI tract in the absence of secondary causes of eosinophilia. The non–eosinophilic esophagitis EGIDs remain understudied and likely underdiagnosed, owing in part to the lack of clarity in the terminology previously used to describe these diseases. The newly established EGID nomenclature framework includes a first-tier description of the specific location of GI tract involvement and a second-tier description with more granular characterizations of disease involvement. EGIDs can involve any segment or layer of the GI tract, so patients can present with a wide array of common, nonspecific GI symptoms. Diagnosing EGIDs requires endoscopic evaluation and biopsies showing increased eosinophilic tissue infiltration in the correct clinical context after ruling out other causes of eosinophilia. Although the pathogenesis is not yet fully understood, EGIDs are likely allergic conditions triggered by food antigen exposure. Most patients are currently treated with corticosteroids, but investigations of other pharmacologic and dietary therapies are ongoing. This article highlights the recently updated EGID nomenclature and summarizes the current understanding of the diagnosis, pathogenesis, and treatment of EGIDs.

Keywords
Eosinophilic gastrointestinal diseases, eosinophilic gastritis, eosinophilic enteritis, eosinophilic colitis, eosinophilic gastroenteritis, eosinophilia, nomenclature

The eosinophilic gastrointestinal diseases (EGIDs) are a group of gastrointestinal (GI) diseases characterized by GI symptoms and pathologic eosinophilic infiltration of specific areas within the GI tract in the absence of secondary causes of eosinophilia.[1] These conditions are considered to be chronic, immune-mediated disorders that may be linked to food allergen exposure.[2-4] Although eosinophilic esophagitis (EoE) is the most common EGID, there is an increasing recognition of other EGIDs involving other areas of the GI tract.[5,6] In 1937, Kaijser reported a case of eosinophilic gastritis (EoG), which is considered the first EGID described in the literature.[7] Since the first

Table. Summary of International Consensus Recommendations for EGID Nomenclature (With Abbreviations)[2]

Primary Area of GI Tract Involvement	Tier 1: Clinical Use	Tier 2: Clinical and Research Use
• Esophagus	Eosinophilic esophagitis (EoE)	
Non-EoE EGIDs[a]		
• Stomach	Eosinophilic gastritis (EoG)	
• Small bowel	Eosinophilic enteritis (EoN)	
– Duodenum		Eosinophilic duodenitis (EoD)
– Jejunum		Eosinophilic jejunitis (EoJ)
– Ileum		Eosinophilic ileitis (EoI)
• Colon	Eosinophilic colitis (EoC)	
• Multiple areas of involvement		
– Esophagus + other		No consensus reached
– Stomach + small bowel		Eosinophilic gastritis and enteritis
– Stomach + colon		Eosinophilic gastritis and colitis
– Duodenum + colon		Eosinophilic duodenitis and colitis

EGID, eosinophilic gastrointestinal disease; GI, gastrointestinal.
[a]The term *eosinophilic gastroenteritis* is being de-emphasized in favor of more specific naming conventions.

report of EoE in 1978, the literature describing the pathophysiology, diagnosis, and management of EoE has grown significantly; however, other EGIDs have remained relatively understudied.[8]

Describing and naming specific EGIDs can be challenging because they can involve multiple areas and depths of the GI tract, and there is substantial variability in the terminology used. This has presented practical challenges and has limited advances in the collective understanding of these diseases. A recent effort by an international group of clinicians and researchers has arrived at a consensus on an updated framework for EGID nomenclature to help improve patient care and inform further research efforts.[2] In addition to highlighting this updated nomenclature, this article will provide an overview of the current understanding of the diagnosis, pathogenesis, and treatment of EGIDs.

New Nomenclature

To understand and diagnose a group of diseases, clarity in terminology and nomenclature is of utmost importance. Previously, there was no consensus on how to refer to the non-EoE EGIDs. The catchall term *eosinophilic gastroenteritis* was frequently used, but this term has often been employed without delineating the involved part of the GI tract. Therefore, a more systematic method for naming these diseases to improve accuracy in clinical diagnosis and inform data collection was necessary. A group of 91 experts developed an international consensus for standardized EGID nomenclature, which was recently published.[2]

The result was a 2-tier framework applicable to both the clinical and research settings (Table).[2] The first tier provides a basic description of the location involved for clinical practice, and the second tier provides more granular nomenclature for clinical specificity and research purposes. Another major change addressed the term *eosinophilic gastroenteritis*, which had previously described almost any non-EoE EGID. Now, the term *EGID* denotes this group of disorders. Specific diseases are now named by the involved areas of the GI tract using an *Eo-* prefix for the abbreviation. Specifically, when the stomach is involved, the term *EoG* is used. When the small bowel is involved, the term *eosinophilic enteritis (EoN)* is used with an option to further specify locations within the small bowel: *eosinophilic duodenitis (EoD)*, *eosinophilic jejunitis (EoJ)*, and *eosinophilic ileitis (EoI)*. When the colon is involved, the term *eosinophilic colitis (EoC)* is used.

The contributing experts considered it important to identify a primary location of the EGID based on the area within the GI tract where symptoms, complications, endoscopic findings, and eosinophilic infiltration were predominant. There was also a need to describe involvement in multiple areas of the GI tract, but this remains challenging, as whether these diseases are distinct from one another or all part of the same spectrum is unclear. For instance, although there are some similarities to EoE, including an association with atopic diseases, there seems to be a unique gene expression in other EGIDs that is

not consistent with that found in EoE.[4,9] Therefore, no consensus was reached for how to describe overlapping esophageal involvement with other affected areas in the GI tract.[2] For example, the group considered using the terms *eosinophilic gastritis with esophageal involvement* or *eosinophilic gastritis and eosinophilic esophagitis*, depending on whether gastric or esophageal symptoms predominated, respectively. Within the non-EoE EGIDs without esophageal involvement, clinicians and researchers should use granularity when possible. For example, disease involving both the stomach and colon should be termed *eosinophilic gastritis and colitis*, whereas disease in the duodenum and colon should be identified as *eosinophilic duodenitis and colitis*. To further classify EGIDs, more detailed characterization based on the layers of the GI wall involved or specific complications will be considered. Because the understanding of EGIDs continues to evolve, the terminology will likely be updated in the context of new data. This article will preferentially use the new terminology and abbreviations, but in cases of prior papers reporting on eosinophilic gastroenteritis and locations that are not specified (stomach and/or small bowel, or other location), the article will use the now historical term.

Approach to Diagnosis

In contrast to EoE, the diagnostic criteria for non-EoE EGIDs remain less defined, as there are currently no published diagnostic guidelines, although these are in progress. The general approach to diagnosis requires the correct clinical presentation in the context of pathologic eosinophilic infiltration of the GI tract. However, diagnosis is challenging because other GI disorders are often considered first,[10,11] and diagnosis is often prolonged, with 1 study reporting a mean delay of 3.6 years.[12] Reasons may include the widely variable symptomatology, low suspicion among clinicians, inadequate number of biopsies during endoscopy, and underrecognition of eosinophils on pathologic evaluation, which also likely lead to underdiagnosis of these diseases.[13]

Prevalence in the United States has been estimated to be 6.3/100,000 for EoG, 8.4/100,000 for eosinophilic gastroenteritis (as reflected by the billing codes rather than the new nomenclature), and 3.3/100,000 for EoC[6]; similar values were reported in another study.[14] However, a recent meta-analysis of the medical literature calculated the prevalence of non-EoE EGIDs to be 1.9%.[15] In contrast to male predominance in EoE, there may be a slight female predominance in non-EoE EGIDs.[6,16] Non-EoE EGIDs can also present at any age,[17] and as many as 50% to 60% of those diagnosed may have at least 1 atopic condition.[18,19] The natural history of these diseases remains unclear, given the paucity of long-term data on disease progression, but the diseases can be generally understood as chronic.[17,20-22]

The clinical presentation of EGIDs can vary widely. Symptoms include nausea, vomiting, abdominal pain, early satiety, diarrhea, bloating, and weight loss, among others. Some patients may present with bothersome nonspecific symptoms, whereas other patients can present with complications such as intestinal obstruction or protein-losing enteropathy.[22] The presenting symptoms of EGIDs often vary by which parts of the GI tract and which layers of the GI tract lumen are involved in a particular patient, with the predominant symptoms often reflecting the predominant anatomic area of involvement.[1,19] For example, patients with EoG may be more likely to present with nausea, vomiting, and abdominal pain, whereas patients with EoN or EoC may be more likely to present with diarrhea.[9] Furthermore, in a study comparing patient-reported symptoms of EoE and non-EoE EGIDs, patients with non-EoE EGIDs reported more frequent symptoms than patients with EoE and were also more likely to report fatigue, isolation, and deep muscle or joint pain.[23]

Because non-EoE EGIDs can involve 1 or more layers of the luminal wall, patients can present with many different complications, including peripheral edema, ascites, iron deficiency anemia, GI bleeding, strictures, ulcers, perforation, and obstruction. The most common manifestation is involvement of the mucosal layer only,[24] but diffuse involvement within the small bowel can lead to malabsorption, protein-losing enteropathy, and even failure to thrive.[25,26] Involvement of the muscular layer can lead to wall thickening and dysmotility that can ultimately cause intestinal obstruction or even perforation. When the subserosa is affected, patients can develop ascites or pleural effusion, in which cases the ascitic or pleural fluid samples typically have markedly elevated eosinophils.[24,25]

A diagnosis of EGID should be considered when relatively common symptoms or complications manifest without another explanation. The initial laboratory evaluation, including complete blood count with differential, complete metabolic panel, ferritin, iron panel, and stool studies, is similar between EGID and other GI diseases.[1] Peripheral eosinophilia, iron deficiency, or hypoalbuminemia should raise clinical suspicion of EGID.[4,24-28] A recent study showed a higher diagnostic yield of biopsies in patients with mild peripheral eosinophilia and hypoalbuminemia.[29] Additionally, imaging studies may show GI wall thickness or irregular narrowing of the small bowel, if there is involvement of the muscular layer of the bowel wall.[30,31] Although initial research has suggested that less-invasive biomarker testing may have a role in

diagnosing non-EoE EGIDs,[32] such testing is not yet used clinically, and an endoscopy with biopsy is needed to complete the diagnostic evaluation.

Endoscopic evaluation is guided by the clinical picture, but upper endoscopy is most often performed. A multicenter study of 373 patients found that the most common endoscopic finding, observed in more than 60% of patients, was a normal appearance.[33] However, many endoscopic findings have been reported in EGIDs, although they are almost all nonspecific. In EoG, these include erythema, ulceration, nodularity, friability, erosions, congestion, and pyloric stenosis. Patients with EoN have demonstrated villous dropout or flattening, erythema, congestion, ulceration, nodularity, friability, erosions, and stenosis. In patients with EoC, erythema, friability, congestion, and ulceration have been found.[3,32-34] As a result, there have been ongoing efforts to develop an endoscopic grading system.[35] Recently, the first endoscopic activity assessment system designed specifically for EoG, the Endoscopic Gastritis Endoscopic Reference System, was studied prospectively. The scores from this system strongly correlated with physician global assessment of endoscopic severity and were significantly correlated with histologic findings.[36]

Endoscopic examination is not only for visual assessment, but also to obtain biopsies to examine for eosinophilia and other histopathologic changes. However, there has been substantial variability in the number and location of biopsies as well as specimen handling,[37,38] and there is not yet a consensus on a preferred approach.[39,40] Because endoscopic appearance is often normal and eosinophilic involvement can be patchy, multiple biopsies should be taken from both normal and abnormal mucosa.[33,34,41] A recent study determined that 8 total gastric biopsies with 4 biopsies of antrum and 4 biopsies of body, as well as 4 biopsies from the duodenum, were needed to maximize the diagnostic sensitivity for EGIDs,[1,42] but this still needs to be confirmed. Because any layer of the GI wall can be infiltrated, full thickness biopsies may be required in circumstances in which EGID is strongly suspected but mucosal biopsies are normal.[24,43,44]

Interpreting biopsy results and the level of GI tract eosinophilia further complicates EGID diagnosis. Unlike in the esophagus, where eosinophils are not normally present,[39,45] eosinophils are normal tissue resident cells in the GI tract distal to the esophagus. Normal values have been estimated as follows: stomach (5-10 eosinophils/high-power field [eos/hpf]), duodenum (10-25 eos/hpf), and terminal ileum and cecum (likely >50 eos/hpf), with a decreasing number in the distal colon.[11,22,46] Thus, the specific thresholds required for documentation of pathologic eosinophilic infiltration continue to be debated.[47,48] The thresholds will also differ depending on the specific area involved.[9] Some proposed thresholds include at least 30 eos/hpf in the stomach,[40] at least 50 eos/hpf in the duodenum, at least 100 eos/hpf in the ascending colon, at least 85 eos/hpf in the descending colon, and at least 65 eos/hpf in the sigmoid colon.[49]

The last and most critical step when considering a diagnosis of non-EoE EGIDs is to fully consider and rule out alternative etiologies of secondary peripheral eosinophilia. These include drug reactions, infections, adrenal disorders, malignancy, connective tissue diseases, vasculitis, Crohn's disease, hypereosinophilic syndrome, graft-vs-host disease, and drug reactions, among others.[22] Additional extensive testing may be required to investigate these conditions, depending on the clinical presentation.

To summarize the general approach to diagnosis, it is important to maintain a high index of suspicion in cases of symptoms persisting without another explanation, acknowledge that patients may not have typical laboratory findings, and thoroughly consider differential diagnoses.[1] Making the diagnosis requires a careful endoscopic examination, taking a sufficient number of biopsies, and effectively communicating with the pathologist.[40] Lastly and crucially, a finding of increased eosinophilic infiltration does not determine that the patient has a non-EoE EGID, as other causes of eosinophilia must be systematically considered and ruled out.

Pathogenesis

Although the pathogenesis of non-EoE EGIDs has not been investigated as thoroughly as that of EoE, understanding of the underlying mechanism is increasing rapidly, particularly for EoG. There are several lines of evidence for an allergic etiology. As noted earlier, there is a strong association with concomitant atopic conditions.[19] Elevated serum immunoglobulin E levels have also been found in these patients,[50] as have mast cells.[51] Prior studies have shown improvement with dietary therapy,[47,52] and a recent prospective dietary trial in adults found that an elemental formula diet led to clinicopathologic improvement in all patients.[53] These and other data strongly suggest that antigen exposure triggers the condition,[54,55] with an associated T helper 2–mediated upregulation of interleukin 5 (IL-5).[4,56] EoG patients have also demonstrated a gastric transcriptome profile with a number of T helper 2 signatures.[4] Of note, emerging data may indicate that the pathogenesis of EoC may be different from other EGIDs and may not have the same allergic basis.[49]

Approach to Management

Treating non-EoE EGIDs remains challenging because there are no therapies that have been approved by the

US Food and Drug Administration and almost all related data are from case reports, small case series, and retrospective studies.[1,20,22] The first randomized trial of an experimental drug therapy was recently published[57] and, as noted previously, the first prospective dietary trial was conducted.[53] Despite the lack of effective treatment options, these patients should be followed closely to help manage symptoms and monitor for potential complications. Repeat endoscopy should also be performed to assess the endoscopic and histologic response following treatment, and to contextualize the symptom response.[33]

The most used class of medications are corticosteroids, but many other pharmacologic agents have been employed to treat non-EoE EGIDs. Clinicians often initially start treatment with systemic corticosteroids such as prednisone, but the results are variable[9] and doses are not well studied or standardized.[58,59] Most patients respond to corticosteroids initially, however.[60] In order to avoid side effects, the dosage and duration are minimized, as systemic corticosteroids should not be used chronically. For the next step in treatment, some data show successful transition from prednisone to budesonide.[61-64] Given the need to target release to different areas within the GI tract, enteric-coated budesonide must be directed to the relevant area of disease involvement. There are formulations of budesonide designed to release in the distal small bowel or colon, and these capsules can be swallowed intact when treating EoI or EoC. To treat EoG, the capsules must be opened and the granules crushed. When treating EoD or EoJ, the capsules can be opened and granules swallowed intact.[1,64,65]

Because long-term use of corticosteroids is not ideal, several other drug classes have been tried for treating non-EoE EGIDs.[60] There have been reports of mast cell agents, including cromolyn and ketotifen, improving symptoms, but the results are conflicting.[66,67] A case report discussed the leukotriene antagonist montelukast as an option.[68] Proton pump inhibitors are used to treat gastric erosions and ulcerations, although data indicating whether this class of medications can reverse the underlying pathology are limited.[1] A humanized anti–IL-5 antibody treatment reduced peripheral and tissue eosinophil counts, but failed to improve symptoms.[69] An anti–immunoglobulin E monoclonal antibody was associated with an improvement in symptoms.[16] A recent phase 2 randomized controlled trial of an anti–Siglec-8 antibody reduced GI eosinophils and symptoms when compared with placebo, but early data from the phase 3 study did not show a symptom benefit.[57] There may also be a role for anti-integrin therapy, as some patients who had previously failed to respond to other immunotherapies seemed to improve with vedolizumab (Entyvio, Takeda).[60,70] Proof-of concept data for an antibody against the IL-5 receptor have been released,[71-73] and this agent is under further study.

Although the data on dietary therapy remain limited, some version of dietary intervention likely has a role in treatment when chosen for highly motivated patients. Historically, most of the available evidence on the dietary treatment of EGIDs has lacked objective evaluation of clinical changes and more often included limited assessment of histologic response.[74] Elimination diets that aim to avoid foods that most commonly cause hypersensitivity, including the 6-food elimination diet, have been studied with mixed results.[52,75] The elemental formula diet, which eliminates food allergens, may show more promise. Earlier data showed some response to amino acid–based formulas in EGID patients with protein-losing enteropathy.[76] As noted previously, the first prospective trial of dietary therapy found that an elemental formula diet met its primary endpoint of histologic response (<30 eos/hpf) in all 15 patients who completed the trial.[53] There was also improvement in the secondary endpoints, including symptomatic improvement, endoscopic severity scoring, and physician global assessment. Further investigation will help determine the specifics of dietary treatment plans in carefully selected patients, as well as the approach to reintroduction of foods from highly restrictive diets.

Conclusion

Although non-EoE EGIDs are rare diseases that can present with a wide array of symptoms, they likely remain underdiagnosed. Because of imprecise terminology used historically, an updated and more systematic nomenclature has been established that may clarify how these diseases are recognized, categorized, and researched. Additionally, efforts to establish diagnostic guidelines are ongoing. Because the diagnosis requires a high index of suspicion, clinicians should consider non-EoE EGIDs in the differential diagnosis when symptoms do not seem to fit with more common etiologies. On endoscopy examination, an adequate number of biopsies is required even in the context of a normal appearance, and communication with the pathologist may also be necessary for quantification of eosinophil counts and descriptions of associated findings. Finally, evaluating for and excluding other causes of eosinophilia are mandatory before confirming an EGID diagnosis. Although understanding of EGID pathogenesis has increased, it remains incomplete. As such, there is a lack of targeted treatment options, and clinicians continue to rely primarily on corticosteroids for treatment. New therapies are actively being investigated through clinical trials.

As with other eosinophil-mediated diseases, many patients who have non-EoE EGIDs face barriers across

multiple domains.[77] Patients have reported a number of medical, psychosocial, and financial barriers based on their clinical presentation and ensuing diagnostic journey. There is a need to further characterize the natural course of the disease over the long term.[3] It is important to determine the optimal diagnostic approach, including the location of biopsies, number of biopsies, and threshold for pathologic eosinophilic counts.[37] A more sophisticated understanding of pathogenesis is needed to help identify clinically meaningful outcomes and guide management strategies.[9] This should include distinguishing pathologic differences depending on which area of the GI tract is predominantly involved.[2] Lastly, there is a need for well-designed investigations of pharmacologic and dietary therapies.

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