A Systematic Histopathology Protocol Led to Discovery of the High Prevalence of Eosinophilic Gastritis and/or Eosinophilic Duodenitis in Patients with Moderate–Severe Gastrointestinal Symptoms: Results from 2 Prospective Studies

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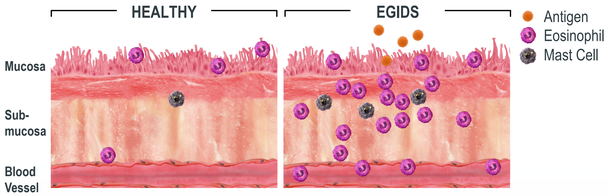
BACKGROUND

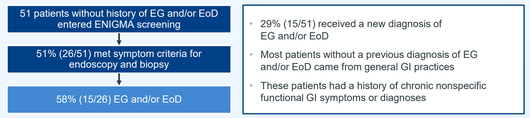
- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in chronic inflammatory diseases in the gastrointestinal (GI) tract, including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis–collectively termed eosinophilic gastrointestinal diseases (EGIDs)[1,2]
- Patients with EGIDs have decreased quality of life due to chronic debilitating and often nonspecific symptoms such as dysphagia, abdominal pain, abdominal cramping, bloating, early satiety, loss of appetite, nausea, vomiting, and diarrhea

Figure 1. Pathogenesis of EGIDs



- ENIGMA was a randomized, controlled, phase 2 trial of adult patients with EG and/or EoD that established the therapeutic potential of lirentelimab–a monoclonal antibody against Siglec-8 that depletes eosinophils and inhibits mast cell activity[3]
- Patients enrolled in ENIGMA were first screened for moderate-severe GI symptoms using a daily patient-reported outcome (PRO) questionnaire
- Patients who met the symptom criteria underwent esophagogastroduodenoscopy (EGD) with biopsy and histopathologic evaluation to confirm diagnoses of EG and/or EoD (≥30 eosinophils per high-power field in ≥5 hpfs (eos/hpf) in gastric biopsies and/or in ≥3 hpfs in duodenal biopsies)
- Among patients enrolled in ENIGMA, 45% had no previous diagnoses of EG and/or EoD; 29% of these patients were found to have EG and/or EoD

Figure 2. New Diagnoses of EG and/or EoD in ENIGMA



- 29% (15/51) received a new diagnosis of EG and/or EoD
- Most patients without a previous diagnosis of EG and/or EoD came from general GI practices
- These patients had a history of chronic nonspecific functional GI symptoms or diagnoses

- This high discovery rate of EG and/or EoD, along with other studies reporting underdiagnosis of EG and/or EoD, prompted further evaluation of the screening protocol
- We therefore conducted a prospective study of the prevalence of EG and/or EoD in patients with chronic functional gastrointestinal symptoms/disorders (FGIDs)
- We used a systematic histopathology protocol in ENIGMA and this prevalence study to determine the discovery rate of EG and/or EoD

METHODS

Figure 3. Biopsy and Histopathology Protocol and Diagnostic Criteria for EG and/or EoD

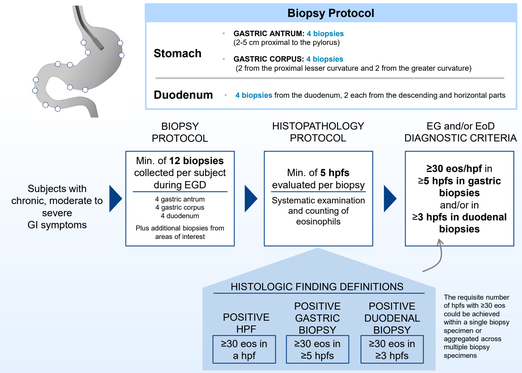
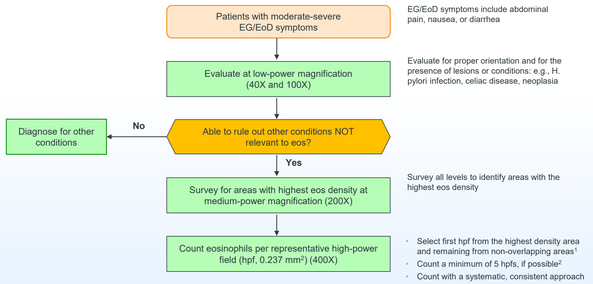


Figure 4. Histopathologic Evaluation Process: Steps for EG and/or EoD



[1]Non-overlapping hpfs could be, but are not required to be, adjacent to the first hpf, depending on the distribution of eosinophils in the specimen
[2]If the size of a specimen is insufficient to evaluate 5 independent fields, eosinophils are to be counted in as many non-overlapping fields as available

Figure 5. Ideal Biopsy Specimen and Countable Eosinophils

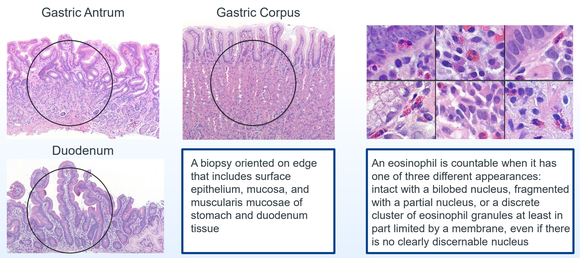
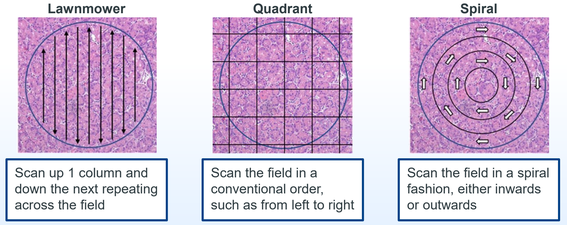
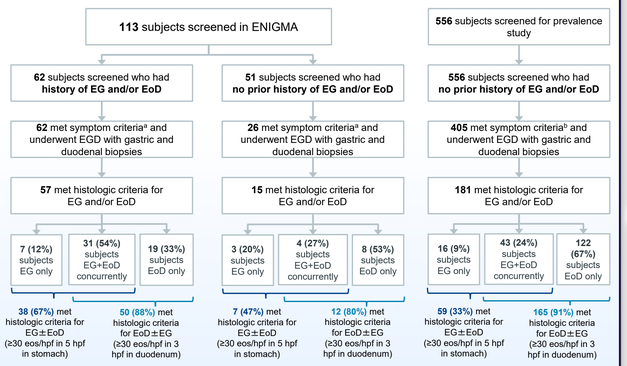


Figure 6. Three Systematic Approaches to Counting Eosinophils



RESULTS

Figure 7. EG and/or EoD Diagnosis Rate in Patients



[a]Moderate–severe symptoms, defined as an average daily symptom score of ≥3 (scale 0-10) over 7 days for abdominal pain, diarrhea, and/or nausea on a PRO questionnaire for ≥2 weeks
[b]Moderate–severe symptoms, defined as an average daily symptom score of ≥3 (scale 0-10) for at least 2 of 3 weeks for abdominal pain, abdominal cramping, nausea, vomiting, diarrhea, bloating, or early satiety on a PRO questionnaire and average Total Symptom Score of ≥3 [scale 0-80]

Table 1. Patient Demographics

Patient Characteristics	ENIGMA		Prevalence
	Prior History of EG and/or EoD N=57	No History of EG and/or EoD N=15	No History of EG and/or EoD N=181
Mean age, years (range)	40 (18-68)	48 (20-74)	45 (19-78)
Female sex, n (%)	33 (58%)	10 (67%)	132 (73%)
White, n (%)	52 (91%)	14 (93%)	154 (85%)
Weight, mean (range), kg	81 (47-171)	88 (59-136)	85 (45-180)
Total Symptom Score at baseline, mean ±SD	31 ±14	32 ±13	31±11
Atopy[a]	37 (65%)	11 (73%)	86 (48%)
Prior history, n (%)			
Eosinophilic gastritis and/or duodenitis (EG/EoD)	57 (100%)	0	0
Functional gastrointestinal disorder[b]	19 (33%)	12 (80%)	169 (93%)
GERD, acid reflux, or heartburn	16 (28%)	8 (53%)	133 (73%)
Peptic ulcer	8 (14%)	1 (7%)	10 (6%)
Chronic gastritis/duodenitis	0	4 (27%)	20 (11%)
Physician-guided treatment, n (%)			
Proton-pump inhibitor	26 (46%)	9 (60%)	62 (34%)
Diet modification	9 (16%)	2 (13%)	8 (4%)
Low-dose systemic corticosteroid[c]	7 (12%)	0	9 (5%)
Topical steroid (budesonide) capsule	7 (12%)	0	4 (1%)

[a]History of asthma, allergic rhinitis, atopic dermatitis, and/or food allergy
[b]Irritable bowel syndrome, GERD, chronic gastritis/duodenitis, or functional dyspepsia
[c]Prednisone ≤10mg daily or equivalent as a pre-existing regimen and taken throughout the study

Figure 8. Symptoms in Patients With and Without Prior Diagnoses of EG and/or EoD

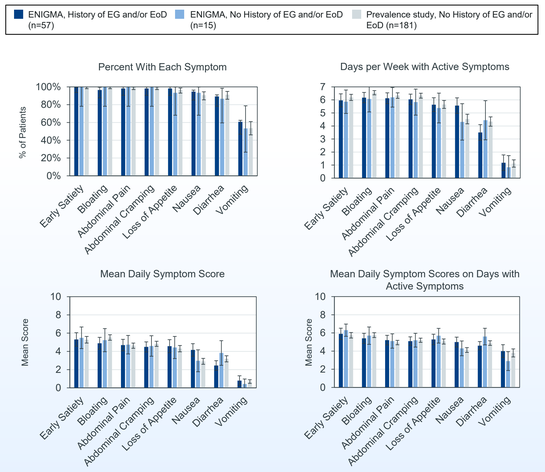
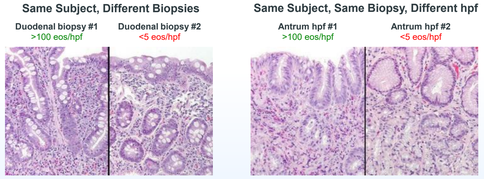


Figure 9. Patchiness of Eosinophils in Tissue



- Due to the patchiness of gastric and duodenal eosinophilia, insufficient biopsy sampling in clinical practice might produce false-negative results and missed diagnoses

CONCLUSIONS/DISCUSSION

- A systematic histopathology protocol with intentional evaluation of gastric and duodenal eosinophilia in patients with chronic, moderate–severe GI symptoms, in 2 prospective studies, identified at least 33% of patients without a previous diagnosis who met histologic criteria for EG and/or EoD
- Eosinophils are patchy in tissue and 5 hpfs must be counted in ≥8 gastric and ≥4 duodenal biopsy samples to identify EG and/or EoD
- Given the high diagnostic yield, a standardized biopsy and histopathology protocol should be used to evaluate patients for EG and/or EoD, so that they can receive an accurate diagnosis and possibly therapeutic intervention

Reference: (1) Caldwell JM, et al. J Allergy Clin Immunol. 2014.; (2) Youngblood BA, et al. Gastroenterology. 2019.; (3) Dellon ES, et al. NEJM. 2020.

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