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Eosinophilic gastrointestinal disorders affect more than just the esophagus

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In 1937, Dr. R. Kaisjer provided the first description of eosinophilic gastroenteritis following review of surgical resections taken from various parts of the gastrointestinal tract.¹ Over the next few decades other descriptions, again derived from whole tissue surgical specimens, followed. With the advent of flexible endoscopy in the 1960s, physicians were provided the necessary tools to procure mucosal biopsy samples from patients, escorting in a new era of defining the resident and pathological inflammatory cells of the intestinal mucosae. In the early 1980's, two publications identified eosinophils as markers of gastroesophageal reflux disease.^{2, 3} The association of esophageal eosinophilia with gastroesophageal reflux disease held firm until the early 1990s when two publications provided the first descriptions of eosinophilic esophagitis (EoE) as a distinct disease entity.^{4, 5} Since then, three Consensus Recommendations and a European Guideline have been published identifying and refining the diagnostic criteria for EoE.^{6–9}

The emergence of EoE as an increasingly recognized distinct clinicopathological entity rekindled interest and raised questions about the role of the eosinophil in gastrointestinal health and disease. For example, do eosinophils play a role in innate host defense and increase as a compensatory mechanism or is their increased presence a manifestation of a pathological inflammatory or allergic condition?^{10, 11} The latter explanation has certainly garnered more attention and when tissue eosinophilia is seen in the context of organ specific symptoms, with peripheral eosinophilia, without evidence of infection, and with resolution following steroid treatment, the diagnosis of an eosinophilic gastrointestinal disease (EGIDs) is strongly considered.

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This interest in EGID has recently extended beyond the esophagus, to encompass the remainder of the GI tract “south” of the diaphragm.^{12, 13} Unlike the esophagus, which is normally devoid of eosinophils, the stomach, intestine and colon are populated by eosinophils under normal healthy conditions. When these levels are elevated in these tissues and other etiologies for eosinophilia are ruled out, patients are diagnosed with EGID. The critical question that leads to the complexity of the study of these disorders is what number of eosinophils is considered abnormal or elevated. Unlike EoE, no universally accepted thresholds for abnormal tissue eosinophilia in the rest of the GI tract exist.

While EoE has clearly emerged as a distinct and well defined entity with a prevalence of 4 in 10,000, epidemiological features of the less common EGIDs, including eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE) and eosinophilic colitis (EC), remain less defined.^{12, 14–19} The literature to date is limited to case series from isolated center’s experiences that may not accurately reflect those of larger EGID patient populations. Adding to the heterogeneous nature of these conditions is that symptoms vary based on the location and layer of organ involvement. For instance, patients with EG and EGE may present with abdominal pain, nausea, vomiting, diarrhea and possibly hematemesis secondary to ulceration and bowel obstruction secondary to stricturing disease. Patients may also present with signs of anemia, malabsorption, hypoalbuminemia, ascites, and edema. The presentation of EC can also be varied and include symptoms of diarrhea, constipation, hematochezia and abdominal pain. Endoscopic findings include edema, ulceration, polyps and friability, but in some cases the mucosa can appear relatively normal. Elimination diets may bring clinicopathological remission, but patients often require treatment with systemic or topical steroids.

To date, clinical experiences suggest that EG, EGE and EC are uncommon diseases but with the increasing accrual of mucosal samples, each is becoming increasingly recognized. Documenting and defining the epidemiology, risk factors and natural history of these EGIDs is of critical importance in order to allow for accurate diagnosis, understanding the pathophysiology and identifying novel therapeutic targets. In this regard, Jensen and colleagues recent publication brings new and important insights.²⁰ Similar to their previous works with EoE, they examined large databases to provide initial prevalence estimates for EG, EGE and EC.^{21–24} They probed a 2 year span of databases representing >75 million United States individuals ranging in age from 0–64 years with commercial insurance. They captured individuals in whom an ICD-9 code specific for EG, EGE or EC was used more than once in the database and extrapolated the findings to estimate the US prevalence of these diseases. Consistent with clinical experiences, their finding revealed that each is rare with an estimated prevalence of EG at 6.3, EGE at 8.4 and EC at 3.3 per 100,000. In this population, EGE was most common in children less than 5 years old. Allergic diseases occurred in approximately 40% of affected individuals and was more common in children. In contrast to EoE, females were more often affected by these EGIDs. This important work provides the first prevalence estimates for EGIDs beyond the esophagus detected in a large population, thus identifying trends that are difficult to recognize in single center studies involving smaller numbers of individuals.

Since the results rely on an insurance database without a validated administrative case definition, involve the use of diagnosis codes without thorough examination of medical records and because diagnostic guidelines are less well defined for EG, EGE and EC than for EoE, the prevalence numbers should be considered estimates and may not precisely reflect the general population. Potential confounders capable of altering the normal numbers of GI eosinophils are numerous and include age, environment, antibiotic use, and diet, among others. Clinical experiences suggest that the interpretation of what constitutes a normal versus abnormal number of eosinophils in GI tissues varies by interpreter. In fact, in some cases, patients may have received an initial diagnosis of EGID but upon review of their pathology and following their clinical course, actually are found to have irritable bowel syndrome. Alternatively, some patients have increased numbers of mucosal eosinophils with features of chronicity and actually have an inflammatory bowel disease. Since a diagnosis of EGID carries therapeutic and long-term consequences, more research from well characterized large patient populations with access to medical records is urgently needed to help define normal and abnormal GI eosinophilia, identify associated clinical features, etiology, determine the natural history and identify novel therapeutic targets for each of these EGIDs.

To address the issues associated with characterization of these less common EGIDs the recently funded NIH U54 funded Consortium for Eosinophilic GastroIntestinal Disease Research (CEGIR-<https://www.rarediseasesnetwork.org/cms/CEGIR>) seeks to identify phenotypic and genotypic features of EGIDs. In a prospective longitudinal study, a variety of clinical outcome measures, histology and molecular markers will be collected from children and adults with EoE, EG and EC. Results from these studies will help clarify the diagnostic features of these diseases and provide an improved framework for the current ICD codes. Outcomes from this work will also include the development of diagnostic guidelines for the remaining EGIDs and provide a deeper understanding of commonly shared and distinct features of each EGID. EGID patients are urged to register on the Contact Registry at <https://www.rarediseasesnetwork.org/cms/CEGIR>.

Clinical experiences and the intriguing data provided by Jensen et al suggest that EG, EGE and EC are unlikely to affect as many people as EoE. Regardless, the future rewards of studying these diseases will be significant in regards to establishing well-defined diagnostic criteria, identifying novel therapeutic targets, understanding pathogenetic mechanisms and better defining the role of the eosinophil in gastrointestinal health and disease.

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