Prospective Endoscopic Activity Assessment for Eosinophilic Gastritis in a Multisite Cohort

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INTRODUCTION: **Eosinophilic gastritis (EG) is a chronic inflammatory disease of the stomach characterized by eosinophil-predominant gastric mucosal inflammation and gastrointestinal symptoms. The aim of this study was to prospectively evaluate endoscopic features in a large series of children and adults with EG to better understand the endoscopic manifestations and develop a standardized instrument for investigations.**

METHODS: **Data were prospectively collected as part of the Consortium for Eosinophilic Gastrointestinal Disease Researchers, a national collaborative network. Endoscopic features were prospectively recorded using a system specifically developed for EG, the EG Endoscopic Reference System (EG-REFS). Correlations were made between EG-REFS and clinical and histologic features.**

RESULTS: **Of 98 patients with EG, 65 underwent assessments using EG-REFS. The most common findings were erythema (72%), raised lesions (49%), erosions (46%), and granularity (35%); only 8% of patients with active histology (≥30 eosinophils/high-power field) exhibited no endoscopic findings. A strong correlation between EG-REFS scores and physician global assessment of endoscopy severity was demonstrated (Spearman $r = 0.84$, $P < 0.0001$). The overall score and specific components of EG-REFS were more common in the antrum than in the fundus or body. EG-REFS severity was significantly correlated with active histology, defined by a threshold of ≥30 eosinophils/high-power field ($P = 0.0002$).**

DISCUSSION: **Prospective application of EG-REFS identified gastric features with a strong correlation with physician global assessment of endoscopic activity in EG. Endoscopic features demonstrated greater severity in patients with active histology and a predilection for the gastric antrum. Further development of EG-REFS should improve its utility in clinical studies.**

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INTRODUCTION

Eosinophilic gastritis (EG) is a Th2-associated inflammatory disease of the stomach characterized by eosinophil-predominant gastric mucosal inflammation and gastrointestinal symptoms. Reported symptoms of EG include abdominal pain, nausea, vomiting, early satiety, diarrhea, and weight loss. EG may occur concomitantly with features consistent with eosinophilic esophagitis (EoE), eosinophilic enteritis, or eosinophilic colitis and falls under the broader category of eosinophilic gastrointestinal disease (EGID) (1). Although less common than EoE, an accurate prevalence of EG is difficult to estimate due to the absence of accepted diagnostic criteria. Based on *International Classification of Diseases, Ninth Revision* coding in a health insurance database, Jensen et al. (2) estimated the prevalence of EG as 6.3 per 100,000 and eosinophilic gastroenteritis as 8.4 per 100,000 in the United States.

Endoscopic features are used as clinically relevant outcomes for the assessment of disease activity in chronic inflammatory gastrointestinal diseases that include EoE, reflux esophagitis, peptic ulcer disease, and inflammatory bowel disease. For these diseases, validated instruments that quantify mucosal injury are used to characterize disease severity and assess therapeutic efficacy in clinical trials. Endoscopic features of EG reported in retrospective studies have included erythema (24%–72%), erosions/ulceration (28%–39%), and nodularity (0%–28%) (1,3–8). A normal appearance has been observed in up to 62% of cases (8). To date, no endoscopic assessment tool exists for EG.

The aim of this study was to prospectively evaluate endoscopic features in a relatively large series of children and adults with EG for the purpose of standardizing nomenclature, improving understanding of the disease manifestations, and developing the foundation for an endoscopic outcome instrument for clinical studies. A secondary aim was to assess the correlation between the severity of endoscopic features and gastric eosinophilia.

METHODS

This study used data that were prospectively collected as part of the Consortium for Eosinophilic Gastrointestinal Disease Researchers (CEGIR), a national collaborative network of 16 academic centers caring for adults and children with eosinophilic gastrointestinal disorders supported by a U54 grant (AI117804) as part of the Rare Disease Clinical Research Network, an initiative of the Office of Rare Diseases Research, and funded through collaboration among NCATS, NIAID, and NIDDK. See supplemental information for listing of CEGIR site investigators and coordinators (Supplementary Digital Content 1, http://links.lww.com/AJG/C432) CEGIR is also supported by the Division of Intramural Research (NIAID) and patient advocacy groups, including the American Partnership for Eosinophilic Disorders, Campaign Urging Research in Eosinophilic Disease, and the Eosinophilic Family Coalition (9,10).

The CEGIR clinical study, Outcomes Measures in Eosinophilic Gastrointestinal disorders Across the ages (OMEGA), is a longitudinal cohort study aimed at understanding the natural history of EoE, EG, and eosinophilic colitis during routine clinical care (11). Patient-reported demographic, clinical, endoscopic, and histologic data were prospectively collected starting in 2015 (9,10,12). Clinical features of subjects were recorded during standard-of-care evaluation with intake and follow-up forms. This study was approved by the institutional review boards of the participating institutions *via* a central institutional review board at Cincinnati Children's Hospital Medical Center. Patient consent was obtained by the participating medical center in accordance with the approved study protocol. All subject data collected for this study were stored at the Data Management and Coordinating Center at the University of South Florida in Tampa, FL. Atopy was defined based on self-report of allergic rhinitis, dermatitis, asthma, and/or food allergy.

For the OMEGA study, EG was defined by the presence of upper gastrointestinal symptoms combined with the histologic finding of ≥30 eosinophils/high-power field (eos/hpf) in 5 high power fields in any part of the gastric mucosa with exclusion of secondary causes of gastric eosinophilia (7,13). During the course of standard-of-care endoscopic examinations, endoscopic features in patients with EG were prospectively recorded in real time using a classification and grading system specifically developed for EG. The system was developed through collaborative input from both pediatric and adult gastroenterologists with expertise in EGID as part of an annual CEGIR meeting held in 2015. A comprehensive list of endoscopic features was assembled, and severity grading was proposed through an iterative process achieved by correspondence with a working group to refine the instrument. The final

Table 1. Eosinophilic Gastritis Reference System classification and grading system for eosinophilic gastritis

Feature	Severity assessment
Erosion/ulceration	0 None 1 Less than 5 erosions 2 Five or more erosions 3 Shallow/superficial ulceration(s) 4 Deep/excavated ulceration <25% of the surface area of specified location 5 Deep/excavated ulceration 25%–50% of the surface area of specified location 6 Deep/excavated ulceration >50% of the surface area of specified location
Granularity	0 None 1 Fine 2 Coarse
Raised lesion (nodularity)	0 None 1 Mild (raised focal nodules with width greater than height) 2 Severe (raised nodules with greater height than width)
Erythema	0 None 1 Mild (pink) 2 Severe (red/hemorrhagic)
Friability/bleeding	0 None 1 Mild (contact bleeding) 2 Severe (spontaneous bleeding)
Folds	0 None 1 Thickened folds
Pyloric stenosis	0 None 1 Present (inability to pass diagnostic 8–10 mm upper endoscope)

Except for pyloric stenosis, scoring is performed for each of 3 regions of the stomach (fundus, body, and antrum) for a maximal total score of 46. Figure 1 provides examples of each feature.

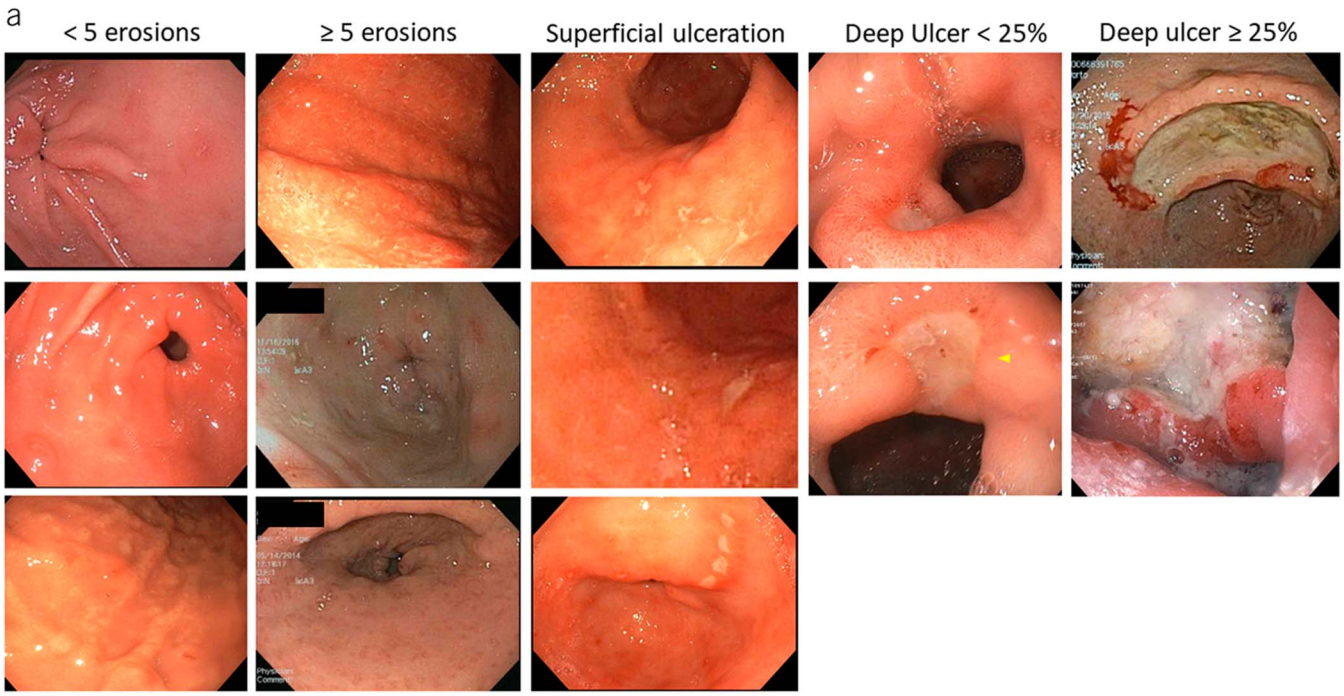
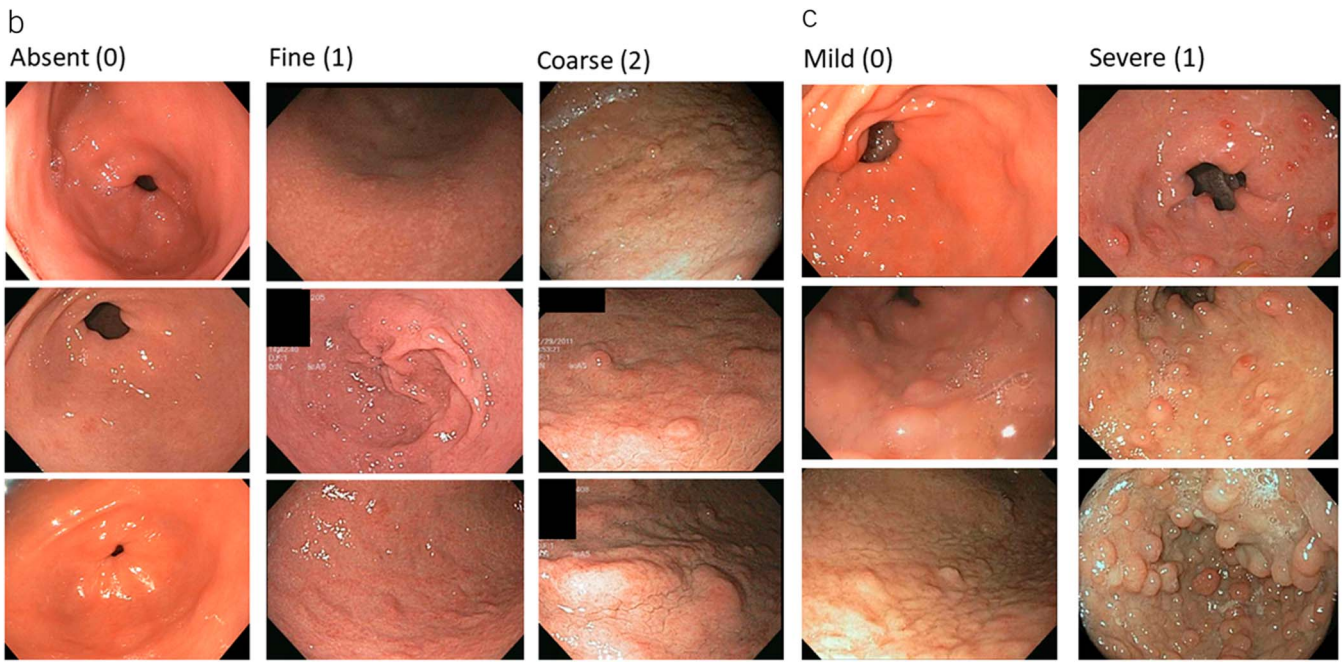


Figure 1. Classification and severity assessment of endoscopically identified gastric features of eosinophilic gastritis that include erosion/ulceration (**a**), granularity (**b**), raised lesions/nodules (**c**), erythema (**d**), thickened folds (**e**), and friability (**f**). Pyloric stenosis was also included as a feature but is not depicted.

instrument termed the EG Endoscopic Reference System (EG-REFS), modeled on the EoE endoscopic scoring metric EREFS (14), included features of erosion/ulceration, granularity, raised lesions, erythema, friability, fold thickness, and pyloric stenosis (Table 1 and Figure 1). EG-REFS scores were separately assessed in the gastric fundus, body, and antrum. A composite EG-REFS score was calculated as the sum of the EG-REFS scores for each feature from the 3 locations. Physician overall global assessment of endoscopic severity was scored on a 5-point Likert scale (from 0, normal, to 5, most severe).

Histologic evaluation

Biopsies were obtained using standard-of-care protocols at each institution. Use of a systematic location and number of biopsies



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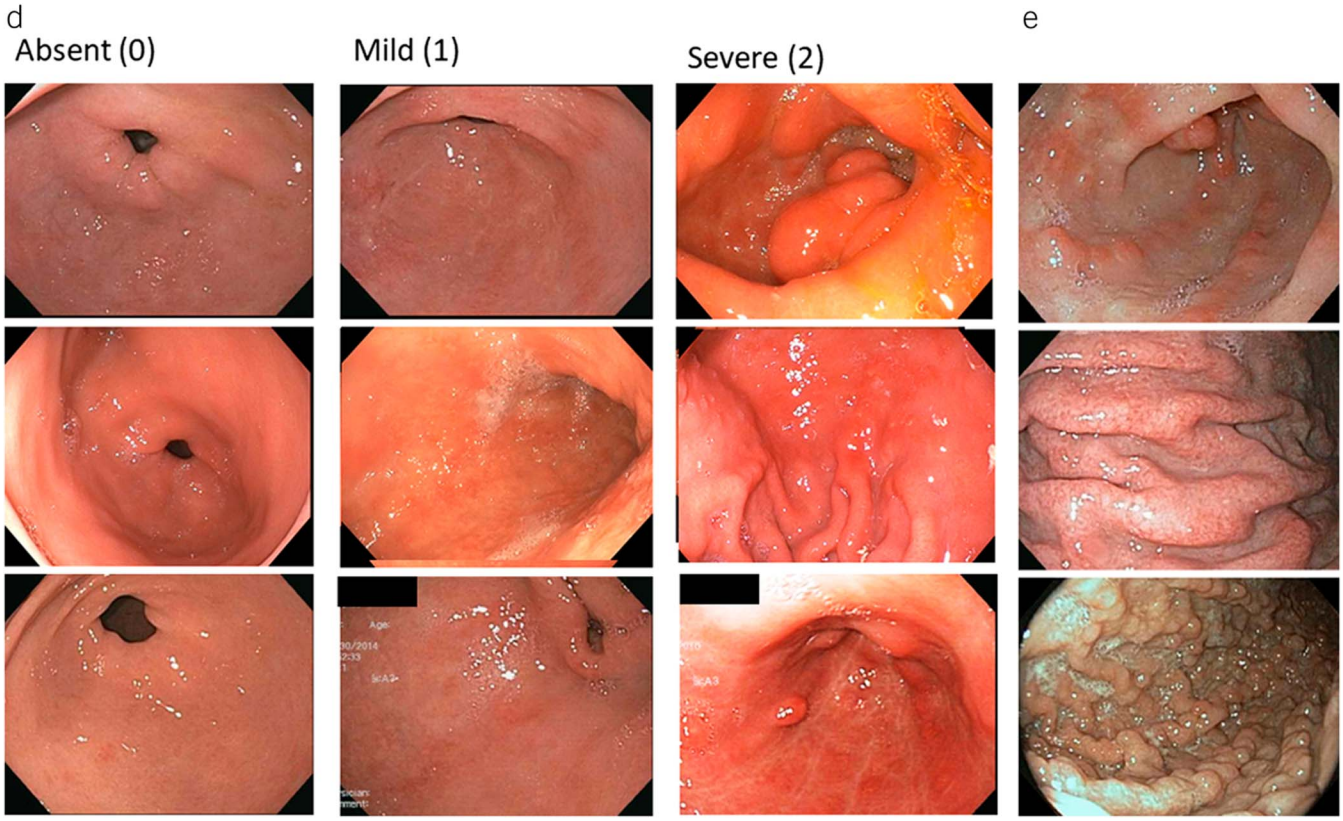

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was not required for the diagnosis of EG. Whole slide images of gastric biopsies (×400 magnification) obtained within ±30 days of PRO completion were reviewed by pathologists comprising the CEGIR Pathology Core (M.H.C., K.E.C., and G.-Y.Y.). Pathologists were blinded to treatment status and therapy at the time the biopsies were procured. Peak and mean eosinophil densities were based on a review of 5 high power fields that were selected with the greatest inflammation.

Symptom evaluation

Symptoms were prospectively assessed using the Severity Of Dyspepsia Assessment (SODA) instrument. Symptom data were included only for the subset of patients with completed questionnaires. For the patients with EG-REFS, only SODA data completed within 30 days of the endoscopic examination were included. Symptoms of abdominal pain, nausea, heartburn, and dyspepsia were reported.

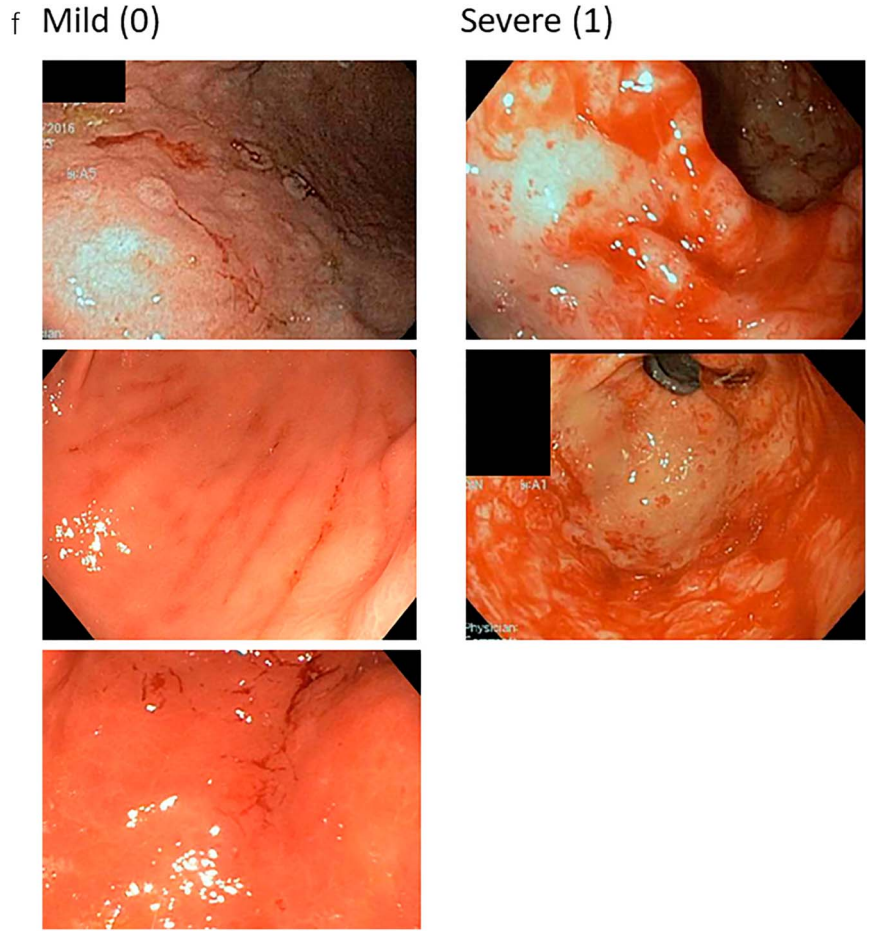
Statistical methods

Demographic and clinical characteristics were summarized using frequency and percentage for categorical variables and median (interquartile range [IQR]) for the continuous variables. For analyses that investigate the association between histology and endoscopy data, visits were identified where histology and endoscopy data were both available. If there was more than 1 visit meeting this criterion, the visit with the most severe inflammatory features based on histologic evaluation was selected for the purpose of evaluating EG-REFS scores. For analyses focused on endoscopy data only, the endoscopy visit date with the highest total score in the fundus, body, and antrum combined was selected if there was more than 1 visit for the participant.

Spearman nonparametric correlations (Spearman r) were used to assess the relationship between the following pairs of measurements: (i) eosinophil density and EG-REFS scores based on region of stomach; (ii) physician global assessment of endoscopic severity and EG-REFS scores based on region of the stomach; (iii) physician global assessment of endoscopic severity and individual features of EG-REFS based on regions of the stomach; and (iv) duration of disease at time of endoscopy and EG-REFS scores. The Wilcoxon rank sum test was used to compare EG-REFS scores between patients with isolated EG vs those with EG combined with esophageal and/or colonic involvement. The Wilcoxon signed rank test for paired data with the Hochberg-Benjamini multiple testing adjustment was used to test for differences in scores among the 3 regions of the stomach. P values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS, Cary, NC).

RESULTS

A total of 98 patients with EG were enrolled in the CEGIR OMEGA study at the time of this study (Table 2). These patients were derived from 9 CEGIR adult and pediatric sites. Among the overall group of 98 patients, 58 patients (59%) experienced gastric involvement in addition to involvement of other regions of the gastrointestinal tract (esophagus and/or colon). Fifty-one patients (53%) experienced concurrent EG and esophageal involvement (>15 eos/hpf). The median age of 17 years reflected a predominantly pediatric subgroup, with 59% younger than 18 years at the time of endoscopy. Similar to the demographic



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characteristics found in the general EoE population, patients with EG were predominantly White (85%). Approximately half were male individuals (53%). Atopy was present in 55%. No patient had evidence of concomitant *Helicobacter pylori* on immunohistochemical staining of gastric biopsies. Most of the patients were on active medical or diet therapy at the time of evaluation. Available symptom data using the SODA instrument demonstrated that 63% experienced abdominal pain, whereas approximately half the patients experienced nausea, heartburn, or bloating.

Sixty-five patients underwent real-time, prospective evaluation of endoscopic features using EG-REFS (Tables 2 and 3). Demographic and disease characteristics were similar between the overall EG cohort of 98 patients and the 65 patients with EG-REFS. Notably, 82% were on active therapy for EG at the time of the endoscopic assessment. Endoscopic abnormalities (EG-REFS score >0) were identified in 53 of the 65 patients (82%). The most common abnormalities included erythema (72%), raised lesions (49%), erosions (46%), and granularity (35%) (Figure 2). Thickened gastric folds and pyloric stenosis were the least prevalent features, identified in less than 17% and 2% of patients, respectively. EG-REFS scores spanned from 0 to 24 of a maximal score of 46 (Figure 2). The median composite EG-REFS score for the cohort was 4 (IQR 1–7). The severity of the composite EG-REFS scores strongly correlated with the endoscopic physician global assessment (Spearman $r = 0.84$, $P < 0.0001$; Figure 3). No significant differences were found in the EG-REFS scores when comparing endoscopic activity in patients with isolated EG (5.0; IQR 1.5–6.5) when compared with those with a combination of EG and esophageal or colonic eosinophilic involvement (3.0; IQR 1.0–7.5) ($P = 0.65$).

Pairwise comparisons demonstrated significant differences in EG-REFS scores between the antrum, body, and fundus, with the greatest severity in the antrum ($P < 0.001$ for all pairwise comparisons) (Table 3 and Figure 4). Erosions or ulcerations were identified in the antrum in 42% of patients but only 16% in the body and 3% in the fundus. Raised lesions or nodules were present in 42% of patients in the antrum, 28% in the body, and 6% in the fundus. Similar gradients of endoscopic activity from the antrum to body to fundus were noted for granularity, erythema, and friability.

Comparing the individual features of EG-REFS with physician global assessment of endoscopic severity demonstrated the strongest correlations for raised lesions (nodularity), erosion/ulceration, erythema, friability, and granularity, particularly in gastric antrum (Table 4). The weakest correlations were noted for thickened folds and pyloric stenosis.

Baseline demographic and clinical characteristics were compared with endoscopic severity. Age at baseline showed a weak correlation with the composite EG-REFS scores ($r = 0.26$, $P = 0.04$). Sex, atopy, and presence of concomitant eosinophilic GI

Table 2. Clinical, demographic, and clinical characteristics of EG cohort

	EG (n = 98)	EG with EG-REFS (n = 65)
Isolated EG (no secondary location), n (%)	40 (40)	24 (37)
EG with esophageal involvement only, n (%)	51 (53)	36 (55)
EG with colonic involvement only, n (%)	2 (2)	2 (3)
EG with both esophageal and colonic involvement, n (%)	5 (5)	3 (5)
Age (yr), median (IQR)	17.1 (12.3, 30.6)	17.8 (12.8, 31.3)
Age younger than 18 yr, n (%)	58 (59)	35 (54)
Male sex, n (%)	51 (53)	37 (57)
Race, n (%)		
White	81 (85.3)	54 (83.1)
African American	8 (8.4)	6 (9.2)
Native American	1 (1.1)	1 (1.5)
Asian	5 (5.3)	4 (6.2)
Duration of disease at endoscopy visit (yr), median (IQR)	NA	4.0 (1.7–7.6)
Atopy, n (%)	54 (55.1)	40 (61.5)
Active therapy, n (%)	72 (73)	53 (82)
Elemental diet only	1 (1)	1 (2)
Elimination diet only	7 (10)	5 (9)
Swallowed topical steroids only	8 (11)	5 (9)
Oral systemic steroids only	2 (3)	2 (4)
Proton pump inhibitor only	7 (10)	5 (9)
Combined therapy (more than 1 therapy of the above)	42 (58)	33 (63)
None	4 (6)	2 (4)
Other only	1 (1)	0
Symptoms based on Severity Of Dyspepsia Assessment, n (%)	N = 27	N = 26
Abdominal pain	17 (63)	17 (65)
Nausea	12 (44)	12 (46)
Heartburn	12 (44)	13 (50)
Bloating	14 (52)	13 (50)

EG, eosinophilic gastritis; EG-REFS, EG Endoscopic Reference System score; IQR, interquartile range; NA, not applicable.

disease outside the stomach (i.e., esophageal or colonic involvement) did not influence the endoscopic activity. Duration of disease defined by date since histologic diagnosis of EG to date of endoscopy for CEGIR was moderately associated with the composite EG-REFS score (Spearman $r = 0.48$, $P < 0.001$; Figure 5). Physician global assessment of endoscopic severity also showed significant but lower correlation with duration of disease ($r = 0.33$; $P = 0.02$). Histologic data were available for 57 of the 65 patients with EG-REFS data. Eight patients had missing histologic data. Forty six percentage (26/57) of patients had active pathology at the time of endoscopy, defined as ≥30 eos/hpf in 5 hpf. Endoscopic abnormalities were demonstrated in 92% of patients with active pathology and in 61% of patients with inactive pathology ($P = 0.0126$). Composite EG-REFS scores were significantly higher in patients with active pathology (median 5.0 [IQR 3.0–7.0]) compared with those in patients with inactive pathology (median 2.0 [IQR 0.0–3.0]); $P = 0.0002$. Furthermore, the peak and mean eosinophil densities demonstrated moderate correlations with EG-REFS activity in the fundus, body, antrum, and overall locations (Table 5). Global endoscopy scores also showed a significant association with active pathology with median scores in patients with active pathology of 4.5 (IQR 2.0–7.0) vs those in patients with inactive pathology of 1.0 (IQR 0.0–4.0); $P = 0.0013$.

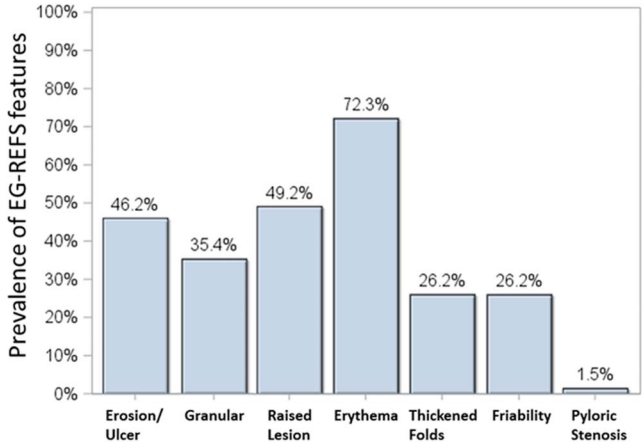

Figure 2. Prevalence of specific endoscopic features of EG-REFS. Erythema was the most commonly identified gastric abnormality, followed by raised nodules and erosion/ulceration. The prevalence and severity assessment may have been affected by the active use of medical or dietary therapies in most of the patients. EG-REFS, Eosinophilic Gastritis Endoscopic Reference System.

DISCUSSION

The EG-REFS classification and grading system prospectively assessed the presence and severity of endoscopically identified gastric abnormalities in a cohort of patients with EG. The most common features identified included erythema, raised lesions, erosions, and granularity that were notably more pronounced in the gastric antrum. In the subset of patients with active histopathology, 92% of patients exhibited 1 or more endoscopic abnormalities identified by EG-REFS. This prevalence is notably higher than that previously reported in several retrospective pediatric and adult series, where only approximately 50% of patients experienced abnormalities (3,4,7). We postulate that the increased detection is related to the prospective data acquisition, experience of the CEGIR investigators, and systematic inclusion of multiple features. It should be noted that one Japanese study that carefully reassessed endoscopic images of the stomach reported higher prevalence of endoscopic abnormalities compared with studies relying on endoscopic reports (6). Of note, this study also identified mucosal cracks (fissures), rings, and white exudate similar to features described in EoE that were not included in EG-REFS (6). The heterogeneity in the prevalence of endoscopic findings may be related to varied

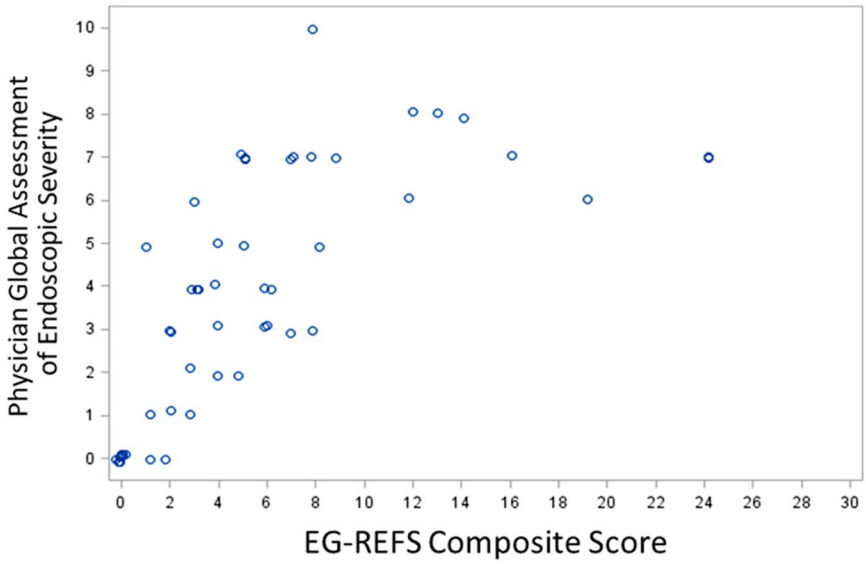

Figure 3. Endoscopic activity of eosinophilic gastritis measured by the composite EG-REFS strongly correlates with physician global assessment of endoscopic severity (Spearman correlation r 0.84, $P < 0.0001$). EG-REFS, Eosinophilic Gastritis Endoscopic Reference System.

demographics, diagnostic criteria, and use of active medical/diet therapies at the time of the endoscopies across studies.

The EG-REFS demonstrated a strong correlation with physician global assessment of endoscopic activity, supporting the face validity of the system to capture the relevant aspects of disease activity determined by the endoscopist. The correlation of EG-REFS with overall severity was primarily due to features of erosion/ulceration, granularity, raised lesions/nodules, erythema, and friability. Abnormalities were significantly more common in the gastric antrum relative to the body or fundus, which correlated with histologic activity. The reason for antral predominance of disease activity is unclear but could be related to distinct mucosal cell types, concordant duodenal-gastric reflux, or distinct functional differences in the different regions of the stomach. Although endoscopic severity did not seem to vary with age, sex, or atopic status, severity was notably greater in patients with a longer duration of disease.

Development of endoscopic assessment tools will allow not only standardization of nomenclature but also may provide a disease metric to complement symptom and histologic features in the assessment of therapeutic response in clinical practice and in medical/dietary trials. Currently, the clinical management of EGID focuses on symptom and histopathologic outcomes. The multitude of symptom manifestations of EG that include abdominal pain, nausea, vomiting, anorexia, and early satiety create challenges in assessment. Owing to adaptive behaviors of food avoidance and variations in sensory perception, symptoms may not accurately reflect disease activity. Moreover, EG may present with iron deficiency anemia, occult bleeding, nutrient malabsorption, or protein-losing enteropathy in the absence of overt symptoms (15). For these reasons, symptom improvement may be an inadequate indicator of response to therapeutic intervention. Histologic assessments are limited as a sole therapeutic marker of disease control especially because EG inflammation can be focal with variable severity and biopsies sample only a small fraction of the overall gastric mucosa. Although data to support this notion are not available for EG, EoE, and inflammatory bowel disease, a correlation between validated patient-reported symptom assessment instruments and histologic activity has been only modest (11,16,17). Such dissociations point to the importance of objective measures of disease activity using metrics such as endoscopic activity.

In EoE, endoscopic features are more strongly correlated with symptoms and the EoE genetic transcriptome than with eosinophil density (10,18,19). A case series correlated gene expression patterns using microarray analyses and endoscopic features among 8 children with EG (20). Substantial overlap in gene expression profiles was found when comparing patients with endoscopic findings of nodules compared with those with ulcerations. In a previously published CEGIR study of EG, we evaluated the association between mucosal eosinophilia and endoscopic activity using EG-REFS and several genes, including *CCL26* (eotaxin-3), *CLC* (Charcot Leyden crystal, an eosinophil-specific marker), *IL13RA2* (IL-13 receptor alpha 2), *IL5*, and *SST* (somatostatin) (21). *CCL26* showed the strongest correlation with any endoscopic features, most notably nodularity and granularity, followed by *IL33*, which inversely correlated most notably with granularity and friability and bleeding (21). Of interest, clustering of EG gene expression profiles separated endoscopic features into 2 general groups. The first group, which was associated with friability/bleeding and erythema, correlated with down-regulation of molecular signatures (*ATP4A*, *IL33*, and *SLC26A7*), whereas the second group was associated with nodularity and granularity correlated with upregulation of type 2 immunity and eosinophil-associated pathways (*CCL26*, *IL13RA2*, and *IL5*). Further studies are needed to better define the clinical and pathophysiologic implications of these findings.

This study has several important limitations. Acknowledging that EG is a rare disease, the sample size of this study was small, limiting the power to detect potentially meaningful associations. The EG-REFS system was based on expert opinion and literature review and is not a validated instrument but represents a first step toward this end. Endoscopic assessments were not obtained in a blinded manner. The sensitivity and specificity of EG-REFS in the diagnosis of EG could not be established because of the lack of validation and heterogeneity of the patient population and

Table 3. Prevalence of endoscopically detected gastric abnormalities specified by region among cohort with prospective endoscopic assessment using EG-REFS

	Fundus (N = 64)	Body (N = 64)	Antrum (N = 65)	Highest score of 3 locations (N = 65)
Total score: median (interquartile range)	0 (0, 0)	1 (0, 2)	2 (1, 5)	3 (1,5)
	n (%)	n (%)	n (%)	
Granularity				
0	57 (89)	48 (75)	46 (71)	42 (65)
1	6 (9)	10 (16)	12 (18)	16 (25)
2	1 (2)	6 (9)	7 (11)	7 (10)
Erosion/ulceration				
0	62 (97)	54 (84)	38 (58)	35 (55)
1	1 (2)	5 (8)	13 (20)	14 (22)
2	0	2 (3)	7 (11)	8 (12)
3	0	2 (3)	5 (8)	5 (8)
4	0	1 (2)	1 (2)	1 (1)
5	0	0	1 (2)	1 (1)
6	1 (2)	0	0	1 (1)
Raised lesion				
0	60 (94)	46 (72)	38 (58)	33 (51)
1	1 (2)	12 (19)	15 (23)	17 (26)
2	3 (5)	6 (9)	12 (18)	15 (23)
Erythema				
0	56 (88)	35(55)	21 (32)	18 (28)
1	6 (9)	22 (34)	34 (52)	35 (54)
2	2 (3)	7 (11)	10 (15)	12 (18)
Friability/bleeding				
0	61 (95)	56 (88)	50 (77)	48 (74)
1	2 (3)	7 (11)	12 (18)	13 (20)
2	1 (2)	1 (2)	3 (5)	4 (6)
Folds				
0	63 (98)	60 (94)	56 (86)	54 (83)
1	1 (2)	4 (6)	9 (14)	11 (17)
Stenosis				
0	NA	NA	64 (99)	64 (99)
1	NA	NA	1 (2)	1 (2)

EG-REFS, Eosinophilic Gastritis Endoscopic Reference System; NA, not applicable.

endoscopist experience. Indeed, awareness of an existing diagnosis of EG may bias reporting of endoscopic features. Because most patients were on active medical or diet therapy at the time of the index endoscopy, the burden of endoscopic abnormalities was likely underestimated, as reflected by the low composite EG-REFS scores. Active therapy may also have affected observations regarding regional differences and temporal progression of EG. Because most patients were children, further studies are needed to confirm the generalizability of the results to an adult population. In addition, our study evaluated only EG patients with mucosal involvement. Muscular and serosal variants of EG without mucosal pathology were not included. Finally, diagnostic criteria for the histopathology and definition of histologic activity used in the study were based on limited data and may change with further consensus and research.

Strengths of the study include the prospective, multicenter collection of baseline demographic, clinical, and endoscopic data that enhanced the accuracy and completeness of data capture for correlation with endoscopic features. Use of real-time endoscopic evaluation is likely a more robust means of assessment of disease activity compared with a retrospective review of endoscopy reports or digital still images. Previous studies have described erythema, nodularity, and ulceration as features of EG, but none have systematically and prospectively assessed these features (3,4,7). Additional features not

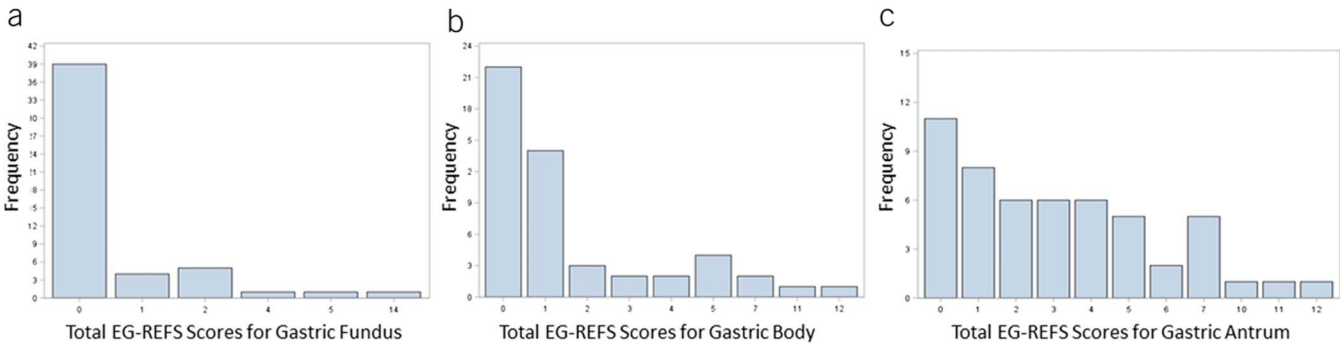

Figure 4. Endoscopic activity of eosinophilic gastritis measured by EG-REFS based on region of the stomach. Pairwise comparisons demonstrated significant differences in EG-REFS scores between the antrum, body, and fundus with significantly greatest severity in the antrum ($P < 0.001$). EG-REFS, Eosinophilic Gastritis Endoscopic Reference System.

Table 4. Correlation of physician global endoscopic severity with individual features of EG-REFS

	Antrum (N = 65)		Body (N = 64)		Fundus (N = 64)	
	Spearman *r*	*P*	Spearman *r*	*P*	Spearman *r*	*P*
Raised lesion	0.60	<0.001	0.46	<0.001	0.36	0.003
Erythema	0.59	<0.001	0.43	<0.001	0.29	0.02
Erosion/ulceration	0.52	<0.001	0.35	0.004	0.13	0.31
Friability/bleeding	0.49	<0.001	0.36	0.004	0.19	0.13
Granularity	0.44	<0.001	0.37	0.003	0.39	0.001
Folds	0.21	0.09	0.30	0.014	0.20	0.11
Pyloric stenosis	0.15	0.24	NA		NA	

EG-REFS, Eosinophilic Gastritis Endoscopic Reference System; NA, this feature was not scored in these regions.

previously well characterized in the literature were included based on the experience of a working group of pediatric and adult gastroenterologists with expertise in EGID. These included granularity, nodules, thickened folds, friability, and pyloric stenosis. Finally, this study is the largest prospective study to date of patients with EG. Identification of patients was greatly facilitated by the multicenter and collaborative CEGIR program and the standardized data collection and management across the consortium (9).

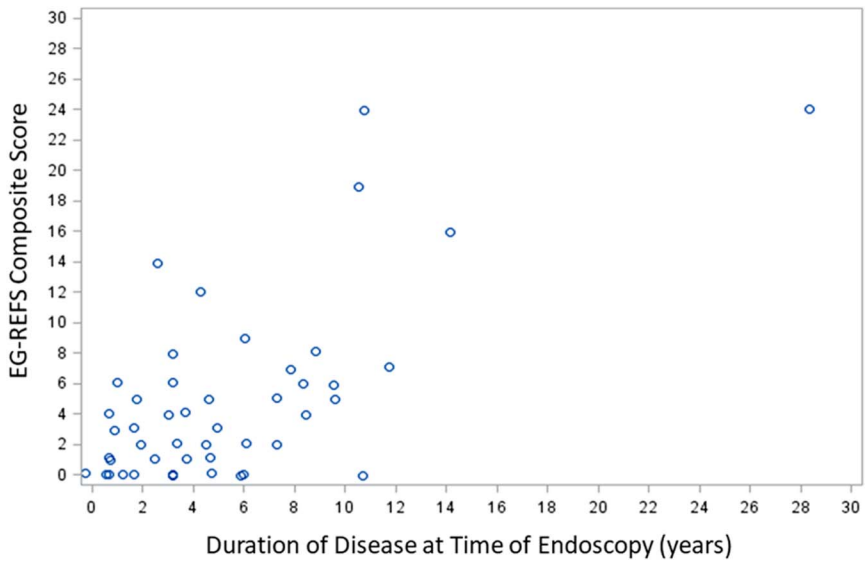

Figure 5. Endoscopic activity of eosinophilic gastritis measured by the composite EG-REFS shows modest correlation with disease duration (Spearman correlation 0.48, $P < 0.001$). EG-REFS, Eosinophilic Gastritis Endoscopic Reference System.

Table 5. Correlations between peak eosinophil density and EG-REFS severity based on region of stomach in patients with eosinophilic gastritis

	Spearman *r* (N = 57)	*P*
Peak eosinophil density		
Total score: fundus (N = 56)	0.38	0.004
Total score: body (N = 56)	0.39	0.003
Total score: antrum (N = 57)	0.32	0.015
Total score across all 3 regions: fundus, body, and antrum (N = 56)	0.43	<0.001
Overall global assessment of endoscopic activity (N = 57)	0.47	<0.001
Mean eosinophil density		
Total score: fundus (N = 56)	0.38	0.004
Total score: body (N = 56)	0.41	0.002
Total score: antrum (N = 57)	0.32	0.014
Total score across all 3 regions: fundus, body, and antrum (N = 56)	0.45	<0.001
Overall global assessment of endoscopic activity (N = 57)	0.46	<0.001

EG-REFS, Eosinophilic Gastritis Endoscopic Reference System.

Future directions should focus on refinement and validation of the EG-REFS. Studies that correlate specific endoscopic features with detailed histopathology beyond eosinophil density would be of interest. Based on the results from this study, specific features such as thickened folds that show limited correlation with the overall severity assessment may be unnecessary. Similarly, the severity scales assigned were based on expert opinion and not clinical outcomes. The low prevalence of specific grades of certain features, such as extensive gastric ulceration, could provide rationale for the simplification of the scales. Studies defining the interobserver and intraobserver reliability of the EG-REFS should also be conducted. Furthermore, application of the EG-REFS to clinical trials will assess the responsiveness of the instrument to therapy and allow for additional refinement.

In summary, we have described the presence and frequency of endoscopic findings in patients with EG prospectively collected through a multicenter study. Furthermore, we have used these data to assess an endoscopic scoring system for the characterization of endoscopically identified gastric features in a relatively large cohort of children and adults with EG. Prospective application of this endoscopic outcome tool revealed that the most common endoscopic abnormalities in EG include erythema, raised lesions, erosions, and granularity and that the antrum has the most visible endoscopic changes. The developed tool was evaluated across pediatric and adult institutional sites, with content validity supported by correlation with global physician assessment of endoscopic findings. Validated outcome measures are increasingly relevant, given the recent rise in scientific interest and investigations in EGIDs. Further refinement and validation of the EG-REFS should improve its potential utility in clinical studies and therapeutics in EGID.

CONFLICTS OF INTEREST

Guarantor of the article: Ikuo Hirano, MD.

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Study Highlights

WHAT IS KNOWN

- ✓ Eosinophilic gastritis (EG) is a rare chronic inflammatory disease of the stomach characterized by eosinophil-predominant gastric mucosal inflammation and gastrointestinal symptoms.
- ✓ Retrospective case series have reported wide variability in both the prevalence and specific endoscopic features in patients with EG.

WHAT IS NEW HERE

- ✓ Prospective application of an endoscopic scoring instrument identified the presence of abnormalities in most of the patients with EG enrolled in a multicenter outcome study.
- ✓ The endoscopic scoring instrument demonstrated strong correlations with physician global assessment of endoscopic activity and moderate correlations with eosinophil density on mucosal biopsies.
- ✓ The most common endoscopically identified features included erythema, raised lesions, erosions, and granularity that were notably more pronounced in the gastric antrum.

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