Eosinophilic gastrointestinal disease below the belt

Robert D. Pesek, MD,[a] and Marc E. Rothenberg, MD, PhD[b] *Little Rock, Ark, and Cincinnati, Ohio*

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Eosinophilic gastrointestinal diseases (EGIDs) are rare diseases of the gastrointestinal tract caused by allergic inflammation and gastrointestinal dysfunction. Initially described in 1978, recognition of these disorders has greatly increased over the past several decades. Thus far, eosinophilic esophagitis (EoE) has received the most focus, leading to significant advances in understanding of disease mechanisms, widely adopted guidelines for diagnosis and management, and ongoing clinical trials to provide expanded treatment options. EGIDs can affect other parts of the gastrointestinal tract and include eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC), yet these diseases are barely understood compared with EoE. Much of the research to date is limited to case series or single-center experiences, and there are no well-established guidelines for diagnosis or management. In this article the current state of EGIDs will be reviewed.

EoE: THE GOLD STANDARD

Originally considered a manifestation of gastroesophageal reflux, EoE is now known to be an immune-mediated disease characterized by T_H2-driven eosinophilic inflammation of esophageal tissues.[1] The incidence and prevalence of EoE have significantly increased over the past 2 decades, with current estimates of incidence to be 10 per 100,000 persons and prevalence between 10 and 57 per 100,000 persons.[2] Significant advances have been made in elucidation of underlying disease mechanisms, identification of endotypes of disease, and standardization of outcome measures. Genetic susceptibility loci have been identified at 5q22 and 2p23, which encode for the T_H2-promoting cytokine thymic stromal lymphopoietin and the esophageal barrier protein calpain-14, as well as variants near the *STAT6* and *LRRC32* genes.[3] Recent work with transcript profiling of esophageal mucosal biopsy specimens has allowed patients to be divided into 3 endotypes, including a relative benign group, an inflammatory group, and a fibrostenotic group.[4]

Early therapeutic trials were hampered by a lack of standardized, patient-reported endoscopic and histologic outcomes that, in part, prevented approval of several novel therapeutics. Over the past 5 years, a variety of tools have been developed in an effort to rectify this issue. The Eosinophilic Esophagitis Activity Index and others address patient-reported outcome measures, including quality of life.[5] The eosinophilic esophagitis endoscopic reference score is widely used to assess endoscopic findings, and the histology scoring system accurately measures histologic changes.[E1-E4] When combined with a better understanding of disease mechanisms, research into improved EoE therapeutics has taken off, with an increasing number of therapies in late-phase clinical trials.

NONESOPHAGEAL EGIDs: CURRENT STATE

With the growing work in patients with EoE, nonesophageal EGIDs have also become increasingly recognized.[E5] Endoscopic evaluation of gastrointestinal complaints frequently includes examination of not only the esophagus but also the stomach, small intestine, and colon. Unlike the esophagus, eosinophils are normal residents of the lower gastrointestinal tract, and increased numbers have been traditionally associated with parasitic infection, hypereosinophilic syndrome, drug/food allergy, or inflammatory bowel disease but might also be a hallmark of EGID. Several studies have attempted to quantify normal gastrointestinal tract eosinophils, as well as thresholds for abnormal levels, but there are currently no consensus recommendations.[E6-E9] Nevertheless, biopsy specimens in these "below the belt" areas frequently contain noticeable eosinophilia at levels that are often greater those considered normal, suggesting an EGID, but uncertainty often exists.

Unlike EoE, there are no hallmark clinical symptoms, such as dysphagia, that provide an objective sense that a nonesophageal EGID is present. Many patients present with nonspecific symptoms, such as abdominal pain, vomiting, and/or diarrhea, and given the rarity of EGIDs, other diseases are often considered first.[E10] Endoscopically, distinct abnormalities, such as nodules, polyps, or ulcerations, might be present, but findings might also

From [a]the Division of Allergy/Immunology, Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, and [b]the Division of Allergy/Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine.

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Corresponding author: Robert D. Pesek, MD, Division of Allergy/Immunology, Arkansas Children's Hospital, 13 Children's Way, Slot 512-13, Little Rock, AR 72202. E-mail: rdpesek@uams.edu.

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TABLE I. Unmet needs, barriers, and future directions in patients with nonesophageal EGIDs

Unmet needs/barriers	Future directions
Rarity of nonesophageal EGIDs limits larger trials and determination of long-term outcomes	• Longitudinal trials to determine disease outcomes with pooling of patient resources through national/international collaboration
Lack of consensus diagnostic criteria	• Establishment of histologic criteria • Development of standardized patient-reported outcomes and histologic scoring tools
Disease mechanisms	• Transcriptomic analysis of EGE/EC • Determination of the role of mast cells • Determination of the role of the gut microbiome in disease pathogenesis • Clarification of overlap between EC and inflammatory bowel disease/celiac disease • Trials of biologics to aid in identification of disease pathways
Lack of US Food and Drug Administration–approved treatment	• Larger multicenter trials of food elimination • Expansion of biologic trials to nonesophageal EGIDs and those with EoE overlap
Need for frequent dual endoscopy/colonoscopy for diagnosis and assessment of disease control	• Development of noninvasive biomarkers for disease activity

be subtle or absent, preventing biopsies from being performed.[E11] Gastrointestinal tract eosinophilia can also occur at multiple sites, worsening the diagnostic confusion.

Currently, there are no standardized scoring tools for assessment of clinical or endoscopic findings in patients with nonesophageal EGIDs, leading to a lack of consistent and widely adopted diagnostic criteria; however, recent efforts of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) have begun to quantify endoscopic, molecular, and histologic findings in patients with EG.[E12] In particular, an EG Diagnostic Panel, a set of informative gastric transcripts, identified patients with active EG, effectively monitored disease activity in longitudinal samples, and correlated with gastric peak eosinophil levels, other gastric pathologic findings, and endoscopic nodularity. Furthermore, investigators showed that blood-based eotaxin-3, thymus and activation-regulated chemokine, IL-5, and thymic stromal lymphopoietin protein levels were significantly increased and able to distinguish patients with EG from control subjects without EG and correlated with gastric eosinophil count. These early findings show the value of a multisite consortium working together on this set of rare diseases and provides an exciting framework for advancing the development of diagnostic criteria and noninvasive biomarkers.

Compounding the lack of standardized criteria for diagnosis, nonesophageal EGIDs appear to be significantly rarer than EoE. Recent work estimates the US prevalence of EG to be 6.3 per 100,000, EGE to be 8.4 per 100,000, and EC to be 3.3 per 100,000 or less than 50,000 cases total.[6] Determining the true prevalence of EC is particularly challenging because colonic eosinophilia can be found in multiple conditions and is frequently overdiagnosed based on currently available criteria and International Classification of Diseases coding.[E13-E14]

As a result of these factors, much of the research done to date is limited to case reports or single centers. Early work in disease mechanisms demonstrates similarities but also distinct differences from EoE. Nonesophageal EGIDs appear to be driven by a similar T_H2 mechanism, with higher levels of IL-4, IL-5, and IL-13 than control subjects. IgE does not play a central role in EoE pathogenesis, and this appears to be the case in patients with nonesophageal EGIDs as well.[7] Prussin et al[E15] found that T_H2 cells in patients with EGE were associated with high expression of IL-5 in contrast to the T_H2 cells seen in patients with IgE-mediated peanut anaphylaxis, in whom IL-4^+ T_H2 cells were more common. Interestingly, in a trial of omalizumab in patients with EG/EGE, treated subjects had decreases in gastric and duodenal eosinophil counts and improvement in clinical symptom scores, highlighting that although IgE is not the primary effector of disease, it might play a role in a subset of patients.[E16] Gastric transcriptomic analysis of EG demonstrates upregulation of IL-4, IL-5, IL-13, and eotaxin-3 (CCL26) and decreased IL-33 levels, which are consistent with findings in patients with EoE. However, more than 90% of EG genes are divergent from those of patients with EoE and differ from those in patients with other gastric disorders, such as *Helicobacter pylori* and stomach cancer.[8,E17] IL-17 is also upregulated, a finding not typically associated with EoE but rather with asthma and eczema.[E18] These findings highlight the importance of genetic analysis in developing and understanding disease pathogenesis and clinical phenotypes.

EC mechanisms might be more complicated to elucidate. There can be substantial overlap with inflammatory bowel disease, which can present with gut eosinophilia and similar clinical features. There might be distinct differences in pathogenesis that can differentiate between patients with these disorders. Patients with allergic proctocolitis express more eotaxin-2 in intraepithelial lymphocytes and demonstrate increased mast cell degranulation compared with that in control subjects or patients with Crohn disease or ulcerative colitis.[E19] Although tissue eosinophils can be found in both patients with EGIDs and those with inflammatory bowel disease, EGIDs are associated with higher peripheral blood eosinophilia and distinctive increases in levels of cytokines that promote eosinophilia compared with ulcerative colitis.[E20]

Treatment for nonesophageal EGIDs remains limited. As with EoE, there are no US Food and Drug Administration–approved medications, and there is a lack of randomized controlled trials that hampers the adoption of standard treatment practices. In small cohorts food elimination diets appear to improve clinical symptoms, as well as histologic abnormalities, although they might be less effective than in patients with EoE.[E21] Corticosteroids can induce disease remission, but topical preparations, which are effective in patients with EoE, provide limited benefit in patients with lower gastrointestinal tract disease. As a result, enteric coated preparations or systemic corticosteroids must be used, increasing the risk of side effects.[E22] Early studies of

biologics, such as vedolizumab and benralizumab, have shown promise in reducing gastrointestinal eosinophilia, the need for systemic steroids, or both, but more work is needed.[9,E23-E24]

FUTURE DIRECTIONS

The field of EGIDs has rapidly expanded over the past several decades. For nonesophageal EGIDs, much work is needed to catch up to the progress seen in the treatment of EoE (Table I). First, clear diagnostic criteria for EG, EGE, and EC must be created. As with EoE, these criteria will likely need to be refined over time as these diseases are better understood.

Second, outcome measures need to be developed, including patient-reported outcomes and endoscopic and histologic assessments. This will pave the way for standardized end points in therapeutic clinical trials and will avoid some of the problems seen in early EoE trials.

Third, additional work is needed to understand pathogenesis. As discussed previously, transcriptomic analysis has demonstrated differences between EoE and EG, and additional studies are needed in patients with other EGIDs and those with multisite disease. Experimental mouse models of EGID might help advance this work. In mouse models of EG/EGE, depletion of eosinophils, as well as antibodies directed against Siglec-8 and CCR3, demonstrated improvement in tissue eosinophils and reductions in inflammatory mediators. Not only does this work identify these molecules as important in EGID pathogenesis, it also identifies potential therapeutic targets.[E25-E27]

Fourth, longitudinal trials are needed to gain a better understanding of disease mechanisms and long-term outcomes. Unfortunately, nonesophageal EGIDs are rare, making longitudinal trials difficult. This will require development of regional, national, and even international collaboration to pool patient and scientific resources. Some of this work has already begun through the National Institutes of Health and the Rare Disease Clinical Research Network. In 2014, CEGIR was established to allow for collaboration and advancement of the field of EGIDs.[10] This collaborative effort has already yielded positive results in patients with EoE and, given the rarity of nonesophageal EGIDs, will be critical to advance the understanding and treatment of these disorders.

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