

Eosinophilic Diseases of Gastrointestinal Tract

Prof. Rok Orel, MD, PhD

University of Ljubljana, Faculty of Medicine, University Children's Hospital, Ljubljana, Slovenia

E-mail: rok.orel@kclj.si

Gastroenterolog 2023; supplement 1: 66–68

Eosinophilic gastrointestinal diseases (EGIDs) are chronic inflammatory disorders of the gastrointestinal (GI) tract characterized clinically by the presence of gastrointestinal symptoms and histologically by eosinophilic predominant inflammation of the GI tract, in the absence of an identifiable secondary cause. Eosinophilic esophagitis (EoE) has relatively high and growing global prevalence, estimated to be 74.42 (95% CI, 39.66–109.19 cases per 100,000 inhabitant-years in the period 2017–2022 (1). EGIDs beyond the esophagus are rare and ill-defined diseases. With intention to define and classify these diseases better, a special international task force of 92 experts from various fields (gastroenterology, allergy, pediatrics, pathologists, researchers) was formed. We published new nomenclature for non-EoE EGIDs based on the location of eosinophilic inflammation and the organ involved in the inflammatory process: eosinophilic gastritis (EoG); eosinophilic enteritis (EoN) with subcategories of eosinophilic duodenitis (EoD), eosinophilic jejunitis (EoJ), eosinophilic ileitis (EoI); and eosinophilic colitis (EoC) (2). When clinically known, subclassification of the different layers of the GI tract should be also described as mucosal, muscular or serosal. Frequently, a term eosinophilic gastroenteritis (EGE) appears in a literature, which includes both EoG and EoN. We recommend to use more accurate recent nomenclature in future publications.

We do not have accurate data on incidence and prevalence of EGIDs beyond the esophagus because most publications to date have focused on case reports and small retrospective series. Estimates of prevalence based on information from insurance databases in North America, over a 2-year period (2009–2011) with data from more than 75 million individuals (ages

0–64 years) suggest that the prevalence of EoG, EGE, and EoC is 6.3 per 100,000, 8.4 per 100,000, and 3.3 per 100,000, respectively (3). Another important problem is that defined and internationally accepted criteria for making a diagnosis exist only for EoE, while for the other EGIDs very different definitions have been used, especially regarding numbers of eosinophils in the biopsies.

Therefore, one of the main goals of the first international international guidelines for diagnosis and treatment of EGIDs beyond EoE was to establish uniform diagnostic criteria, including the number of eosinophils per high power field (4). Although this paper is focused on pediatric population, it includes data from adult patients and presents the first international consensus on this topic. Similarly to EoE, both clinical symptoms and histologic inflammation are required to establish the diagnosis.

Symptoms and signs depend on part of GI tract and layer of the wall affected. They are not specific for non-EoE EGIDs, and alternative conditions should be considered before the confirmation of the diagnosis. Abdominal pain, GI bleeding, vomiting and diarrhea are most frequent. Loss of appetite, weight loss and hypoproteinemia may be present in some patients. When muscular layer is affected mechanical obstruction and motility problems appear. The typical sign of serosal involvement is ascites. Its analysis reveals feature of exudate with high number of eosinophils.

Although elevated eosinophil blood count may be present in some patients it is neither frequent or specific. Endoscopy with multiple biopsies is fundamental for EGIDs diagnostics. Endoscopy may show deep ulcers

that can bleed and even perforate through the gastrointestinal wall, shallow mucosal erosions, diffusely friable and bleeding-prone mucosa, thickened gastric or small bowel folds, pronounced nodularity or granularity, to mucosal edema and redness. However, even more frequently macroscopis appearance of the mucosa is normal and only histologic examination reveals eosinophilic inflammation (5). In patients with muscular layer involvement, narrowing of the lumen can sometimes be seen, and several cases of gastric outlet obstruction mimicking pylorostenosis have been reported. Sometimes surgical full bowel wall thickness biopsy is needed to establish diagnosis.

Unlike the esophagus, which does not contain eosinophils, the immune milieu of the gastrointestinal (GI) tract distal to the esophagus contains a resident population of eosinophils. Therefore, when preparing diagnostic criteria for non-EoE EGIDs, we focused on studies dealing with normal numbers of eosinophils in different parts of GI tract to establish threshold numbers for histologic diagnosis. They are represented in a Table 1.

Etiopathology of majority of EGIDs is poorly understood. While EoE is clearly predominantly Th2 mediated immune disorder triggered by environmental, mostly food allergens, it seems that very diferent immune mechanisms play the role in other EGIDs (4). The role of food allergy in the pathogenesis of EoG, EoN, and EoC is likely as diverse. some patients

respond to dietary avoidance treatment, a non-IgE-mediated food allergy may be responsible, whereas the others require the use of topical or systemic steroids, suggesting an alternative inflammatory response. Etiopathology of EoC is the least well understood. Its molecular profile is not consistent with Th2 inflammatory pattern, however, a clinical series has identified patients with non-IgE-mediated food allergic reactions.

Topical steroids, proton pump inhibitors (PPIs)as well as elimination diets are recommended first-line therapy for EoE, both for induction and maintenance of remission (6,7). Better understanding of underlying immune mechanisms is leading to development of new drugs targeting specific immune pathways. Anti-IL-4 and anti-IL-13 monoclonal antibody dupilumab is the first biologic drug that gain regulatory approval for the treatment of EoE, while several other new drugs are in the pipeline (8). As all non-EoE EGIDs are rare, all data about efficiency of different therapeutically approaches have been extrapolated from case reports and case series (4). Systemic oral steroids have been effective in inducing clinical and histological remission in non-EoE EGIDs, however, there are no date on selection criteria of which patients should be treated with oral steroids, nor on the optimal dose or duration of treatment. There is much less evidence about the efficiency of topical steroids, but they may be useful in selected patients. Elimination diets may also induce clinical improvement or remission in a proportion of patients with non-EoE EGIDs but there

Table 1. Suggested threshold peak eosinophil counts for the diagnosis of non-EoE-EGIDs

Site	Consensus threshold peak eos/0.27 mm ² HPF	Consensus threshold peak eos/mm ²
Stomach	≥ 30	≥ 110
Duodenum	≥ 50	≥ 185
Terminal Ileum	≥ 60	≥ 220
Cecum and Ascending Colon	≥ 100	≥ 370
Transverse and Descending Colon	≥ 80	≥ 300
Rectum and Sigmoid Colon	≥ 60	≥ 220

are very limited data on histological response. Case series suggest that avoidance of cow's milk may be effective in some children. Equally than in EoE patients, there is no evidence to support the use of food allergy tests to guide dietary restriction therapy. At this moment there is insufficient data to make a recommendation for or against the use of antihistamines, leukotriene inhibitors, mast cell stabilizers, PPIs, immunomodulatory or biological drugs as treatment of non-EoE EGIDs. Endoscopic dilation and surgery may be considered in selected cases with significant objective signs of obstruction.

The natural history of non-EoE EGIDs is uncertain. Some patients may have waxing and waning courses while the others seem to permanently cured. There are no studies that have examined the role of maintenance treatment in patients with non-EoE EGIDs. Therefore, the potential benefits and risks of long-term treatment should be discussed with patients.

References

1. Hahn JW, Lee K, Shin JI, et al. Global Incidence and Prevalence of Eosinophilic Esophagitis, 1976-2022: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2023; 17:S1542-3565(23)00483-4. doi: 10.1016/j.cgh.2023.06.005.
2. Dellon ES, Gonsalves N, Abonia JP, et al. International Consensus Recommendations for Eosinophilic Gastrointestinal Disease Nomenclature. *Clin Gastroenterol Hepatol* 2022.
3. Jensen ET, Martin CF, Kappelman MD, et al. Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates From a National Administrative Database. *J Pediatr Gastroenterol Nutr* 2016;62(1):36-42.
4. Papadopoulou A, Amil-Dias J, Auth MK, et al. Joint ESPGHAN/NASPGHAN Guidelines on Childhood Eosinophilic Gastrointestinal Disorders beyond Eosinophilic Esophagitis. *J Pediatr Gastroenterol Nutr* 2023 Jul 4. doi: 10.1097/MPG.0000000000003877.
5. Pesek RD, Reed CC, Collins MH, et al. Association Between Endoscopic and Histologic Findings in a Multicenter Retrospective Cohort of Patients with Non-esophageal Eosinophilic Gastrointestinal Disorders. *Dig Dis Sci*. 2020 Jul;65(7):2024-2035.
6. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J* 2017; 5: 335-358.
7. Hirano I, Chan ES, Rank MA, et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. *Gastroenterology* 2020;158:1776-1786.
8. Aceves SS, Dellon ES, Greenhawt M, Hirano I, Liacouras CA, Spergel JM. Clinical guidance for the use of dupilumab in eosinophilic esophagitis: A yardstick. *Ann Allergy Asthma Immunol* 2023;130:371-378.