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Determination of Optimal Eosinophil Thresholds for Diagnosis of Eosinophilic Gastritis and Duodenitis: A Pooled Analysis of 4 Prospective Studies

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ABSTRACT

Objectives: Consensus is lacking regarding the number of eosinophils (eos) required for diagnosis of eosinophilic gastritis (EoG) and eosinophilic duodenitis (EoD). Additionally, thresholds that require multiple high-power fields (hpfs) may not be practical for clinical use, resulting in delayed or missed diagnoses. This pooled analysis of 4 prospective studies assessed thresholds for multiple and single hpfs used to diagnose EoG and EoD.

Methods: Studies included the phase 2 ENIGMA1, the phase 3 ENIGMA2, an EoG/EoD prevalence study, and a healthy volunteer study. Eosinophils were quantified in the epithelium and lamina propria for controls and symptomatic participants. Symptomatic participants were further divided by histologic diagnosis of EoG/EoD. Peak eos counts were assessed, and area under the receiver operating characteristic (AUROC) curve was analyzed to identify eos cutoffs for detection of EoG/EoD using the Youden index and sensitivity and specificity equality approaches.

Results: Based on the highest specificity analysis in 740 patients, the optimal eos threshold was determined to be 20 eos/hpf in 5 gastric hpfs for EoG (71% sensitivity; 94% specificity) and 33 eos/hpf in 3 duodenal hpfs for EoD (49% sensitivity; 100% specificity). For single-field analysis, the optimal eos thresholds were 33 eos/hpf (EoG) and 37 eos/hpf (EoD), both corresponding to 93% sensitivity and 93% specificity.

Conclusions: Highly specific single gastric and duodenal hpf thresholds may have more clinical applicability than thresholds requiring multiple hpfs and could better facilitate development of practical histopathologic guidelines to aid pathologists and clinicians in the detection and diagnosis of EoG and/or EoD.

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STUDY HIGHLIGHTS

What is known

- Diagnosis of eosinophilic gastritis and duodenitis is challenging because guidelines regarding eosinophil count thresholds are lacking
- Assessment of multiple high-power fields when quantifying eosinophils is time-consuming and may be clinically impractical

What is new here

- Pooled-data analysis identified highly specific eosinophil count thresholds for diagnosing eosinophilic gastritis and duodenitis with a single high-power field
- These single high-power field thresholds may have more clinical applicability than thresholds requiring multiple high-power fields
- These thresholds can be used to inform future diagnostic guidelines

INTRODUCTION

Eosinophilic gastrointestinal (GI) diseases (EGIDs) are characterized by GI symptoms and the pathologic infiltration of eosinophils (eos) in the absence of another identified cause (1-3). The term EGID encompasses several specific eosinophilic disorders, including eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), and eosinophilic duodenitis (EoD) (1). Diagnosis of EGIDs can be challenging because symptoms (e.g., nausea, abdominal pain, vomiting, early satiety, diarrhea, weight loss, food allergy/intolerance) are nonspecific and often overlap with other GI conditions (4, 5). In addition, diagnosis is often delayed owing to an absence of diagnostic guidelines for non-EoE EGIDs in adult patients (1, 5-7). There is also a lack of disease awareness related to low suspicion of EGIDs during workup, insufficient number and location of biopsies obtained from esophagogastroduodenoscopies (EGD), failure to obtain biopsies during EGD, and failure to enumerate eos in gastric and duodenal biopsies (5, 8-10).

Further complicating the diagnostic process is the lack of consensus among experts regarding the number of eos required for diagnosis. Several studies have used varying eos count thresholds suggested by expert opinion and literature review, including for stomach (e.g., ≥30 eos in 5 high-power fields [hpfs] (11), ≥30 eos/1 hpf (4), ≥70 eos/hpf (12), ≥20 eos/hpf (13, 14)) and duodenum/small bowel (e.g., ≥52 eos/hpf (11), ≥30-50 eos/hpf (4), ≥30 eos/hpf (14), ≥20 eos/hpf (13, 15)). However, studies examining eos thresholds are somewhat limited, as they rely on retrospective approaches or samples from patients who were undergoing endoscopy for a clinical indication but had “normal” samples, which might lead to biased results (16). The few studies of autopsy data may be unreliable because rapidly occurring postmortem autolytic changes preclude an accurate histologic assessment of the gastrointestinal mucosa (17, 18).

Although for clinical trials, the US Food and Drug Administration has accepted cutoffs of ≥30 eos/hpf in ≥5 hpfs for the diagnosis of EoG and in ≥3 hpfs for the diagnosis of EoD, the threshold requirements for regulatory approval of therapeutics may not necessarily reflect

thresholds used in clinical practice; furthermore, time constraints of the histopathologic examination make thresholds requiring counting eos in multiple hpfs impractical (5). Accordingly, an evidence-based approach is needed to establish appropriate eos thresholds for the diagnosis of EoG and EoD to improve the detection of patients with EGIDs and decrease the time to diagnosis. Therefore, the primary objectives of this study were to assess thresholds that have used multiple hpfs to diagnose EoG and EoD, compare them to thresholds used in clinical trials, and determine reliable thresholds for a single hpf.

METHODS

Participant Population

This was a pooled analysis of 4 prospective studies that included 3 clinical trials of adult participants (≥18 years old) with moderate-to-severe, chronic unexplained GI symptoms (phase 2 ENIGMA1 [NCT03496571] (19), phase 3 ENIGMA2 [NCT04322604] (20), and a study to identify the prevalence of EoG and EoD) (21) and a healthy volunteer study (21). All studies were performed in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice Guidelines, the institutional review boards of the trial sites, and applicable laws. All participants provided written informed consent before trial entry.

Symptom entry criteria from the phase 3 ENIGMA2 study (20) were applied to identify participants for this pooled analysis. Patients with the following symptoms were screened: bloating, nausea, early satiety, loss of appetite, and abdominal cramping and abdominal pain. After we excluded individuals with *Helicobacter pylori* and/or celiac disease, participants from the ENIGMA1, ENIGMA2, and prevalence studies were eligible if they had weekly average total symptom scores (TSS6; score range: 0-60) ≥10 for at least 2 weeks of screening and abdominal pain, diarrhea, and/or nausea scores ≥3 at baseline. The TSS6 was calculated from a daily patient-reported outcome questionnaire on which participants rate the presence and severity (on

a scale of 1 to 10) of bloating, nausea, early satiety, loss of appetite, and abdominal cramping and pain; this scale was similar to that utilized in prior trials (TSS8, which included vomiting and diarrhea, not reported in the TSS6) (19). These symptomatic participants who exhibited TSS of ≥10 underwent an EGD with biopsy (Supplementary Table). Controls from the healthy volunteer study had TSS6 scores ≤1, indicating no active GI symptoms when they underwent EGD with biopsy.

Eosinophil Quantification

The systematic eos quantification methodology that we used has been described previously (5). Multiple biopsies (≥12) were taken from all participants according to a standardized protocol: 8-10 gastric biopsies (including at least 4 from the antrum and 4 from the body), 4-6 duodenal biopsies, and up to 4 esophageal biopsies (only if the patient had a history of EoE or if EoE features were observed during EGD) (19, 21, 22). For the purpose of this study, biopsy results from the initial screening endoscopy (for the trials) or from the single endoscopy (for the prevalence study) were evaluated for all participants.

In brief, biopsy sections were first surveyed at low power (40X and 100X) to evaluate how much tissue was present and note any unexpected pathology. Sections were then viewed at medium power (200X), and the most eosinophil-dense areas in each fragment were identified; in these areas, chosen whenever possible among the best-oriented portions of the mucosa, 5 nonoverlapping hpfs (400X, each measuring 0.237 mm^2) were selected for counting. Eosinophils were counted only in the mucosa (i.e., epithelium and lamina propria). Eosinophils in the *muscularis mucosae*, submucosa, or *muscularis propria* were not counted.

Participant Stratification

On the basis of TSS scores and eos counts, participants were stratified into a "control" group, which comprised asymptomatic, healthy volunteers (n=33) with a TSS6 score <1, and a "patient" group, which comprised symptomatic participants and included a pooled population from the ENIGMA1, ENIGMA2, and prevalence study (n=707). These symptomatic participants were then further divided by histologic diagnosis. Participants met histologic criteria for EoG if they had ≥30 eos/hpf in ≥5 gastric hpfs and met histologic criteria for EoD if they had ≥30 eos/hpf in ≥3 duodenal hpfs (gold standards as defined by the US Food and Drug Administration). Otherwise, participants were considered not to have met histologic diagnostic criteria.

Statistical Analysis

The distribution of peak eos counts was assessed for each of the participant groups of interest (controls, symptomatic participants who met histologic criteria, and symptomatic participants who did not meet histologic criteria), and the mean of the peak counts was calculated. A Welch's *t* test was used to analyze differences in mean eos count and peak eos count between groups.

We analyzed the area under the receiver operating characteristic (AUROC) curve for all participants, taking into account participants' symptoms and histology, to identify the best eos cutoff while considering the sensitivity and specificity for detection of EoG and EoD. We used two approaches. First, we determined the Youden index, which indicates the point on the receiver operating characteristic (ROC) curve where sensitivity and specificity are optimized (23). The Youden index was calculated as the maximum (sensitivity + specificity – 1). A Youden index value of 1 indicates no false negatives or false positives (and is similar conceptually to an area under the curve of 1.0). Second, we used sensitivity and specificity equality calculated as the absolute value of (sensitivity – specificity), which measures the absolute difference between

sensitivity (rate of true positives) and specificity (rate of true negatives). Sensitivity and specificity are equal when the resulting calculation is 0. For both approaches, the eos peak count was the exposure, and the outcome was histologic EoD or EoG. Optimal eos thresholds were determined from the higher specificity outcome of either the Youden index or sensitivity and specificity equality analyses.

RESULTS

Participant Characteristics

In this analysis, 740 participants were included (ENIGMA1 [n=74], ENIGMA2 [n=324], EoG/EoD prevalence study [n=309], healthy control study [n=33]). Of the 707 symptomatic participants from ENIGMA1, ENIGMA2, and the prevalence study, 388 (55%) had histologic evidence of EoG and/or EoD. Upon further breakdown by disease, 53 (14%) had EoG, 231(60%) had EoD (2 were excluded for missing duodenal biopsies), and 106 had EoG and EoD (27%). Conversely, 319 (45%) did not meet histologic criteria (Supplementary Figure). Of the 33 controls, 2 (6%) had histologic evidence of EoD (21).

Participant characteristics are reported in Table 1; of note, the healthy volunteers were younger and had a lower proportion of females than the other groups. As expected by study entry criteria, the healthy volunteers (n=33) had TSS of approximately 0, compared with elevated scores in symptomatic participants (n=707; mean±standard deviation [SD], 29±10), EoG/EoD (n=388; mean±SD, 30±10), and eos <30/hpf groups (n=319; mean±SD, 29±10). Mean tissue eos counts for stomach and duodenum are presented in Figures 1 and 2, respectively. The mean (SD) gastric counts were 7 (5), 25 (34), 68 (50), and 13 (8) in the controls, symptomatic participants overall, symptomatic participants with histologic EoG, and symptomatic participants without EoG, respectively. The mean (SD) duodenal counts were 19 (7), 33 (21), 49 (19), and 19 (7) in the controls, symptomatic participants overall, symptomatic participants with histologic EoD, and symptomatic participants without EoD, respectively. Of

note, counts did not differ on the basis of concomitant proton pump inhibitor (PPI) use (data for prevalence study only; data not shown).

ROC Curve Analysis in Symptomatic Participants for 5 Gastric hpfs and 3 Duodenal hpfs

The ROC curve analysis included the 707 participants with symptoms (TSS score ≥10) from ENIGMA1, ENIGMA2, and the prevalence study and the 33 healthy controls. The AUROC curve for disease classification was 0.74 with 3 duodenal hpfs and 0.78 with 5 gastric hpfs (Figure 3). In the analysis for 5 gastric hpfs, the Youden index was highest (0.645) at 20 eos/5 hpfs, corresponding to a sensitivity of 71% and specificity of 94%. Equality of sensitivity and specificity (difference value, 0.002) was achieved at a threshold of 18, corresponding to a sensitivity of 76% and specificity of 76%. In the analysis for 3 duodenal hpfs, the Youden index was highest (0.487) at 33/3 hpfs, corresponding to a sensitivity of 49% and a specificity of 100%. Equality of sensitivity and specificity (difference value, 0.005) was achieved at a threshold of 24, corresponding to a sensitivity of 69% and a specificity of 69%. Based on the higher specificity analysis, the optimal eos threshold was 20 eos/hpf in 5 gastric hpfs for EoG and 33 eos/hpf in 3 duodenal hpfs for EoD.

ROC Curve Analysis in Symptomatic Participants for 1 Gastric hpf and 1 Duodenal hpf

The AUROC curve for disease classification was 0.94 with both 1 duodenal hpf and 1 gastric hpf (Figure 4). In the analysis to determine thresholds for 1 gastric hpf, the Youden index was highest (0.889) at 30 eos/hpf, corresponding to a sensitivity of 98% and specificity of 91%. Equality of sensitivity and specificity (difference value, 0.002) was achieved at a threshold of 33, corresponding to a sensitivity of 93% and specificity of 93%. In the analysis to determine thresholds for 1 duodenal hpf, the Youden index was highest (0.871) at 37 eos/hpf, corresponding to a sensitivity of 95% and specificity of 93%. Equality of sensitivity and specificity (difference value, 0.001) was achieved at a threshold of 37, corresponding to a

sensitivity of 93% and specificity of 93%. Based on the higher specificity analyses, the optimal eos threshold was 33 eos/hpf in 1 gastric hpf for EoG and 37 eos/hpf in 1 duodenal hpf for EoD.

ROC Curve Analysis for Empirically Selected Thresholds in the Duodenum

Owing to the difference in our calculated optimal duodenal threshold in 1 hpf (37 eos/hpf) from thresholds reported previously (≥50-52 eos/hpf) (4, 11), we examined the operating characteristics in 4 other potential clinical cutoff points in the duodenum. For 40 eos/hpf, the Youden index was 0.784, with a sensitivity of 82% and specificity of 96%. For 45 eos/hpf, the Youden index was 0.659, with a sensitivity of 66% and specificity of 99.8%. For 50 eos/hpf, the values were 0.500, 50%, and 100%, respectively, for the Youden index, sensitivity, and specificity, and for 52 eos/hpf, the values were 0.442, 44%, and 100%, respectively.

DISCUSSION

In combination with patient history and symptoms, quantification of eos from gastric and duodenal biopsies is required for diagnosing EoG and EoD. However, multiple different eos count thresholds have been reported in the literature, and currently there are no diagnostic guidelines in adults or evidence-based determinations of the optimal eos thresholds to support the diagnosis (1, 4-7, 11, 12, 15, 24). Lack of agreed-upon thresholds also may contribute to the delay in diagnosis, together with delayed referral to gastroenterologists, delays in obtaining EGDs, lack of thorough diagnostic evaluation, insufficient or no biopsies collected for eos quantification, and time constraints in clinical practice (5, 7, 9).

Accordingly, in this analysis, we sought to determine optimal eos thresholds in multiple and single hpfs from the stomach and duodenum for the detection of EoG and EoD by using data from 3 studies of symptomatic participants and 1 healthy volunteer study. Of symptomatic patients in these studies, only 55% met histologic criteria for EoG and/or EoD, underscoring the need for more specific histologic criteria. Our analysis based on the highest specificity revealed

that thresholds for EoG of 20 eos/5 hpfs or 33 eos/1 hpf in the stomach, and thresholds for EoD of 33 eos/3 hpfs or 37 eos/1 hpf in the duodenum, minimize false-positive rates. Although the specificity analyses performed here suggest that these thresholds are valid, additional consideration should be given to which specific values align with practice considerations and implementation. For example, a single hpf duodenal count of 50 eos/hpf will have 100% specificity (i.e., no falsely categorized patients, as no controls have a duodenal count this high) at the expense of a lower sensitivity (i.e., versus our counts of 40 and 45 eos/hpf) and missing "true" patients.

Although various thresholds have been proposed, there is still little agreement on the number of eos per hpf regarded as pathologic in either gastric or duodenal mucosa (4, 11, 15, 16, 24). Part of the difficulty is that eos are normal tissue-resident cells in both the stomach and the duodenum, unlike the esophagus, where they are not normally present (11). One recommended approach to this problem is to select a value that is approximately twice that of the highest reported normal value, which led to the recommendation of 52 eos/hpf as a threshold for the duodenum (11). The suggestion for using multiple hpfs was an attempt to require more diffuse involvement and avoid an EGID diagnosis when only one focal area was involved (7). Inherent to this methodology, however, is a dependence on what normal values are, and from whom "normal" tissue is obtained. In an autopsy-based study and a population-based study of normal volunteers undergoing endoscopy, the peak values ranged from ~5 to 12 eos/hpf for the stomach and ~16 to 19 in the duodenum (25, 26). Other studies used endoscopy controls as "normal," selecting patients who might be symptomatic but who have a normal endoscopic appearance, normal biopsy results, and no other identified GI conditions (15, 16, 24, 27-33). When these studies are summarized, peak gastric counts are generally below 10, but they can range as high as 15 to 16 eos/hpf, and peak duodenal counts range up to ~30 eos/hpf, though most reported values are lower (16). These values generally match what we found in our healthy control cohort, lending validity to our findings. One prior study assessed the diagnostic

specificity of various eos count thresholds depending on the number of hpfs required (16). It showed 98% specificity for >20 gastric eos in 1 hpf, as well as 95% specificity for >40 duodenal eos in 1 hpf. Although these results were obtained from participants in whom no abnormalities were detected by endoscopy, the values closely correspond to values reported in our healthy volunteer population. These data lend credence to our findings and potentially support more practical peak eos count thresholds in just 1 hpf. The exact threshold chosen would necessitate a balance of sensitivity, specificity, and clinical applicability. Lastly, although other conditions such as functional dyspepsia are also associated with increased duodenal eos counts, the thresholds reported in this analysis would likely exclude patients with functional dyspepsia, for whom counts have been reported to be 9 to 12 eos/hpf (26, 34, 35).

Limitations of this study include pooling of different studies rather than using one unified protocol; however, this pooled approach provided a large sample size of symptomatic individuals, and we harmonized the entry criteria for the current analysis. Additionally, while this analysis included a relatively small sample size of healthy volunteers, this group was highly characterized by detailed histologic assessments, TSS scores, and documented symptoms; was prospectively enrolled; and—to our knowledge—represents a unique resource in the field. These are asymptomatic and healthy subjects recruited from several sites who underwent purely research endoscopies expressly to obtain sufficient gastric and duodenal tissue for comparative analyses. This analysis included the use of large prospective and high-quality studies, which together produced the largest study assessing diagnostic thresholds for eos counts to date. However, given the limited clinical data available, we were unable to adequately examine the role of other important patient characteristics in the current analysis (e.g., allergic disease, other biomarkers). Although baseline PPI use was reported in 49% (32/65) of patients in ENIGMA (19) and 29% (116/405) of patients in the prevalence study (21), complete PPI data were not available for all studies. Further, although prior infection was not assessed, patients were screened and excluded if they had evidence of active *Helicobacter pylori* infection or celiac

disease. Future research efforts are underway to better characterize clinicopathologic factors that may affect gastric and duodenal eosinophilia (e.g., PPI use) (36), though a prior study suggested that PPI use did not affect gastric or duodenal eos counts in a clinically meaningful way (16). Additionally, eos counts were determined by experts in the field using quantification methods that are published and standardized. Lastly, our analyses included multiple statistical approaches to assess thresholds, which permitted the identification of ideal thresholds and will allow future recommendations for practical thresholds.

In conclusion, in this pooled analysis of 4 prospective studies (2 clinical trials, an EoG/EoD prevalence study, and a healthy volunteer study), we developed the largest dataset yet reported to assess eos count thresholds for the diagnosis of EoG and/or EoD. Using healthy volunteers as controls, we found highly specific thresholds both for a requirement of multiple hpfs and for use of a single hpf, which may have more clinical applicability and gain broader acceptance by pathologists, thus aiding in the detection of more patients with EoG and/or EoD (8). Our data suggest that 30 eos in a single hpf in the stomach and 37 eos/hpf in the duodenum could be reasonably selected to histologically define patients with EoG/EoD. Additionally, thresholds with 100% specificity (e.g., 50 eos/hpf) may align well with implementation in clinical practice, identifying “true” patients at the cost of lower sensitivity. The thresholds identified here could additionally be used to help develop future practical and histopathologic diagnostic guidelines.

Supplemental Figure - http://links.lww.com/CTG/B33

Supplemental Table - http://links.lww.com/CTG/B34

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TABLES

Table 1. Baseline Demographics

Participant characteristics	Pooled symptomatic patients n=707	EoG and/or EoD n=388	Eosinophils <30 n=319	Healthy volunteers n=33
Age, mean (range), y	43 (17-78)	43 (17-78)	42 (18-76)	34 (18-51)
Female sex, n (%)	508 (72)	266 (69)	242 (76)	13 (39)
White, n (%)	626 (89)	336 (87)	290 (91)	33 (100)
Weight, median (range), kg	81 (31-171)	82 (43-171)	79 (31-163)	80 (46-113)
Blood eos ≥250 cells/µL, n (%)	189 (27)	146 (38)	43 (13)	3 (9)
IgE ≥70 kU/L, n (%)	264 (37)	167 (43)	97 (30)	7 (21)
History of atopy, n (%)[a]	357 (50)	225 (58)	132 (41)	5 (15)
History of EoG and/or EoD, n (%)[b]	105 (15)	94 (24)	11 (3)	0 (0)
Gastric eos/5 hpfs, mean ± SD	25 ± 34	38 ± 41	10 ± 7	7 ± 5
Duodenal eos/3 hpfs, mean ± SD	33 ± 21	45 ± 21	19 ± 7	19 ± 7
TSS [0-60], mean ± SD	29 ± 10	30 ± 10	29 ± 10	0.1 ± 0.2

EoD, eosinophilic duodenitis; EoG, eosinophilic gastroenteritis; eos, eosinophils; hpfs, high-power fields; IgE, immunoglobulin E; kU/L, kilounits per liter; SD, standard deviation; TSS, total symptom score. [a]Asthma, allergic rhinitis, atopic dermatitis, and/or food allergy. [b]A history of the condition was considered to be present if a documented clinical diagnosis had been made by the patient's physician and was noted in the patient's clinical chart history.

FIGURES

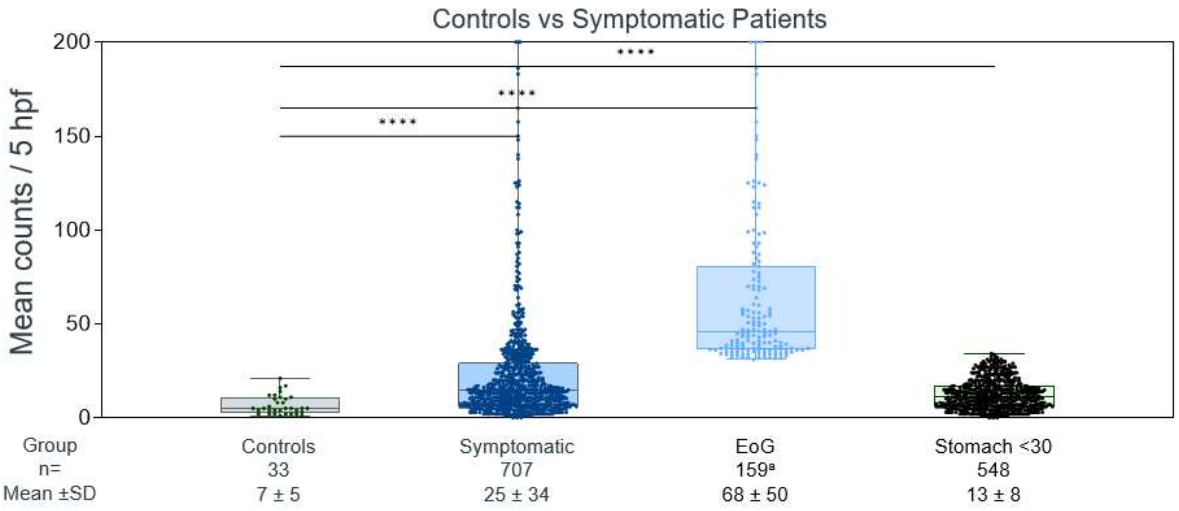


Figure 1. Mean tissue eos counts in stomach. Mean of the peak tissue eos counts in 5 hpfs for controls, participants with EoG, and participants with stomach eos counts <30. Caps represent minimum and maximum, boxes represent 25th and 75th percentiles, and the center line corresponds to the median. Welch's unpaired *t* test, ****P<0.0001. [a]6 outliers in the EoG group not displayed, with mean gastric eos counts of 201, 201, 210, 214, 228, and 300. EoG, eosinophilic gastritis; eos, eosinophils; hpf, high-power field; SD, standard deviation.

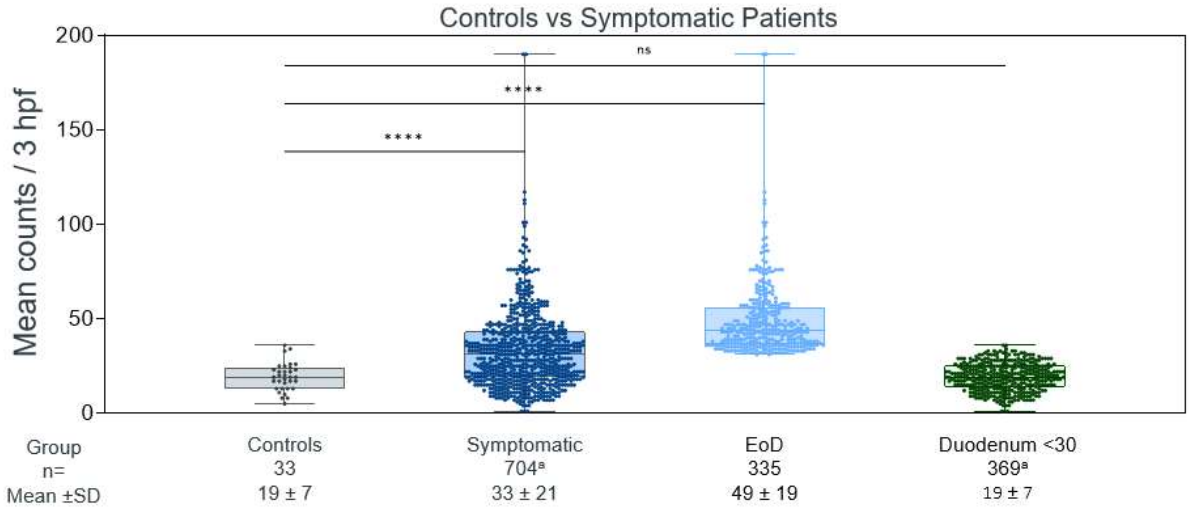


Figure 2. Mean tissue eos counts in duodenum. Mean of the peak tissue eos counts in 3 hpfs for controls, participants with EoD, and participants with duodenum eos counts <30. Caps represent minimum and maximum, boxes represent 25th and 75th percentiles, and the center line corresponds to the median. Welch's unpaired *t* test, ****P<0.0001; ns, not significant. [a]3 patients did not have duodenal biopsy samples (n=2 with EoD; n=1 duodenum <30). [b]2 individuals included in the control group had histologic evidence of EoD (21). EoD, eosinophilic duodenitis; eos, eosinophils; hpf, high-power field; SD, standard deviation.

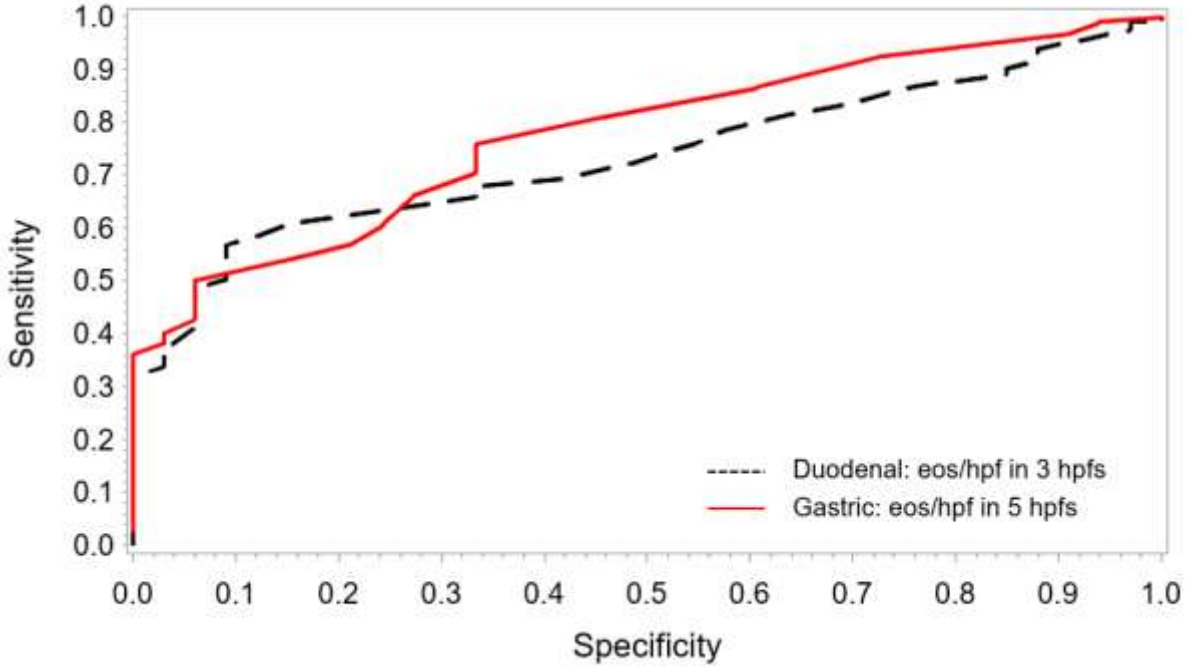


Figure 3. ROC curves for determining eos count thresholds in 5 gastric hpfs and 3 duodenal hpfs. Optimal eos threshold was determined to be 20 eos/hpf in 5 gastric hpfs for EoG and 33 eos/hpf in 3 duodenal hpfs for EoD. Curves correspond to an AUROC of 0.74 for 3 duodenal hpfs and 0.78 for 5 gastric hpfs. AUROC, area under the receiver operating characteristic; EoD, eosinophilic duodenitis; EoG, eosinophilic gastritis; eos, eosinophil; hpf, high-power field; ROC, receiver operating characteristic.

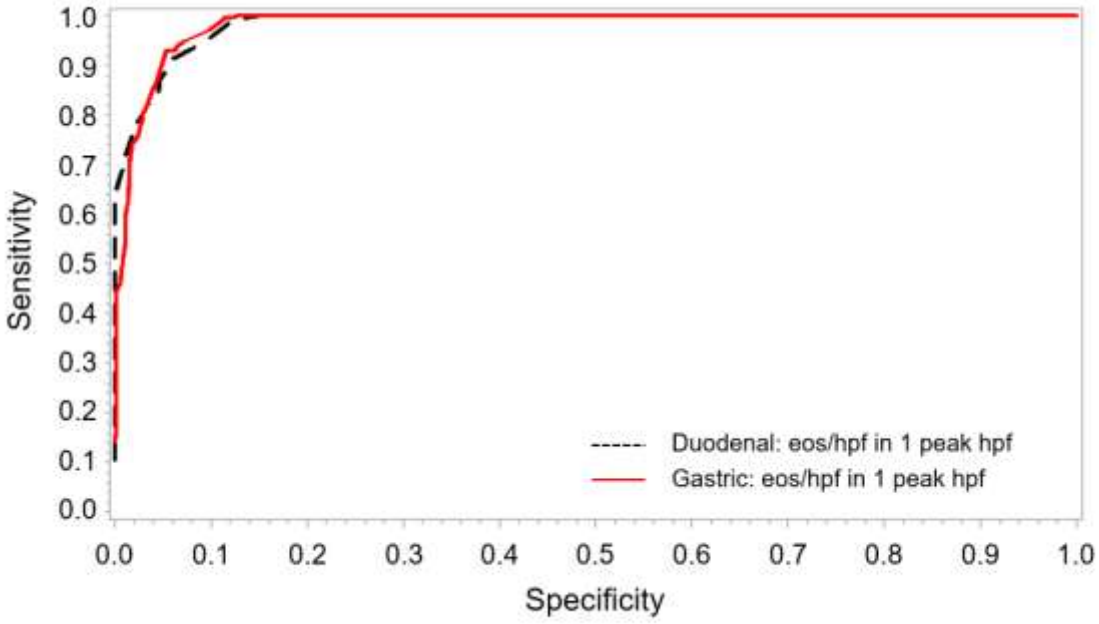


Figure 4. ROC curves for determining eosinophil count thresholds in 1 gastric hpf and 1 duodenal hpf. Optimal eos threshold was determined to be 33 eos/hpf in 1 gastric hpf for EoG and 37 eos/hpf in 1 duodenal hpf for EoD. Curves correspond to an AUROC of 0.94 for 1 duodenal hpf and 0.94 for 1 gastric hpf. AUROC, area under the receiver operating characteristic; EoD, eosinophilic duodenitis; EoG, eosinophilic gastritis; eos, eosinophil; hpf, high-power field; ROC, receiver operating characteristic.

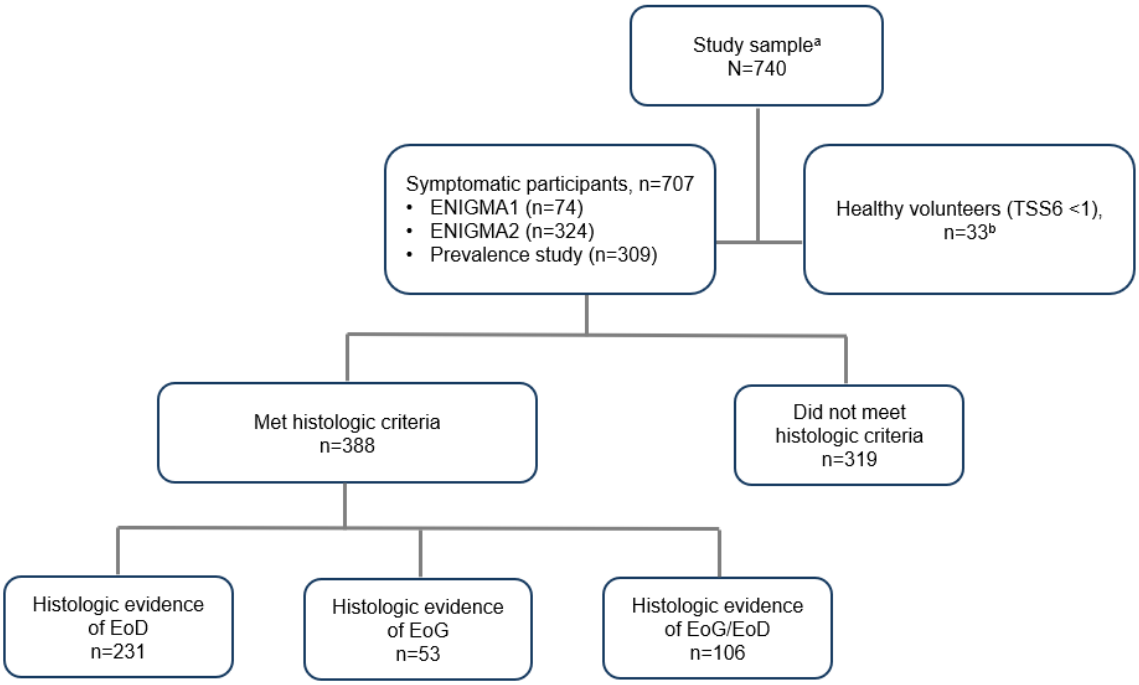
Determination of Optimal Eosinophil Thresholds for Diagnosis of Eosinophilic Gastritis and Duodenitis: A Pooled Analysis of 4 Prospective Studies

Supplementary Table. Screening Protocol

Symptom PRO	EGD With Biopsy	Histologic Criteria
Symptomatic Participants • Prior diagnosis or suspected EoG/EoD entered screening • TSS6 ≥10 and abdominal pain, diarrhea, or nausea ≥3 on PRO questionnaire ***Healthy Controls*** • TSS6 ≤1	***All Participants*** Multiple biopsies (≥12) were taken from each participant according to a standardized protocol: • 8-10 gastric biopsies • 4-6 duodenal biopsies • Up to 4 esophageal biopsies (only if participant had a history of EoE or if EoE features were observed during EGD)	***All Participants*** Single pathologist evaluated stained biopsy samples and counted eosinophils Entry criteria: • ≥30 eos/hpf in 5 hpfs (stomach) and/or ≥30 eos/hpf in 3 hpfs (duodenum) • No other known cause for GI symptoms or tissue eosinophilia

EGD, esophagogastroduodenoscopy; EoD, eosinophilic duodenitis; EoE, eosinophilic esophagitis; EoG, eosinophilic gastritis; eos, eosinophils; GI, gastrointestinal; hpf, high-power field; PRO, patient-reported outcome; TSS, total symptom score.

Determination of Optimal Eosinophil Thresholds for Diagnosis of Eosinophilic Gastritis and Duodenitis: A Pooled Analysis of 4 Prospective Studies



Supplementary Figure. Participant flow chart. [a]The total study sample reflects individuals with gastric and duodenal biopsy samples. [b]Two healthy volunteers had histologic evidence of EoD. EoD, eosinophilic duodenitis; EoG, eosinophilic gastritis; TSS6, 6-Point Total Symptom Score.