Eosinophils Beyond the Esophagus: A Review of Non-EoE Eosinophilic Gastrointestinal Diseases

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Abstract: For eosinophilic esophagitis (EoE), the most well researched of the eosinophilic gastrointestinal diseases (EGIDs), there is a plethora of knowledge for its diagnosis and management; however, much less guidance is available for the non-EoE EGIDs. Efforts have been made to characterize the clinical features, epidemiology, diagnosis, and natural history of EGIDs, as the frequency of the non-EoE EGIDs has continued to rise. The diagnosis of the different non-EoE EGIDs, eosinophilic gastritis, enteritis, and colitis, can be challenging because of their rarity and heterogeneous presentations which can lead to delayed diagnosis and poor health-related quality of life in affected patients. Guidelines for histologic evaluation and diagnostic criteria for non-EoE EGID are actively being developed. Effective management of non-EoE EGIDs is possible with currently available assessments and therapies, with more treatments on the horizon, highlighting the need for improved understanding of non-EoE EGIDs. This article will review the diagnosis and management of the non-EoE EGIDs, focusing on the consensus nomenclature, nuances in diagnosis, and management options.

Keywords
Eosinophilic gastrointestinal disease, eosinophilic gastritis, eosinophilic enteritis, eosinophilic gastroenteritis, eosinophilic colitis

Eosinophilic gastrointestinal diseases (EGIDs) represent a group of disorders characterized by eosinophilic infiltration of the gastrointestinal (GI) tract causing symptoms of organ dysfunction.[1] Although clinical symptoms may vary widely based upon the site and depth of disease, the unifying pathophysiology of EGIDs is a chronic, immune-mediated inflammation driven by an atopic response to food allergens without a secondary cause of tissue eosinophilia.[2] The therapeutic approach toward managing EGIDs focuses on reducing or eliminating the inflammation through either medications or diet to avoid potential food allergens.[3] The most common and best understood EGID is eosinophilic esophagitis (EoE), with decades of research supporting evidence-based clinical guidelines for its diagnosis and management.[4-6] The group of non-EoE EGIDs, including eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC), owing to their rarity and heterogeneous symptom presentation, is a burgeoning area of development.[2,7-11] This article will summarize the current

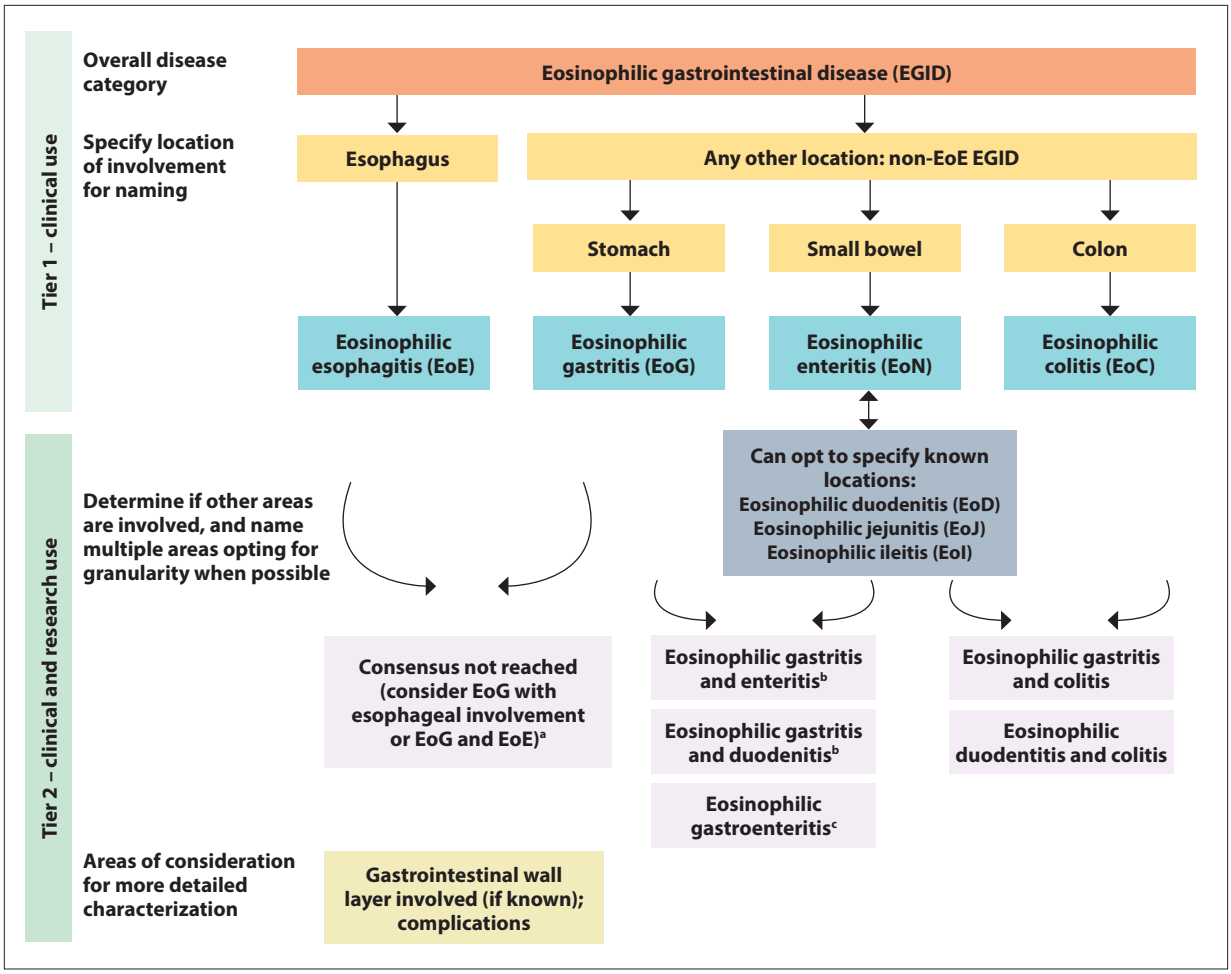

Figure 1. International consensus recommendations for EGID nomenclature.
[a]Additional research needed for this combined naming. [b]Perferred terms. [c]Should only be used to indicate both stomach and small bowel involvement. Adapted with permission from Dellon ES et al.[10]

understanding of non-EoE EGIDs, review the consensus recommendations for EGID nomenclature, and provide a suggested treatment algorithm with sample cases to illustrate the diagnosis and management of EoG.

Nomenclature for Eosinophilic Gastrointestinal Diseases

An important historical barrier to developing a clear understanding and diagnostic criteria for nonesophageal EGIDs has been ambiguity in disease definition and nomenclature.[3] This ambiguity was most pronounced for eosinophilic gastroenteritis, which had previously been used to refer to eosinophilic disease in the stomach, small bowel, or a combination of both. The resulting lack of clarity served as the impetus for an international consensus effort to establish a consistent, standardized nomenclature system for EGIDs.[10] The consensus nomenclature system designates EGIDs as an umbrella term for all GI diseases with pathologic eosinophilic infiltration, which are subclassified as EoE and non-EoE EGIDs. The non-EoE EGIDs are further named according to the site of organ involvement: EoG is specific to the stomach; EoN is specific to the small bowel (with option to specify further as duodenitis, jejunitis, and/or ileitis); and EoC is specific to the colon. Additional considerations are involved when multiple locations of disease are present, which occurs in an estimated 41% of patients with non-EoE EGIDs and is more common in children.[12] When 2 or more sites of disease are present, all locations are to be specifically named (ie, eosinophilic gastritis and enteritis; eosinophilic gastroenteritis may also be used only if there is both gastric and intestinal disease).[10] The primary EGID location is determined based upon the predominant symptoms and endoscopic features (eg, if the predominant presentation was eosinophil-rich gastric eosinophilia, the disease would be primarily classified as EoG). When known, the depth of involvement should be noted together with associated

complications (eg, serosal EoG and mucosal EoG with presence of tissue eosinophilia and eosinophil-rich ascites). This nomenclature is highlighted in Figure 1.

Owing to the relatively recent establishment of standardized nomenclature for non-EoE EGIDs in 2022, the majority of existing literature summarized in the current review may be limited by ambiguous terminology. One notable example is the International Classification of Disease (ICD) coding system, which does not align with recommended nomenclature (3 codes currently exist: K20.0 for EoE, K52.81 for EoG or eosinophilic gastroenteritis, and K52.82 for EoC), yet has been the basis for many epidemiologic studies of non-EoE EGIDs.

One important contribution of standardized nomenclature for non-EoE EGIDs is that it has been the first step toward the development of clinical guidelines, which had been previously lacking. In 2023, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published clinical guidelines for childhood non-EoE EGIDs.[11] The published pediatric guidelines formally adopted the consensus nomenclature, recommending the prefix eo followed by the specific organ involved as the naming convention. Guidelines for adults remain forthcoming.

Clinical Features, Epidemiology, Diagnosis, and Natural History of Non-EoE Eosinophilic Gastrointestinal Diseases

Eosinophilic Gastritis and Enteritis

EoG and EoN have frequently been grouped together in literature as eosinophilic gastroenteritis prior to the development of consensus nomenclature and were originally classified in 1970 based upon the predominant intestinal layer involved (mucosal, muscular, and serosal).[13,14] The most common form of disease is the mucosal variant, which accounts for 44% to 57% of cases and affects the inner most layer of the bowel wall with typical endoscopic features.[15,16] Classic symptoms of the mucosal variant of EoG and EoN include abdominal pain, nausea, vomiting, bloating, diarrhea, and early satiety. In cases of significant small bowel involvement, findings of malabsorption and protein-losing enteropathy can be seen.[15,16] The muscular form of EoG and EoN may present with obstructive symptoms such as pyloric or duodenal stenosis and gastric outlet obstruction that can present with signs of more profound abdominal pain, nausea, and vomiting; these cases comprise 12% to 30% of patients.[15,16] Lastly, the serosal forms of EoG and EoN, characterized by eosinophilic-rich ascites with associated abdominal bloating, distension, and pain, comprise 12.5% to 49% of cases.[15,16] It is important to note that owing to the rarity of both muscular and serosal variants of the disease, clinical characteristics and outcomes of these disease forms are poorly described compared with the mucosal variant of the disease. The symptoms of EoG and EoN are nonspecific, with the most common being nausea and vomiting (54%), followed by abdominal pain (48%).[12] Other potential symptoms include, but are not limited to, bloating, poor appetite, early satiety, diarrhea, and weight loss.[17] Evidence of pathologic tissue eosinophilia is the cornerstone of diagnosis; however, other clinical features that may suggest EoG or EoN are an elevated peripheral eosinophil count and/or low serum albumin level—both are associated with higher biopsy diagnostic yield.[18] Although an initial retrospective study suggested that normal endoscopic appearance is the most common finding in EoG,[19] a recent prospective study of 98 EoG patients found this to be the minority (8% of patients).[20] The study reported common endoscopic findings of erythema (72%), raised lesions (49%), erosions (46%), and granularity (35%). These results led to the development of the EG Endoscopic Reference System (EG-REFS), which incorporates features of erosion/ulceration, granularity, raised lesions, erythema, friability, fold thickness, and pyloric stenosis.[20] EG-REFS scores (separately assessed in the fundus, body, and antrum with a composite score calculated as a sum of all 3 locations) were found to strongly correlate with physician global assessment of endoscopic severity, with antral involvement being more common than fundus or body. The rarity and nonspecific symptoms of EoG and EoN highlight the importance of maintaining a high index of suspicion in order to make a diagnosis, particularly if features of peripheral eosinophilia, hypoalbuminemia, or atopic milieu are present.

The frequency of EoG, EoN, and EoC has been gradually rising from 2005 through 2016.[12] Accurate and precise estimates of prevalence and incidence have been hindered by the lack of standardized, consistent definitions and terminology prior to 2022, although one study of ICD codes in an insurance claims database estimates the prevalence of EoG to be 6.3 per 100,000.[21] The risk of EoG and EoN is higher among relatives of patients with EoE, raising the possibility of genetic risk factors.[22] However, a study of genome-wide transcript profiles also showed that EoG has a transcriptome markedly distinct from EoE, with an overlap of only 7%.[23] A retrospective study of 142 EoG patients across 6 centers in the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) showed that 57% had at least 1 other atopic disease; in 123 patients with eosinophilic gastroenteritis, 73% had another atopic disease.[12] Favorable results from pediatric and adult studies of empiric elimination and elemental diets provide additional evidence for EoG and

EoN being food allergen–driven atopic inflammatory diseases, similar to EoE.[24-26] Unlike EoE, which is typically a chronic disease, there have been 3 clinical courses described in EoG and EoN. These were characterized in a 2011 cohort study, with 44% of patients having a single flare of disease without recurrence, 36% of patients developing a recurring course with multiple flares interspersed among periods of remission, and 21% of patients developing a chronic course without remission.[15] A recent retrospective study of EGIDs in adults and children demonstrated that a continuous course was most common in EoG (78%), whereas patients with eosinophilic gastritis and enteritis (29%) and eosinophilic enteritis and colitis (50%) had the highest proportion of progressive and relapsing disease, respectively.[27] This study also showed that while a continuous disease course was common in children (71%), adults typically experienced relapsing (39%) and progressive disease (18%).[27] Another recent pediatric study demonstrated that 18% of patients experienced disease complications, including upper GI bleeding, moderate or severe anemia, hypoalbuminemia, bowel perforation, bowel obstruction, surgery, and hospitalization, further emphasizing the need for early intervention and treatment to prevent disease complications.[28] The varying natural history of EoG and EoN, like the wide spectrum of symptoms these diseases may produce, demonstrates the significant heterogeneity in clinical presentation that differentiates non-EoE EGIDs from EoE. It is also important to note that in addition to the paucity of literature about non-EoE EGIDs, existing literature has been heterogeneous in how studies define disease as well as clinical courses, and most studies do not have complete histologic, endoscopic, or symptom outcome measures, as they are mostly retrospective in nature. The fact that symptoms are very heterogeneous can further complicate assessment and may cause some symptom/histology disconnect, similar to what is seen with EoE.[29] This heterogeneity of symptoms and disease presentation has led to delayed diagnosis for many patients, contributing negatively to health-related quality of life.[8,30,31] Despite the heterogeneity seen in studies, chronicity is a required feature of non-EoE EGIDs and should be considered when diagnosing these diseases.

Eosinophilic Colitis

EoC is the rarest and most enigmatic EGID, with an estimated prevalence of 3.3 per 100,000.[21] Like other EGIDs, there is a high prevalence of comorbid atopic conditions, which is present in 48% of cases. Symptoms are similarly nonspecific and may include abdominal pain (60%), diarrhea (52%), nausea and vomiting (38%), and bloody stools (24%).[21,32] The muscular form of EoC may result in obstructive symptoms as well as perianal disease.[33-35] The focus of study in EoC has been elucidating the underlying pathophysiology. One study of RNA sequencing from colonic biopsies in patients with EoC, Crohn's disease, and normal controls found that compared with other EGIDs, EoC had minimal evidence of a strong allergic type 2 immune response.[7] Furthermore, scores based upon the EoC transcriptome were reversible with disease remission, which distinguished EoC from Crohn's disease. These findings suggest that EoC is a distinct disease from not only inflammatory bowel disease (IBD), but also other EGIDs. Evidence of abnormal tissue eosinophilia without a secondary cause is required in the diagnosis of EoC, like with all EGIDs. However, this is practically more nuanced in EoC owing to the wide spectrum of what is considered abnormal based upon colonic segment. Originally, histology above twice the normal number of eosinophils per high-power field (eos/hpf) in the lamina propria was proposed.[34] These initial thresholds ranged from at least 100 eos/hpf in the proximal colon, at least 84 eos/hpf in the transverse and descending colon, and at least 64 eos/hpf in the rectosigmoid colon; similar thresholds were utilized in recent consortium research.[7] Accurate diagnosis of EoC therefore requires the endoscopist and pathologist to be aware of the varying spectrum of normal tissue eosinophilia and separate biopsy specimens into the appropriate colonic segments. Alternative diagnoses need to be carefully considered in EoC, which remains a diagnosis of exclusion, with particular attention paid to the possibilities of IBD, autoimmune disease (eg, lupus, eosinophilic granulomatosis with polyangiitis), and hypereosinophilic syndrome.[32]

Non-EoE Eosinophilic Gastrointestinal Diseases With Esophageal Eosinophilia

As more is learned about non-EoE EGIDs, it is becoming increasingly apparent that many patients present with multisegment involvement (ie, combination of EoG and EoN). Although traditionally EoE was defined as a disease isolated to the esophagus without involvement of other organs, this conceptual definition was created 2 decades before non-EoE EGIDs were well understood.

There are often 2 scenarios encountered that include esophageal involvement. The first is in patients with EoG/EoN/EoC who have concomitant esophageal eosinophilia without much symptomatology. More needs to be understood about the significance of these esophageal eosinophils and whether these patients will ultimately develop symptoms and clinical presentation of EoE. The second more common scenario is patients who have symptoms, endoscopic features, and histologic confirmation of EoE in addition to EoG, EoN, or EoC. In this scenario, treatment should be targeted and focused both on esophageal dysfunction as well as the other organs involved. One ret-

Table. Suggested Histologic Criteria for Non-EoE EGIDs[a]

Disease location	Histologic cutoff needed	Chronic symptoms present
Eosinophilic gastritis	≥30 eos/hpf[b] ≥40 eos/hpf[c]	Yes
Eosinophilic enteritis	≥50 eos/hpf[b] in duodenum ≥60 eos/hpf[c] in duodenum ≥60 eos/hpf in jejunum and ileum	Yes
Eosinophilic colitis	≥100 eos/hpf in cecum and ascending colon ≥80 eos/hpf in transverse and descending colon ≥60 eos/hpf in rectum and sigmoid	Yes

EGIDs, eosinophilic gastrointestinal diseases; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field.

[a]EGIDs are clinicopathologic diseases, so both histologic thresholds as well as chronicity of symptoms need to be present to make a diagnosis.

[b]Consistent with prior pediatric guidelines.[11]

[c]Based on reassessment and extrapolation of normal eosinophilic values in the GI tract.[47]

rospective review showed that 43% of patients had EGID with esophageal involvement, and those patients had a longer diagnostic delay, had more dysphagia, required more chronic therapy, and exhibited more progressive disease than patients with isolated EGID.[27]

Approach to Diagnosis of Non-EoE Eosinophilic Gastrointestinal Diseases

The diagnostic approach to non-EoE EGIDs requires consideration of initial presentation to pursue the appropriate diagnostic workup, and thorough evaluation in each case to exclude alternative diagnoses.[11] If mucosal disease is suspected, endoscopic evaluation following biopsy protocols is necessary. If symptoms suggest muscular disease with obstructive features, cross-sectional imaging is required with full-thickness or surgical specimens often providing tissue for diagnosis. Lastly, if symptoms suggest serosal disease with ascites, ultrasound or cross-sectional imaging is appropriate with diagnostic paracentesis serving to provide evidence of abnormal eosinophilia. If disease involvement suggests extensive small bowel involvement, workup with double balloon enteroscopy or video capsule endoscopy may need to be pursued.

Nuances in Histologic Evaluation

In the absence of clear histologic diagnostic guidelines prior to 2023, the historical threshold utilized for the diagnosis of EoG was 30 or more eos/hpf in at least 5 hpfs in any part of the gastric mucosa.[23,34,35] In randomized trials, a threshold of 30 or more eos/hpf in at least 3 hpfs had also been adopted for eosinophilic duodenitis (EoD),[35] although up to 25 eos/hpf may be seen in normal duodenal mucosa.[34] In the first publication of formal pediatric guidelines for diagnosis of EoG and EoD, the ESPGHAN/NASPGHAN agree with utilizing a threshold of 30 or more eos/hpf for EoG but recommended a higher threshold of 50 or more eos/hpf for EoD.[11] Biopsies of the upper GI tract, when EoG and EoD are suspected, should include the gastric antrum, body, and duodenum.

In our practice, we obtain at least 8 specimens from the stomach, ideally targeted to areas of overt inflammation (at least 4-6 in the antrum, and the remainder in the body), as well as 6 specimens from the duodenum (including at least 2 from the duodenal bulb). For eosinophilic ileitis (EoI) and EoC in the lower GI tract, the ESPGHAN/NASPGHAN guidelines recommend thresholds of at least 60 eos/hpf for the terminal ileum, at least 100 eos/hpf in the cecum and ascending colon, at least 80 eos/hpf in the transverse and descending colon, and at least 60 eos/hpf in the rectum and sigmoid colon (Table).[11] To accurately interpret eosinophil counts, colonoscopy biopsy specimens should thus be separated into 4 bottles at the minimum when EoI or EoC is suspected (terminal ileum, cecum/ascending colon, transverse/descending colon, and rectum/sigmoid colon). The CEGIR is leading a multidisciplinary working group to develop and refine these consensus guidelines, which will provide additional insight into the diagnostic criteria.

Management of Non-EoE Eosinophilic Gastrointestinal Diseases

The therapeutic goals in management of EGIDs include resolution of symptoms as well as endoscopic and histologic abnormalities in the short term, with prevention of disease-related complications in the long term (Figure 2).[11] The most commonly used therapies in management of EoG and EoN have included proton pump inhibitors (PPIs), swallowed topical corticosteroids, systemic corticosteroids (often used to induce remission), and food elimination diets.[11,12] Although clinicians are often familiar with topical corticosteroid administration for EoE, administering topical corticosteroids in the treatment of non-EoE EGIDs requires an understanding of which intestinal site of disease is the target. To treat EoG and target the stomach, enteric-coated budesonide capsules must be opened, and the granules inside crushed and often solubilized in liquid or in a small amount of applesauce or like food.[17,36] To target the proximal small bowel, patients

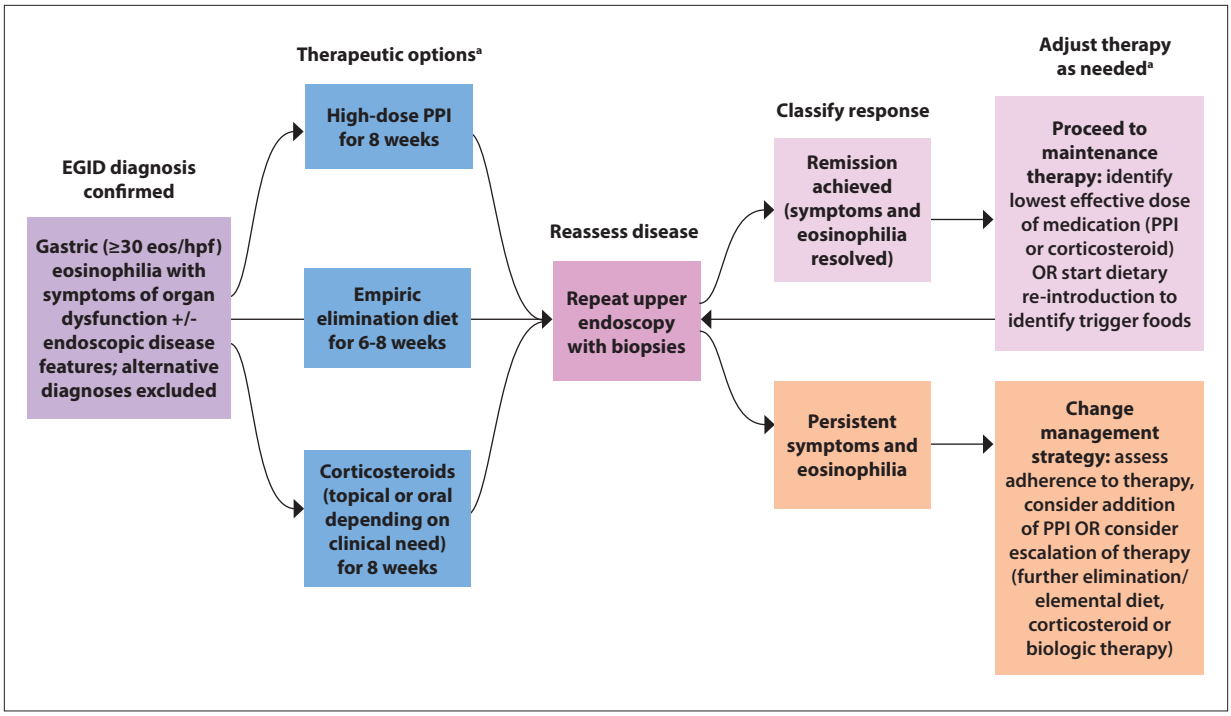

Figure 2. Suggested treatment algorithm for non-EoE EGIDs.

EGIDs, eosinophilic gastrointestinal diseases; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; PPI, proton pump inhibitor.
[a]Allergy referral as indicated for allergic comorbidities and environmental exposures.

must be instructed to open enteric-coated budesonide capsules and swallow the granules inside. Targeting the distal small bowel requires swallowing the capsules intact, like in the treatment of Crohn's ileitis.[17] Cromolyn sodium and ketotifen, both mast cell stabilizers, have also been used as adjunctive, corticosteroid-sparing therapies with some success described in small case series.[33] Mesalamine agents have also been utilized in cases of EoC.[12] In select patients who may want an alternative means of corticosteroid-sparing therapy, empiric elimination diets or elemental diets may be considered after careful evaluation of nutritional status. A 2023 multicenter prospective study of an elemental diet for 15 adults with EoG and/or EoN demonstrated a promising 100% histologic response rate after 6 weeks of treatment. This study also showed improved endoscopic and symptomatic features as well as improvement in gene dysregulation based on transcriptomic signature.[26] Although endoscopy with biopsies remains the primary modality to assess treatment response for mucosal EGIDs, an additional metric that may be useful to monitor disease activity is peripheral eosinophilia.[11]

Multiple biologic therapies are on the horizon for non-EoE EGIDs, either undergoing active study in clinical trials or being described in case reports and series.[37] The first published study of a biologic for EoG and EoD evaluated an anti–Siglec-8 antibody lirentelimab (AK002, Allakos) in a randomized placebo-controlled trial. The initial phase 2 study showed promising results (treatment response in 63% of patients given lirentelimab compared with 5% of patients given placebo; $P<.001$).[35] These encouraging data led to a phase 3 trial, with early results reporting that lirentelimab met histologic coprimary endpoints but ultimately missed symptomatic endpoints.[38] In a study of patients with hypereosinophilic syndrome and GI tissue eosinophilia, benralizumab (Fasenra, AstraZeneca) completely depleted peripheral and GI tissue eosinophilia, but clinical response was heterogeneous.[39] Although all study patients reported improvement of symptoms initially, some developed recurrent symptoms or flares without accompanying peripheral or tissue eosinophilia, typically with liberalizing diet or tapering background therapy. In another recent single-site randomized controlled phase 2 trial of benralizumab in adult and adolescent EoG patients, 77% of patients in the benralizumab arm achieved histologic remission after 12 weeks (compared with 8% of patients in the placebo arm).[40] However, significant differences were not detected across patient-reported outcomes, EG-REFS score, EoG histology total score, or peripheral eosinophil counts.[41] Dupilumab (Dupixent, Sanofi and Regeneron) is a promising candidate, currently approved by the US Food and Drug Administration for EoE, that anecdotally has led to symptomatic and histologic

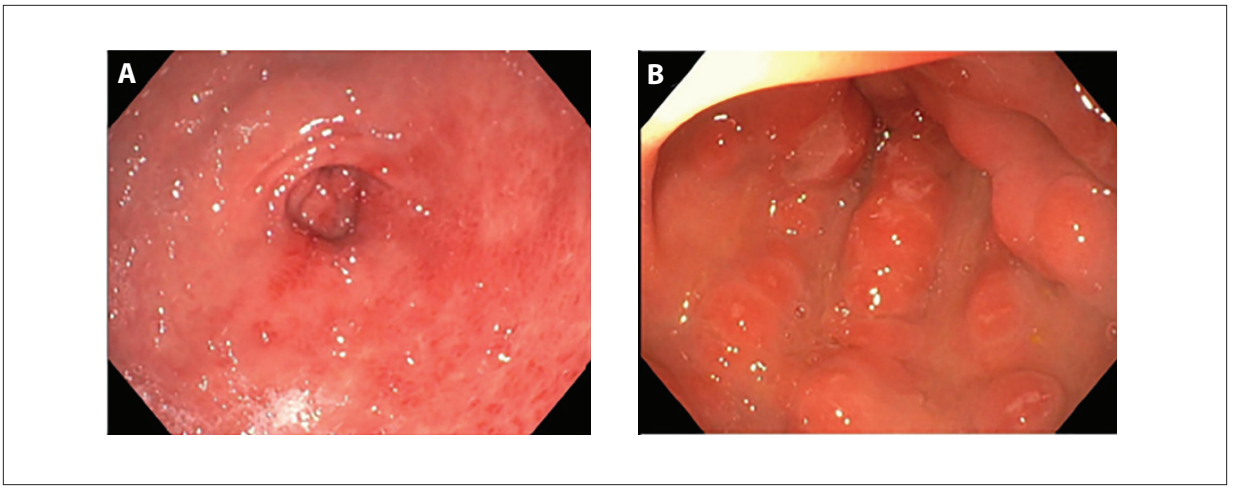

Figure 3. Endoscopic images of 2 different patients with eosinophilic gastritis. Panel A shows gastric erythema, loss of vascular pattern, and some nodularity in a 50-year-old woman with history of asthma and allergic rhinitis, chronic episodic epigastric pain, nausea, vomiting, early satiety, and diarrhea. Symptoms are mild. Biopsies of the stomach demonstrate greater than 80 eos/hpf, and duodenal biopsies show 25 eos/hpf. She has peripheral eosinophilia, with an absolute eosinophil count of 800 cells/μL. Treatment with PPIs and crushed budesonide 9 mg daily results in resolution of her tissue eosinophilia on follow-up endoscopy. Clinically, her symptoms and peripheral eosinophilia have resolved. She is maintained on PPI therapy and is ultimately able to deescalate crushed budesonide to 3 mg daily. Panel B shows large deep gastric ulcers in a 30-year-old woman with severe epigastric abdominal pain, nausea, vomiting, and inability to adequately maintain her nutrition causing a 15-lb weight loss. She is admitted to the hospital with dehydration. Laboratory results show peripheral eosinophilia of 1600 cells/μL and low albumin of 3.2 g/dL. Biopsies show prominent eosinophilia (up to 100 eos/hpf). Due to the severity of her symptoms, she is started on intravenous pantoprazole and systemic treatment with prednisone 40 mg daily. After several days of therapy, her symptoms abate, and she is discharged home on PPI therapy and a prednisone taper, followed by transition to crushed budesonide. Her disease has been well maintained on crushed budesonide, and follow-up endoscopy shows continued remission.

eos/hpf, eosinophils per high-power field; PPI, proton pump inhibitor. Images courtesy of Dr Gonsalves.

improvement across case reports and series for non-EoE EGIDs.[41-43] It is currently in a phase 2 and 3 clinical trial among adult and adolescent patients who have EoG with or without EoD through the CEGIR (NCT05831176). Potential targets for future study include the Janus kinase inhibitor upadacitinib (Rinvoq, AbbVie), with treatment success described in a report of an EoG and EoD patient who had been refractory to lirentelimab and an elemental diet.[44] Two other case reports have been published suggesting that vedolizumab (Entyvio, Takeda) may also provide benefit in treatment of EGIDs.[45,46] These biologic therapies under study are anticipated to fill an important gap in care for patients with persistent, severe, and/or refractory non-EoE EGIDs.

Although there is significant promise in these agents, several of the completed studies have highlighted the disconnect between histologic remission and symptomatic remission, which is a trend seen in recent EoE studies. In non-EoE EGIDs, this disconnect can be even more pronounced given the heterogeneity of symptom presentation. Similar to the approach in EoE, in clinical care of non-EoE EGIDs, it is important to understand why symptoms may persist after histologic remission is obtained. In patients who have achieved histologic remission but still have ongoing symptoms, it is important to consider dysmotility (gastric emptying scan to rule out gastroparesis with ongoing nausea) as well as potential imaging to rule out more distal disease (computed tomography enterography or magnetic resonance enterography) and assess for potential functional bowel disease/hyperawareness/hypervigilance. In the latter cases, referral to a behavioral health psychologist can be helpful. In patients with symptomatic improvement but ongoing histologic inflammation, treatment should be tailored based on degree of histologic and endoscopic inflammation. In patients with marginal histologic inflammation and endoscopic change who have dramatic symptom response, it is important to continue to follow these patients clinically to determine disease trajectory and need to escalate treatment. In patients who are symptomatically improved but still with significant histologic and/or endoscopic changes, escalation of treatment would be suggested to help prevent disease complications listed previously.

Overall, treatment choices for non-EoE EGIDs are based on the organ involved, the disease severity, and discussion with patients on their goals of care. Treatment

options should be tailored and may vary based on the overall disease presentation with some patients needing combination therapy. Two examples of approaches to treatment are outlined in Figure 3.

Conclusion

EGIDs outside of the esophagus are rare disorders that are a current focus of research to improve the clinical care of affected patients. In recent years, consensus nomenclature has allowed for the development of clinical guidelines to optimize and standardize care for non-EoE EGIDs. Pediatric guidelines are now available, with guidelines for adults in the process of being developed. Disease presentation varies widely and is dependent on the site involved, depth of involvement, and long-term course; over half of patients experience a chronic course of disease with relapsing or continuous symptoms. Corticosteroid treatments, both systemic and topical, have been a cornerstone of management together with elimination diets and adjunctive medications such as PPIs and mast cell stabilizers. Biologic therapies are the next frontier in management, and clinical trials are underway with multiple other candidates reviewed in case reports. Early diagnosis is critical to improving clinical care and quality of life in patients with non-EoE EGIDs.

Disclosures

Dr Lam has no relevant conflicts of interest to disclose. Dr Gonsalves is a consultant for Apogee, Exact Sciences, Eupraxia, Uniquity, EsoCap, Sanofi, Regeneron, Takeda, and BMS; serves on the speakers' bureau for Sanofi, Regeneron, and Takeda; and receives publication royalties from UpToDate.

References

1. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol.* 2004;113(1):11-28.
2. Walker MM, Potter M, Talley NJ. Eosinophilic gastroenteritis and other eosinophilic gut diseases distal to the oesophagus. *Lancet Gastroenterol Hepatol.* 2018;3(4):271-280.
3. Gonsalves N. Eosinophilic gastrointestinal disorders. *Clin Rev Allergy Immunol.* 2019;57(2):272-285.
4. O'Shea KM, Aceves SS, Dellon ES, et al. Pathophysiology of eosinophilic esophagitis. *Gastroenterology.* 2018;154(2):333-345.
5. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE Conference. *Gastroenterology.* 2018;155(4):1022-1033.e10.
6. Hirano I, Chan ES, Rank MA, et al; AGA Institute Clinical Guidelines Committee; Joint Task Force on Allergy-Immunology Practice Parameters. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. *Gastroenterology.* 2020;158(6):1776-1786.
7. Shoda T, Collins MH, Rochman M, et al; Consortium of Eosinophilic Gastrointestinal Diseases Researchers (CEGIR). Evaluating eosinophilic colitis as a unique disease using colonic molecular profiles: a multi-site study. *Gastroenterology*. 2022;162(6):1635-1649.
8. Jensen ET, Aceves SS, Bonis PA, et al; CEGIR investigator group. High patient disease burden in a cross-sectional, multicenter contact registry study of eosinophilic gastrointestinal diseases. *J Pediatr Gastroenterol Nutr*. 2020;71(4):524-529.
9. Reed CC, Genta RM, Youngblood BA, Wechsler JB, Dellon ES. Mast cell and eosinophil counts in gastric and duodenal biopsy specimens from patients with and without eosinophilic gastroenteritis. *Clin Gastroenterol Hepatol.* 2021;19(10):2102-2111.
10. Dellon ES, Gonsalves N, Abonia JP, et al. International consensus recommendations for eosinophilic gastrointestinal disease nomenclature. *Clin Gastroenterol Hepatol.* 2022;20(11):2474-2484.e3.
11. Papadopoulou A, Amil-Dias J, Auth MKH, et al. Joint ESPGHAN/NASPGHAN guidelines on childhood eosinophilic gastrointestinal disorders beyond eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr.* 2024;78(1):122-152.
12. Pesek RD, Reed CC, Muir AB, et al; Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR). Increasing rates of diagnosis, substantial co-occurrence, and variable treatment patterns of eosinophilic gastritis, gastroenteritis, and colitis based on 10-year data across a multicenter consortium. *Am J Gastroenterol.* 2019;114(6):984-994.
13. Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. *Medicine (Baltimore).* 1970;49(4):299-319.
14. Pineton de Chambrun G, Dufour G, Tassy B, et al. Diagnosis, natural history and treatment of eosinophilic enteritis: a review. *Curr Gastroenterol Rep*. 2018;20(8):37.
15. Pineton de Chambrun G, Gonzalez F, Canva JY, et al. Natural history of eosinophilic gastroenteritis. *Clin Gastroenterol Hepatol*. 2011;9(11):950-956.e1.
16. Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut.* 1990;31(1):54-58.
17. Dellon ES. Eosinophilic gastrointestinal diseases beyond eosinophilic esophagitis. *Am J Gastroenterol.* 2022;117(5):697-700.
18. Brenner EJ, Greenberg SB, Chang NC, Corder SR, Cowherd EL, Dellon ES. Peripheral eosinophilia and hypoalbuminemia are associated with a higher biopsy diagnostic yield for eosinophilic gastroenteritis. *Clin Res Hepatol Gastroenterol.* 2021;45(5):101746.
19. Pesek RD, Reed CC, Collins MH, et al; Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR). Association between endoscopic and histologic findings in a multicenter retrospective cohort of patients with non-esophageal eosinophilic gastrointestinal disorders. *Dig Dis Sci.* 2020;65(7):2024-2035.
20. Hirano I, Collins MH, King E, et al; CEGIR investigators. Prospective endoscopic activity assessment for eosinophilic gastritis in a multisite cohort. *Am J Gastroenterol.* 2022;117(3):413-423.
21. Jensen ET, Martin CF, Kappelman MD, Dellon ES. Prevalence of eosinophilic gastritis, gastroenteritis, and colitis: estimates from a national administrative database. *J Pediatr Gastroenterol Nutr.* 2016;62(1):36-42.
22. Allen-Brady K, Colletier KJ, Woller S, et al. Eosinophilic gastritis and enteritis are increased in families with eosinophilic esophagitis. *Am J Gastroenterol.* 2023;118(2):263-268.
23. Caldwell JM, Collins MH, Stucke EM, et al. Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. *J Allergy Clin Immunol.* 2014;134(5):1114-1124.
24. Chehade M, Magid MS, Mofidi S, Nowak-Wegrzyn A, Sampson HA, Sicherer SH. Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up. *J Pediatr Gastroenterol Nutr.* 2006;42(5):516-521.
25. Gonsalves N, Doerfler B, Yang GY, Hirano I. S1861 A prospective clinical trial of six food elimination diet or elemental diet in the treatment of adults with eosinophilic gastroenteritis. *Gastroenterology.* 2009;136(5):A-280.
26. Gonsalves N, Doerfler B, Zalewski A, et al. Prospective study of an amino acid-based elemental diet in an eosinophilic gastritis and gastroenteritis nutrition trial. *J Allergy Clin Immunol.* 2023;152(3):676-688.
27. Ketchem CJ, Reed CC, Dellon ES. The natural history of eosinophilic gastrointestinal diseases is influenced by age of onset and location of involvement. *Am J Gastroenterol.* 2024;119(9):1813-1820.
28. Quinn LA, Burger C, Nguyen B, et al. Natural histories and disease complications in a cohort of 151 children with gastric or duodenal eosinophilia. *Am J Gastroenterol.* 2024;119(7):1298-1308.
29. Safroneeva E, Pan Z, King E, et al; Consortium of Eosinophilic Gastrointestinal Disease Researchers. Long lasting dissociation of esophageal eosinophilia and symptoms after dilation in adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol.* 2022;20(4):766-775.e4.
30. Bedell A, Taft T, Craven MR, Guadagnoli L, Hirano I, Gonsalves N. Impact on health-related quality of life in adults with eosinophilic gastritis and gastroenteritis: a qualitative assessment. *Dig Dis Sci.* 2018;63(5):1148-1157.
31. Taft TH, Hirano I, Gonsalves N. Initial validation of the eosinophilic gastritis

and gastroenteritis quality of life scale. *Gastro Hep Adv.* 2025;4(5):100627.
32. Impellizzeri G, Marasco G, Eusebi LH, Salfi N, Bazzoli F, Zagari RM. Eosinophilic colitis: a clinical review. *Dig Liver Dis.* 2019;51(6):769-773.
33. Uppal V, Kreiger P, Kutsch E. Eosinophilic gastroenteritis and colitis: a comprehensive review. *Clin Rev Allergy Immunol.* 2016;50(2):175-188.
34. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. *Gastroenterol Clin North Am.* 2014;43(2):257-268.
35. Dellon ES, Peterson KA, Murray JA, et al. Anti-Siglec-8 antibody for eosinophilic gastritis and duodenitis. *N Engl J Med.* 2020;383(17):1624-1634.
36. Prussin C. Eosinophilic gastroenteritis and related eosinophilic disorders. *Gatroenterol Clin North Am.* 2014;43(2):317-327.
37. Rossi CM, Lenti MV, Merli S, et al. Primary eosinophilic gastrointestinal disorders and allergy: clinical and therapeutic implications. *Clin Transl Allergy.* 2022;12(5):e12146.
38. Allakos announces topline phase 3 data from the ENIGMA 2 study and phase 2/3 data from the KRYPTOS Study in patients with eosinophilic gastrointestinal diseases. https://www.biospace.com/allakos-announces-topline-phase-3-data-from-the-enigma-2-study-and-phase-2-3-data-from-the-kryptos-study-in-patients-with-eosinophilic-gastrointestinal-diseases. Published December 21, 2021. Accessed July 21, 2025.
39. Kuang FL, De Melo MS, Makiya M, et al. Benralizumab completely depletes gastrointestinal tissue eosinophils and improves symptoms in eosinophilic gastrointestinal disease. *J Allergy Clin Immunol Pract.* 2022;10(6):1598-1605.e2.
40. Kliewer KL, Murray-Petzold C, Collins MH, et al. Benralizumab for eosinophilic gastritis: a single-site, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Gastroenterol Hepatol.* 2023;8(9):803-815.
41. Sia T, Bacchus L, Tanaka R, Khuda R, Mallik S, Leung J. Dupilumab can induce remission of eosinophilic gastritis and duodenitis: a retrospective case series. *Clin Transl Gastroenterol.* 2024;15(1):e00646.
42. Mori F, Renzo S, Barni S, et al. Dupilumab treatment of eosinophilic gastrointestinal disease in an adolescent. *Pediatr Allergy Immunol.* 2023;34(6):e13973.
43. Watanabe S, Uchida H, Fujii R, et al. The efficacy of dupilumab in induction and maintenance of remission in an adult patient with steroid-dependent eosinophilic enteritis (EoN). *Clin J Gastroenterol.* 2023;16(4):527-531.
44. Fu J, Sia T, Solecki R, et al. Clinical and histologic remission achieved with upadacitinib in a patient with refractory eosinophilic gastritis and duodenitis. *J Allergy Clin Immunol Pract.* 2024;12(6):1649-1651.
45. Kim HP, Reed CC, Herfarth HH, Dellon ES. Vedolizumab treatment may reduce steroid burden and improve histology in patients with eosinophilic gastroenteritis. *Clin Gastroenterol Hepatol.* 2018;16(12):1992-1994.
46. Grandinetti T, Biedermann L, Bussmann C, Straumann A, Hruz P. Eosinophilic gastroenteritis: clinical manifestation, natural course, and evaluation of treatment with corticosteroids and vedolizumab. *Dig Dis Sci.* 2019;64(8):2231-2241.
47. Turapov T, Uchida AM, Pletneva MA, Peterson KA. Gastrointestinal tissue quantification in healthy adult volunteers. *Gastroenterology.* 2025;169(1):158-160.e2.