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A multicenter, retrospective cohort study on the diagnosis, treatment and natural history of eosinophilic gastrointestinal disorders in the Netherlands

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Non-Eosinophilic Esophagitis Eosinophilic Gastrointestinal Diseases (non-EoE EGIDs) are poorly understood. Evaluate clinical manifestations, diagnostics and treatment of non-EoE EGIDs at four hospitals in the Netherlands from 1991 to 2019. For this retrospective cohort study, centralized nationwide network and registry for cyto- and histopathology in the Netherlands (PALGA) was used. Seventy patients consented to participate. Median duration of follow up was 26 months, and median age was 36 years. About 44% had eosinophilic colitis (EoC) and 30% had > 1 GI location (multisite EGID). Most patients (91%) had mucosal type, 6% muscular and 3% serosal EGID. Three patients (4%) did not have follow up. Relapsing remitting in 21% (14/67) patients, with most being multisite (43%; 9/21). Single flares in 57% and chronically symptomatic in 22% of population. Concomitant atopy was seen in 29%. Normal endoscopy results in 61%; ileum was commonly identified normal area. Partial or complete symptom improvement to treatment seen in 71%. Results of the longitudinal retrospective Dutch study do not show progression from single site to multisite EGID or change in EGID type. We conclude that identifying patients requires further research as majority of patients had normal endoscopy and vague abdominal symptoms.

Keywords Eosinophilic esophagitis, Eosinophilic gastroenteritis, Eosinophilic gastritis, Eosinophilic enteritis, Eosinophilic colitis, Eosinophilic gastrointestinal disorders

Abbreviations

EGE	Eosinophilic gastroenteritis
EGID	Eosinophilic gastro intestinal disorders
EoC	Eosinophilic colitis
EoE	Eosinophilic esophagitis
EoG	Eosinophilic gastritis
EoN	Eosinophilic enteritis
GI	Gastrointestinal

Eosinophilic gastrointestinal diseases (EGID) are characterized by infiltration of eosinophils into the gastrointestinal tissue, without an identifiable secondary cause[1–3]. Eosinophilic esophagitis (EoE) is the most common and investigated EGID condition. Non-EoE EGID include eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC)[2]. Multiple GI locations with eosinophilia were historically categorized as 'eosinophilic gastroenteritis' (EGE). Expert consensus proposed new nomenclature[2,3] to standardize by location, with or without dominant symptoms[2,4]. EoN is further categorized as eosinophilic duodenitis [EoD), eosinophilic jejunitis (EoJ) and eosinophilic ilieitis (EoI)[2].

Underlying pathophysiology is thought to be type 2 driven immune-mediated chronic inflammation caused by food allergen triggers[1,5–7]. For consistency, EGID discussed here will reference non-EoE EGIDs. EGID is

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associated with a family history of allergic disorders, food allergies and/or atopy[6,8], like EoE[9]. There is variable prevalence[10,11], but a recent systematic review identified prevalence in non-EoE symptomatic EGID as 1.9% of general population[10]. Clinical presentation is dependent on depth of disease and age of onset[7]. Endoscopic and histologic criteria is not well defined for universal application despite being the foundation of the diagnostic process[2–4,12–14]. A normal esophagus lacks eosinophils which makes a threshold easier to determine when abnormal. However, it is normal to see eosinophils in the rest of the gastrointestinal (GI) tract. Recent pediatric EGID consensus made specific recommendations for eosinophil counts in the stomach, small bowel, and colon[3], but such consensus for adults are pending[2].

Given the rarity of EGID, variability in presentation, and lack of diagnostic criteria, it is a challenge to make the diagnosis with certainty[4,7]. There is limited understanding of the natural history and prognosis of the disease[2,15]. Meta analyses and systematic reviews on treatments are based on sparse and heterogenous data[10,11]. There are various single and multicenter experiences[10,15–21], but the criteria for EGID, number of patients and duration of follow up are variable. There is a need to better understand non-EoE EGID for diagnosis, treatment and long term planning[2,4,7].

The intent of this publication is to present data on the clinical, endoscopic, histologic findings, natural history, treatment strategies and prognosis of patients with EGID from a large Dutch cohort.

Methods

For this retrospective cohort study, the nationwide network and registry for cyto- and histopathology in the Netherlands (Automated National Pathological Anatomy Archive -PALGA) was used[22]. PALGA database contains the complete national data from all 46 pathology laboratories and has had national coverage since 1991. Methodology outlining the process and details collected on patients are outlined in Supplementary Appendix A. The selection of patient pathology reports for the study is in Fig. 1. The pathology reports were de-personalized, and patient's physicians and pathology laboratories had to give consent to decode the reports. All participating patients gave informed consent to review their clinical records for this particular study, and publication of results in a de-identified manner. The IRB (Medisch Ethische Toetsingscommissie Amsterdam) did not need a formal expedited review in keeping with Dutch law. The study protocol was approved by IRB (Medisch Ethische Toetsingscommissie Amsterdam) and signed on Jan 31st 2019, which is available on reasonable request.

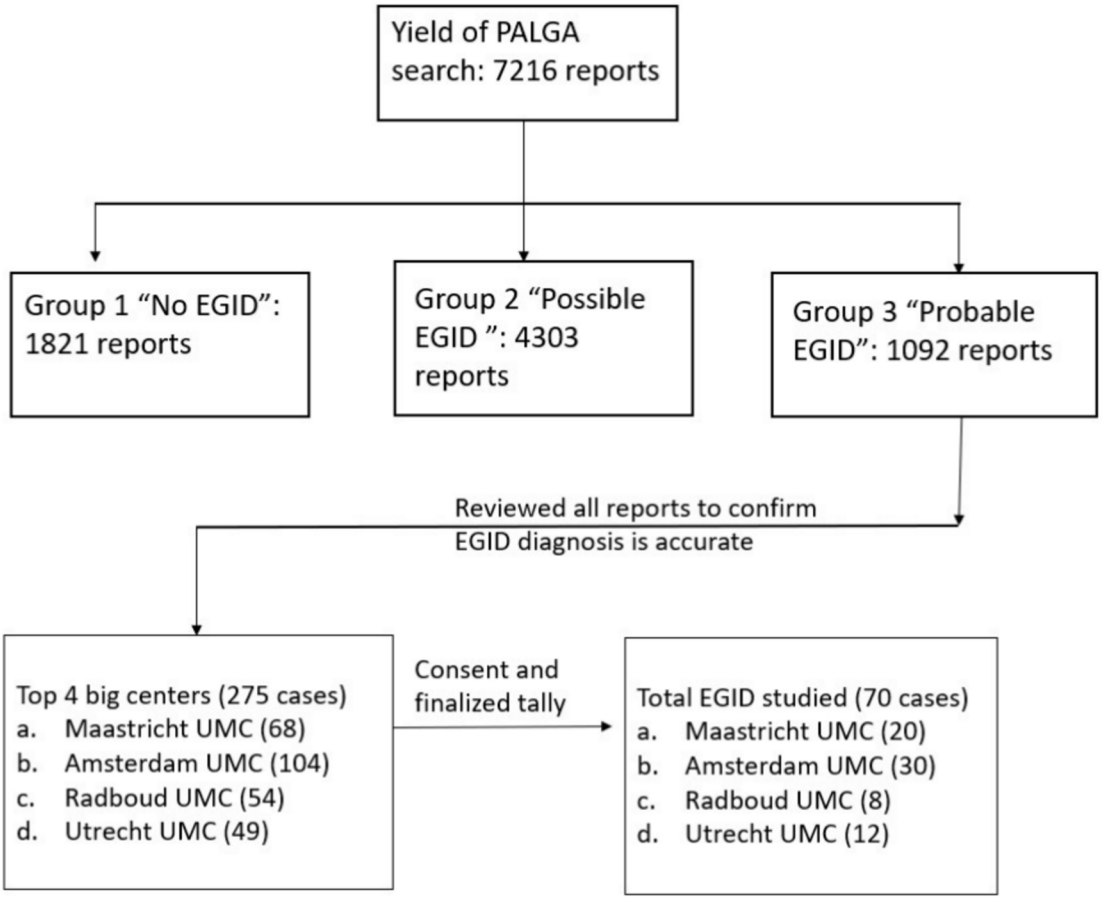

Fig. 1. Patient selection flow chart.

Authors confirm the study was completed in accordance with approved protocol, University regulations and the Declaration of Helsinki.

Diagnostic criteria

EGID diagnosis was confirmed by the combination of clinical symptoms and histologic findings of abnormal eosinophil counts in the GI tract on biopsies. The cut offs were obtained from histologic criterion published by Collins[13], as these have been used in prospective large multicenter studies defining cases of EGIDs[21,23]. Exclusion of secondary causes of eosinophilia was required before inclusion in the EGID cohort. Description of histopathologic inflammation, the pathologist's confidence in the diagnosis, and exclusion of secondary cause was sufficient where eosinophil counts were not reported. A retrospective chart review of consented patients was performed until October 2021.

Statistical analysis

The primary aim of this study was to characterize the clinical, endoscopic, and histologic presentation of EGID. Secondary aim was to document follow up, treatment and natural history of EGID. All data extracted were decoded in Castor (GCP-ICH compliant electronic data capture program; Amsterdam, 2021). Statistical analyses were performed using IBM SPSS Statistics, version 28. Data was reviewed and accuracy confirmed by authors (MG, LH and AM). Normally distributed continuous numerical variables were described as means and standard deviation. Non-normal distributed variables were described as medians and interquartile range (IQR Q1-3). Categorical variables were expressed as absolute (n) and relative (%) frequencies. Differences between variables were compared using parametric and non-parametric tests where appropriate. This study was approved by local IRB and ethics board.

Results

Population

A total of 70 patients consented (30 from Amsterdam UMC, 20 from Maastricht UMC, 12 Utrecht UMC and 8 Radboud UMC) to be studied (Fig. 1). The demographics and test results by EGID type are in Table 1. Median age at diagnosis was 36 years (IQR 17–56); 19 were children (27%). The cohort consisted of 34 males (49%). EGID in > 1 location (multisite EGID) was diagnosed in 21 patients (30%). Details of the involved areas in multisite EGID are in Table 2. Remaining 49 patients had single site EGID. Atopic disease was reported in 20 patients (29%) (Table 1). For patients with documented serum eosinophils, 19/45 (42%) had hypereosinophilia, with no trend for association by EGID type. Stool for parasites were negative in all tested patients.

Clinical symptoms

Diarrhea (60%), abdominal pain (49%), weight loss (24%) and nausea (24%) were top complaints in the cohort. Breakdown of subjects by EGID category are shown in Table 2. Two patients with serosal EGID (1 multisite and 1 EoG) had eosinophilic ascites. Follow up clinically was completed at 28 months for multisite EGID patient, and 8 months for EoG patient. Both patients had response to treatment and did not redevelop symptoms. Three patients (2 multisite EGIDs and 1 EoN) with mucosal EGID had protein losing enteropathy. There were four cases that required surgery or hospitalization, and all were muscular EGID phenotype (1 multisite, 1 EoC, 1 EoN and 1 EoD). One patient was a 66-year-old woman with four discrete episodes of sigmoid volvulus since 2012, managed endoscopically. After her fourth visit in 2017, surgical resection of the involved area was performed for definitive care. Pathology identified lamina propria and muscularis mucosa eosinophilia, fibrosis in the muscle layers and around Auerbach's plexus, consistent with muscular EoC. She was asymptomatic at three month follow up, and has not presented back since. Second patient was a 15-year-old with an acute abdomen at the time of presentation, requiring laparotomy. Resection identified Meckel's diverticulum by appendix, and dense eosinophilia in the associated ileum. Lamina propria, muscularis mucosa and muscle fibers of muscularis propria had eosinophilia involvement, diagnostic for muscular EoN. He has not needed GI treatments since surgery. Third patient was a 14-year-old with duodenal stenosis and ulceration diagnosed with EoD at time of presentation by scope. Treatment with gastric dilation and PPI was beneficial. Endoscopic appearance over four years showed narrowing that required dilation for patient symptoms. He was able to discontinue dilation after four years but continues on PPi. Fourth patient was a 54-year-old with abdominal pain secondary to hamartoma of the papilla of Vater. She had biopsies of papilla, duodenum, stomach and esophagus within one year of the original presentation at a tertiary center (part of reassessment of her diagnosis). Biopsies identified eosinophilia related swelling of the papilla, stomach and duodenum. She was diagnosed as multisite EGID. She required papillotomy, stent exchanges in the biliary ducts and tapering regiment of oral prednisone. She was tapered off prednisone over five months and had complete resolution in symptoms. She was asymptomatic at the seven month follow up, and has not required GI treatment in > 10 years. Muscular EGID did not have recurrence or progression to serosal variant by end of study period.

Endoscopic and histologic findings

Endoscopic appearance at time of diagnosis is shown in Table 3. Multisite EGID are presented as a group in Table 3, and then redistributed by site of disease involvement in Supplementary Appendix B. Normal appearance was the most described finding in multisite EGID (42–88%) (Table 3). When patient data was analyzed by area of disease involvement, colon had the highest rate of abnormality (66%) (supplementary Appendix B).

Histopathology reports (Table 4) describe eosinophilic infiltration in epithelium (89%), lamina propria (72%) and submucosa (14%) in the cohort. Muscularis mucosa (12/70 patients; 17%) and muscularis propria (2/70 patients; 3%) involvement were infrequently reported. Multisite EGID had low levels of inflammatory changes reported (Table 4). When data was aggregated by site of disease involvement (supplementary Appendix C), all

	Total patients (n = 70) (%)	Multi-site (n = 21) (%)	EoG (n = 10) (%)	EoN (n = 8) (%)	EoC (n = 31) (%)
Age (mean)	36 (17–56)	29 (16–44)	36 (22–68)	39 (24–62)	41 (2–61)
Male (%)	34 (49)	11 (52)	3 (30)	4 (50)	16 (52)
Atopic (%)	20 (29)	8 (38)	5 (50)	4 (50)	3 (10)
Asthma	6 (9)	2 (10)	1 (10)	2 (25)	1 (3)
Rhinosinusitis	10 (14)	5 (24)	1 (10)	2 (2%)	2 (7)
Food allergy	8 (11)	5 (24)	3 (30)	0 (0)	0 (0)
Eczema	1 (1)	0 (0)	0 (0)	0 (0)	1 (3)
Stool test, completed and negative (%)	44 (63)	16 (76)	8 (80)	3 (38)	17 (55)
Blood eosinophil count completed (y/n) (%)	45 (64)	15 (70)	8 (80)	6 (75)	16 (52)
Blood eosinophil count (median) (× 10^9/L)	0.41 (0.18–1.53)	0.40 (0.28–1.55)	0.30 (0.13–1.68)	1.08 (0.13–2.38)	0.38 (0.17–1.15)
Elevated blood eosinophil count (× 10^9/L) (%)	19 (42)	7 (47)	3 (38)	2 (33)	7 (44)
Clinical presentation (%):					
Heartburn	5 (7)	3 (14)	2 (20)	0 (0)	0 (0)
Early satiety	3 (4)	1 (5)	2 (20)	0 (0)	0 (0)
Loss of appetite	7 (10)	5 (24)	1 (10)	1 (13)	0 (0)
Burping	1 (1)	0 (0)	1 (10)	0 (0)	0 (0)
Bloating	5 (7)	0 (0)	2 (20)	2 (25)	1 (3)
Nausea	17 (24)	6 (29)	5 (50)	6 (75)	0 (0)
Vomiting	14 (20)	5 (24)	4 (40)	5 (63)	0 (0)
Hematemesis	3 (4)	0 (0)	2 (20)	1 (13)	0 (0)
Abdominal pain	34 (49)	11 (52)	5 (50)	6 (75)	12 (39)
Obstipation	2 (3)	0 (0)	0 (0)	0 (0)	2 (7)
Diarrhea	42 (60)	16 (76)	2 (20)	1 (13)	23 (74)
Bloody diarrhea	10 (14)	1 (5)	1 (10)	0 (0)	8 (26)
Melena	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)
Variable bowel movements	4 (6)	1 (5)	0 (0)	0 (0)	3 (10)
Weight loss	17 (24)	7 (33)	3 (30)	2 (25)	5 (16)
Ascites (eosinophilic)	2 (3)	1 (5)	1 (10)	–	–
Protein loosing enteropathy	3 (4)	2 (10)	–	1 (13)	–

Table 1. Characteristics and clinical presentation of EGID patients by category of disease. *Multi-site* more than 1 area of GI tract involved with eosinophilia, *EoG* eosinophilic gastritis, *EoN* eosinophilic enteritis, *EoC* eosinophilic colitis.

EoIC (n = 6)	eosinophilic ileitis and colitis
EoGD (n = 5)	eosinophilic gastritis and duodenitis
EoGC (n = 3)*	eosinophilic gastritis and colitis
EoDC (n = 3)	eosinophilic duodenitis and colitis
EoGDC (n = 1)	eosinophilic gastritis, duodenitis and colitis
EoGDIC (n = 1)	eosinophilic gastritis, duodenitis, ileitis and colitis
EoEG (n = 1)	eosinophilic esophagitis and gastritis
EoEC (n = 1)	eosinophilic esophagitis and colitis

Table 2. Breakdown of multisite EGID by areas of involvement and total number of patients in each subgroup (n = 21). *one patient with EoGC had eosinophilic esophagitis.

regions had similar rates of abnormality. Severity of presentation was not an indicator for detailed pathology reporting. Based on pathology and clinical data, mucosal phenotype was seen in 64 (91%) patients, muscular in four (6%) and serosal in two (3%) patients.

Treatment and follow up

Due to variability of follow up, the first treatment in management is captured in Table 5. There was no preference for an agent when results reviewed by treatment center. Topical steroids were most often used (24%), followed by oral prednisone (14%) and nutritional supplements (13%). For three patients with concomitant EoE, no treatment was used in two patients, and elimination diet in one patient (targeting EoC). Treatments for multisite EGID are listed by site of involvement in supplementary Appendix D. Due to limited number of patients treated with specific agent (Table 5), statistical analysis could not be completed. No adverse events or drug discontinuation

Endoscopic findings	Multisite EGID (n = 21) (%)	EoG (n = 10) (%)	EoD (n = 5) (%)	EoI (n = 3) (%)	EoC (n = 31) (%)
Normal appearance					
Stomach	5/12 (42)	3 (30)	–	–	–
Duodenum	6/8 (75)	–	0 (0)	–	–
Ileum	7/8 (88)	–	–	1 (33)	–
Colon	10/15 (67)	–	–	–	11/29* (38)
Stomach	12	10			
Erythema	3 (25)	3 (30)			
Edema	1 (8)	1 (10)			
Gastritis	3 (25)	5 (50)			
Nodularity	1 (8)	0 (0)			
Ulcers	0 (0)	1 (10)			
Polyps	1 (8)	0 (0)			
Duodenum	8		5		
Erythema	1 (13)		1 (20)		
Edema	0 (0)		0 (0)		
Duodenitis	1 (13)		2 (40)		
Nodularity	0 (0)		0 (0)		
Ulcers/aphthous	0 (0)		2 (40)		
Polyps	0 (0)		0 (0)		
Ileum	8			3	
Erythema	0 (0)			0 (0)	
Edema	0 (0)			0 (0)	
Ileitis	1 (13)			1 (33)	
Nodularity	0 (0)			0 (0)	
Ulcers/aphthous	0 (0)			2 (67)	
Polyps	0 (0)			0 (0)	
Colon	15				29
Erythema	1 (7)				8 (28)
Edema	1 (7)				7 (24)
Colitis	1 (7)				9 (31)
Nodularity	0 (0)				0 (0)
Ulcers/aphthous	3 (20)				2 (7)
Polyps	1 (7)				2 (7)

Table 3. Endoscopic abnormalities by category of disease at time of diagnosis (multisite EGID vs. single organ EGID). *Multi-site* more than 1 area of GI tract involved with eosinophilia, *EoG* eosinophilic gastritis, *EoD* eosinophilic duodenitis, *EoI* = eosinophilic ileitis; EoC = eosinophilic colitis. *2 rectum suction biopsies acquired to make diagnosis, and do not have endoscopic description.

were reported with treatment. One-third of EoG and EoN chose to follow up but have no treatment. Second line treatment was needed for 14 patients (20%); multisite EGID being most represented (43%) and EoC (6%) the least. Treatments were variable regardless of location of disease, with single or combination of agents used. There were no patients treated with biologics.

Timeline to treatment efficacy was variable in the cohort (Table 5). Median duration of follow up was 26 months (IQR 8–68). Only three patients had no follow up data. Symptom assessment was available in 96% patients. Symptomatic improvement was seen in 71%: EoC had the most improvement to treatment (85%) and EoG the least (50%). Topical steroids were most often used (39%) in EoC and oral steroids in multisite EGID (Table 5). No change in symptoms despite intervention was reported in 24% of the cohort, and multisite EGID was the most represented group (43%). No cancers were reported and none of the patients re-developed, or newly developed, complications by end of the study period. Median time to scope was 11 months (IQR 4–19). Approximately 2/3 of patients had endoscopic resolution of inflammation. None of single site EGID patients on follow up endoscopy were noted to transition to multisite EGID by end of study period. Comparative reporting by pathologist was not often systematically performed. In those with longitudinal follow up, single flares were seen in 57% (38/67 patients) of the cohort. Relapsing remitting in 21%; multisite EGID had the highest representation (43%; 9/21 patients). Chronically symptomatic flares in 22%; EoC patients (9/31; 29%) had the longest follow up data.

Histologic findings	Multisite EGID (n = 21) (%)	EoG (n = 10) (%)	EoD (n = 5) (%)	EoI (n = 3) (%)	EoC (n = 31) (%)
Stomach (N)	12	10			
Epithelial involvement	8 (67)	6 (60)			
Lamina propria involvement	4 (33)	3 (30)			
Muscularis mucosa involvement	3 (14)	1 (10)			
Submucosa involvement	2 (10)	0 (0)			
Muscularis propria involvement	0 (0)	0 (0)			
Eosinophilic microabscesses	0 (0)	0 (0)			
Eosinophilic degranulation	5 (42)	0 (0)			
Background inflammation	1 (8)	8 (80)			
Fibrosis	0 (0)	0 (0)			
Architecture abnormalities	–	1 (10)			
Duodenum (N)	8		5		
Epithelial involvement	4 (50)		2 (40)		
Lamina propria involvement	3 (38)		4 (80)		
Muscularis mucosa involvement	1 (13)		1 (20)		
Submucosa involvement	1 (13)		1 (20)		
Muscularis propria involvement	0 (0)		0 (0)		
Eosinophilic microabscesses	1 (13)		0 (0)		
Eosinophilic degranulation	0 (0)		0 (0)		
Background inflammation	4 (50)		4 (80)		
Fibrosis	0 (0)		–		
Architecture abnormalities	0 (0)		–		
Ileum (N)	8			3	
Epithelial involvement	8 (100)			1 (33)	
Lamina propria involvement	4 (50)			3 (100)	
Muscularis mucosa involvement	0 (0)			0 (0)	
Submucosa involvement	–			2 (67)	
Muscularis propria involvement	0 (0)			1 (33)	
Eosinophilic microabscesses	1 (13)			0 (0)	
Eosinophilic degranulation	0 (0)			0 (0)	
Background inflammation	3 (38)			1 (33)	
Fibrosis	0 (0)			–	
Architecture abnormalities	1 (13)			–	
Colon (N)	15				31
Epithelial involvement	11 (73)				22 (71)
Lamina propria involvement	7 (47)				22 (71)
Muscularis mucosa involvement	1 (7)				6 (23)
Submucosa involvement	–				4 (13)
Muscularis propria involvement	0 (0)				1 (3)
Eosinophilic microabscesses	2 (13)				1 (3)
Eosinophilic degranulation	0 (0)				5 (16)
Background inflammation	8 (53)				20 (65)
Fibrosis	1 (7)				1 (3)
Architecture abnormalities	3 (20)				3 (10)

Table 4. Histologic abnormalities described by category of disease at EGID diagnosis (surgical and biopsy). *Multi-site* more than 1 area of GI tract involved with eosinophilia, *EoG* eosinophilic gastritis, *EoD* eosinophilic duodenitis, *EoI* eosinophilic ileitis; *EoC* eosinophilic colitis.

Discussion

This study evaluates a substantial group of EGID patients for their clinical course and natural history during a 28 year period in the Netherlands. Median time of follow up was 26 months for 96% of the population, with longest recorded follow up of 26 years in EoC. Given the rarity of this disorder, the findings here are an interesting commentary on the natural history of EGID.

EGID patients tended to be young with no gender disparity. There is variability on gender predominance reported in literature, with some showing female inclination[19,23], and others not[16,24]. Due to low numbers of patients by disease location, it is difficult to draw conclusions on gender predilection. Percentage of patients with

	Total patients (n = 70) (%)	Multi-site (n = 21) (%)	EoG (n = 10) (%)	EoN (n = 8) (%)	EoC (n = 31) (%)
First line treatment					
Budesonide/Entocort[$]	17 (24%)	2 (10%)	2 (20%)	1 (13%)	12 (39%)
Prednisone[$]	10 (14%)	7 (33%)	–	2 (25%)	1 (3%)
PPI[$]	2 (3%)	–	1 (10%)	1 (13%)	–
5ASA (Mesalazine)[$]	3 (4%)	–	–	–	3 (10%)
Nutritional supplement	9 (13%)	1 (5%)	–	–	8 (26%)
Elimination diet	7 (10%)	2 (10%)	2 (20%)	–	3 (10%)
Cromolyn[$]	3 (4%)	1 (5%)	–	1 (13%)	1 (3%)
Montelukast	1 (1%)	1 (5%)	–	–	–
Antihistamines	1 (1%)	1 (5%)	–	–	–
No treatment	7 (10%)	2 (10%)	3 (30%)	2 (25%)	–
Surgical resection	2 (3%)	–	–	1 (13%)	1 (3%)
Combination of meds	8 (11%)	4 (19%)[#]	2 (20%)[&]	–	2 (6%)[$]
Symptom improvement*					
Improved	43 (61)	11 (52%)	3 (30%)	4 (50%)	25 (81%)
Partially improved	7 (10)	1 (5%)	2 (20%)	1 (12%)	3 (4%)
No improvement	17 (24)	9 (43%)	3 (30%)	3 (38%)	2 (6%)
No follow up data	3 (4)	–	2 (20%)	–	1 (3%)
Endoscopic follow-up					
Completed (y/n)	37 (53)	12 (57)	5 (50)	5 (63)	15 (48)
Time to endoscopy in months, median (IQR)	11 (4–19)	7 (5–16)	12 (6–12)	3 (3–15)	14 (9–30)
Endoscopic abnormalities present (y/n)	13 (36)	3 (23)	2 (20)	3 (60)	5 (33)
Tissue eosinophilia (y/n)	19 (53)	7 (54)	2 (20)	3 (60)	7 (47)
Clinic follow up					
Completed (y/n)	36 (51)	9 (48)	6 (60)	5 (63)	16 (52)
Follow-up duration over study period in months, median (IQR)	26 (8–68)	28 (15–73)	8 (6–26)	16 (7–36)	29 (10–106)

Table 5. First line Treatment and follow-up by category of EGID population. *Multi-site* more than 1 area of GI tract involved with eosinophilia, *EoG* eosinophilic gastritis, *EoN* eosinophilic enteritis, *EoC* eosinophilic colitis, *PPI* proton pump inhibitors. *5ASA* 5 amino-salicylate acid. *Clinical improvement was based on review of treating physician's assessment and change in patient symptoms recorded in the chart. [&]Combination in EoG—One patient received prednisone/PPi and second patient received oral budesonide/PPI. [$]Combination in EoC—One patient received budesonide enemas/5ASA and second patient received oral prednisone/5ASA. [#]Combination in multisite—Full details in Table 5.

atopy in multisite and single site EGID was equivalent despite EoC having the lowest association at 10% (not statistically significant). Larger studies have shown an association of EoC with atopy[6,19,24], but pathogenesis have noted EoG, EoN and EoE (not EoC) having a common type 2 inflammatory pathway[6,7]. Looking at noninvasive detection of EGID, blood eosinophilia was available in 64%, but only 42% patients had elevation; confirming its low yield in diagnostics[3]. All patients were evaluated for secondary causes of EGID, reducing false positives in the cohort.

Top complaints in the cohort were diarrhea, abdominal pain, nausea and weight loss. The lack of specificity makes it challenging to give recommendations on when to scope for EGID, given poor endoscopic correlation to disease presence. Imaging studies do not contribute to diagnosis[3], creating a challenge on how to screen. Only a few patients had complications prompting investigations. Majority of these patients presented relatively soon after onset of symptoms. They were likely to have serosal or muscular type. It was not possible to confirm if patients had vague symptoms preceding diagnosis as this was a retrospective study. It would be valuable to assess for this in prospective studies, as there may be a diagnostic delay, as in EoE[25,26]. One patient had recurrent history of volvulus, but their management was in keeping with standard of care[27,28]. In the cohort with complications, approximately half of them had multisite EGID. Extent of disease might correlate with likelihood of complications and this subgroup had normal endoscopic appearance too; revealing the complex picture on diagnostics. Our study indicates a potentially low likelihood of severe phenotype (i.e. serosal) manifesting later in the course of EGID. Serosal type is considered a distinct entity[15], but it was not clear if it can also be a consequence of untreated mucosal EGID. This study suggests serosal EGID does not manifest from delayed diagnosis or untreated EGID. Our study highlights the improbability of single site progressing to multisite EGID, as no switching between categories of EGID was seen. We did not identify patients with normal histology progress to eosinophilia in their GI tract. It is possible single site EGID has a different natural history than multisite, and longer follow up data is required.

Normal endoscopic appearance is common at time of diagnosis, in line with retrospective[16–21,23,24,29,30] and prospective studies[12,31]. We note small bowel as having the highest percentage of normal appearance (72% of

ileum), which is like CEGIR data[23]. A large portion of small bowel is left unchecked, so underreporting of EoN is highly likely[7]. There is limited evaluation of jejunum in this study, with only one patient having normal mucosal appearance on capsule endoscopy (no biopsies). Small bowel evaluation via standard scope is limited to proximal duodenum and distal ileum. It is recommended to take 4–8 samples in the small bowel[14,31], but there is no consensus on location. A recent review of the frequency and number of biopsies to work up EGID by experts highlighted significant variability in both, reiterating importance of a formalized approach[32]. Cut offs to assess eosinophil range within the GI tract remains variable, making it hard to perform a systematic review of the available data[12,15,16,18–21,23,24,31]. Thus, it is prudent to do a thorough evaluation of both upper and lower tracts to stage disease when considering EGID, but what that looks like for the small bowel remains unclear and is pending expert recommendations.

Multisite EGID was defined as > 1 area with eosinophilia to avoid confusion with older nomenclature (i.e. EGE). In the literature, EGE was used to identify colonic/ileal or gastric/duodenal disease[18,20]. While 2022 nomenclature recommends use of EGE in those with gastric and small bowel involvement[2,4], we provide descriptive information. None of the multisite patients started off with single site EGID in our cohort. The update in the nomenclature and classification was done to improve categorization for research purposes and improve communication[2,4]. For example, a patient with gastric and colonic eosinophilia can either be EoG and EoC, or EoC dominant if they are struggling with bloody diarrhea. However, such classification creates duplication in documenting frequency of cases in a retrospective series like ours. It forces physicians to choose one type of EGID early in the disease, when patients may exhibit symptoms from secondary sites in the future. Treatments are limited, so choosing type of EGID might create the perception that only a few treatments ought to be employed. It can be argued that currently denoted single site EGID may not be truly single site given the patchy nature of eosinophils present in EGID[13,31–33] like EoE[25,26,34] and inconsistent scope practices.

Choosing treatment and duration of follow up to detect clinical response is challenging. There are no approved treatments due to variable definitions of disease, no systematic approach to management, or long term follow up data to guide care[7,14]. In our cohort, EoC had the highest response to treatment, in line with publications. EoG and EoN had the lowest response which might be due to limited understanding of disease process[7,14]. There was no difference in symptom response for combination or single agent treatment across EGID types. Most publications like ours show a high rate of topical or systemic steroids. However, CEGIR publication described PPIs as their most common agent[21], suggesting a potential pathophysiology to explore[7]. Follow up strategy was used by 1/3 of EoG and EoN; and those that chose this option described milder disease burden. This option was not associated with complications or hospitalizations and might be a good choice in select patients. Biologics were not used in this cohort, which might reflect lack of availability given time periods studied, and risk for high immune suppression in a poorly understood disease. Anti-IL4/5/13 with lower immune suppression have recently published robust efficacy in EoE, but results in EGID are limited to retrospective studies[35].

The median follow up was ~ 2.5 years, which is one of the longest periods published when looking comprehensively at this population since 2011[15–21,24]. CEGIR[21] looked at all EGID types, but follow up was 6 months. The longest follow up data for all patients is the seminal French study in 2011[15] that followed 43 patients for a median of 13 years, and highlighted the three phenotype of EGID. In their study, 74% of treated patients received oral steroids and responded. Unlike the French study, the Dutch cohort was treated with a variety of agents, and oral steroids were not the most effective. The most likely population to be treated with oral steroids was multisite EGID (33%), which was also the most represented in the second line treatment group, highlighting the challenges of this disease.

We can comment on the frequency of relapsing remitting, single flare and chronically symptomatic EGID given duration of follow up here. Multisite EGID were most likely to have relapsing remitting, which could be related to symptoms from various locations of the GI tract. Serosal and muscular EGID were often in remission by end of the study period, but longer follow up might show a different trajectory.

There were limitations to the study. Population studied were symptomatic, so asymptomatic patients were not captured. If the endoscopist felt warranted to complete scopes, there is bias of sampling mucosa. The number of samples and time to evaluate mucosa for abnormalities may be higher in this study. It is possible the lack of a systematic approach to number, location of biopsies and eosinophil cut offs may have affected the detection of EGID. However, this is unlikely given the duration of follow up. Only one patient out of 70 had a 5-year delay in diagnosis, but they were not a true miss as their volvulus management followed standard of care. One of the caveats to diagnosing EGID remains the limitations in depth of tissue. Mucosal biopsies miss deeper layers, and so detection of muscular and serosal EGID may be under reported. As current method of assessing tissue for muscular and serosal patients is limited[2], early stages of these phenotypes may have been missed. In our cohort, there were no patients with a history of normal GI pathology preceding EGID diagnosis, but this was a retrospective study of symptomatic patients. Pathology reports were not re-evaluated as criterion in adults have not been universally adopted by consensus[2,7]. The clinical picture of the patient in conjunction with expert pathologist reporting at tertiary care hospitals was the requirement of enrollment in this study.

In conclusion, this paper presents over the course of 28 years the EGID experience at four tertiary care centers in the Netherlands. Normal endoscopic appearance is common and mucosal EGID is the most diagnosed phenotype. Variable treatment strategies can be employed if follow up is continued to monitor for relapsing–remitting, chronic or single flare disease. Results of this longitudinal study do not show progression from single site EGID to multisite or change in EGID variant.

Data availability

The dataset is available from the corresponding author on reasonable request. The data analyzed is published here and in the supplementary section.

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References

1. Rothenberg, M. E. Eosinophilic gastrointestinal disorders (EGID). *J. Allergy Clin. Immunol.* **113**(1), 11–28 (2004).
2. Dellon, E. S. et al. International consensus recommendations for eosinophilic gastrointestinal disease nomenclature. *Clin. Gastroenterol. Hepatol.* **20**(11), 2474–2484 (2022).
3. Papadopoulou, A. et al. Joint ESPGHAN/NASPGHAN guidelines on childhood eosinophilic gastrointestinal disorders beyond eosinophilic esophagitis. *J. Pediatr. Gastroenterol. Nutr.* **78**(1), 122–152 (2024).
4. Rothenberg, M. E. H. S. et al. Impressions and aspirations from the FDA GREAT VI Workshop on eosinophilic gastrointestinal disorders beyond eosinophilic esophagitis and perspectives for progress in the field. *J. Allergy Clin. Immunol.* **149**(3), 844–853 (2022).
5. Uppal, V., Kreiger, P. & Kutsch, E. Eosinophilic gastroenteritis and colitis: A comprehensive review. *Clin. Rev. Allergy Immunol.* **50**(2), 175–188 (2016).
6. Oliva, S. & McGowan, E. C. Associations of eosinophilic gastrointestinal disorders with other gastrointestinal and allergic diseases. *Immunol. Allergy Clin. North Am.* **44**(2), 329–348 (2024).
7. Shoda, T. T. R., Sakai, N. & Rothenberg, M. E. Common and disparate clinical presentations and mechanisms in different eosinophilic gastrointestinal diseases. *J. Allergy Clin. Immunol.* **153**(6), 1472 (2024).
8. Seema Khan, S. R. O. Eosinophilic gastroenteritis. *Gastroenterol. Clin. North Am.* **37**(2), 333–348 (2002).
9. Dellon, E. S. L. C. et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference. *Gastroenterology* **155**(4), 1022–1033 (2018).
10. Licari, A. et al. Epidemiology of nonesophageal eosinophilic gastrointestinal diseases in symptomatic patients: A systematic review and meta-analysis. *J. Allergy Clin. Immunol. Pract.* **8**(6), 1994-2003e2 (2020).
11. Lucendo, A.J.S.-M.B., Arias, Á., Redondo, O. & Tenias, J. M. Efficacy of dietary treatment for inducing disease remission in eosinophilic gastroenteritis. *J. Pediatr. Gastroenterol. Nutr.* **61**(1), 56–64 (2015).
12. Hirano, I. C. M. et al. prospective endoscopic activity assessment for eosinophilic gastritis in a multisite cohort. *Am. J. Gastroenterol.* https://doi.org/10.14309/ajg.0000000000001625 (2022).
13. Mh, C. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. *Gastroenterol. Clin. North Am.* **43**(2), 257–268 (2014).
14. Barchi, A. et al. The dual lens of endoscopy and histology in the diagnosis and management of eosinophilic gastrointestinal disorders: A comprehensive review. *Diagnostics (Basel)* **14**(8), 858 (2024).
15. de Pineton Chambrun, G. G. F. et al. Natural history of eosinophilic gastroenteritis. *Clin. Gastroenterol. Hepatol.* **9**(11), 950-956.e1 (2011).
16. Zhang, L. D. L. et al. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics, a retrospective study of 42 patients. *Scand J. Gastroenterol.* **46**(9), 1074–1080 (2011).
17. Ko, H. M. M. R., Yershov, O. & Chehade, M. Eosinophilic gastritis in children: Clinicopathological correlation, disease course, and response to therapy. *Am. J. Gastroenterol.* **109**(8), 1277–1285 (2014).
18. Reed, C. W. J. & Dellon, E. S. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. *Dig Liver Dis.* **47**(3), 197–201 (2015).
19. Mansoor, E., Saleh, M. A. & Cooper, G. S. Prevalence of eosinophilic gastroenteritis and colitis in a population-based study, from 2012 to 2017. *Clin. Gastroenterol. Hepatol.* **15**(11), 1733–1741 (2017).
20. Hui, C. K. H. N. A prospective study on the prevalence, extent of disease and outcome of eosinophilic gastroenteritis in patients presenting with lower abdominal symptoms. *Gut Liver* **12**(3), 288–296 (2018).
21. Pesek, R. D. et al. Increasing rates of diagnosis, substantial co-occurrence, and variable treatment patterns of eosinophilic gastritis, gastroenteritis, and colitis based on 10-year data across a multicenter consortium. *Am. J. Gastroenterol.* **114**(6), 984–994 (2019).
22. Casparie, M. T. A. et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol.* **29**(1), 19–24 (2007).
23. Pesek, R. D. et al. Association between endoscopic and histologic findings in a multicenter retrospective cohort of patients with non-esophageal eosinophilic gastrointestinal disorders. *Dig. Dis. Sci.* **65**(7), 2024–2035 (2020).
24. Jensen, E. T. M. C., Kappelman, M. D. & Dellon, E. S. Prevalence of eosinophilic gastritis, gastroenteritis, and colitis: Estimates from a national administrative database. *J. Pediatr. Gastroenterol. Nutr.* **62**(1), 36–42 (2016).
25. Warners, M. J. et al. Incidence of eosinophilic esophagitis in the Netherlands continues to rise: 20-year results from a nationwide pathology database. *Neurogastroenterol. Motil.* https://doi.org/10.1111/nmo.13165 (2018).
26. Warners, M. J., Oude Nijhuis, R. A. B., de Wijkerslooth, L. R. H., Smout, A. & Bredenoord, A. J. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. *Am. J. Gastroenterol.* **113**(6), 836–844 (2018).
27. Atamanalp, S. S. & Atamanalp, R. S. The role of sigmoidoscopy in thediagnosis and treatment of sigmoid volvulus. *Pak. J. Med. Sci.* **32**(1), 244–248 (2016).
28. Halabi, W. J. et al. Colonic volvulus in the United States: Trends, outcomes, and predictors of mortality. *Ann. Surg.* **259**(2), 293–301 (2014).
29. Turner, K. O. D., Sinkre, R. A., Neumann, W. L. & Genta, R. M. Primary colonic eosinophilia and eosinophilic colitis in adults. *Am. J. Surg. Pathol.* **41**(2), 225–233 (2017).
30. Díaz Del Arco, C. T. C., Muñoz, L. E., Olivares, D. & Fernández Aceñero, M. J. Eosinophilic colitis: experience in a large tertiary hospital. *Rom. J. Morphol. Embryol.* **58**(3), 783–789 (2017).
31. Dellon, E. S. et al. Determination of biopsy yield that optimally detects eosinophilic gastritis and/or duodenitis in a randomized trial of lirentelimab. *Clin. Gastroenterol. Hepatol.* **20**(3), 535-45e15 (2022).
32. Dellon, E. S. C. M. et al. Substantial variability in biopsy practice patterns among gastroenterologists for suspected eosinophilic gastrointestinal disorders. *Clin. Gastroenterol. Hepatol.* **14**(12), 1842–1844 (2016).
33. Hurrell, J. M., Genta, R. M. & Melton, S. D. Histopathologic diagnosis of eosinophilic conditions in the gastrointestinal tract. *Adv. Anat. Pathol.* **18**(5), 335–348 (2011).
34. van Rhijn, B. D., Verheij, J., Smout, A. J. & Bredenoord, A. J. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol. Motil.* **25**(1), 47-52e5 (2013).
35. Sia, T. et al. Dupilumab can induce remission of eosinophilic gastritis and duodenitis: A retrospective case series. *Clin. Transl. Gastroenterol.* **15**(1), e00646 (2024).

Author contributions

Conceptualization, LH and AB.; Methodology, MLH, AM and AB.; Data analysis, MLH, MG; Writing—Original Draft Preparation, MLH, MG and AB. Writing—Review and Editing, MG, MLH, AM and AB.; Supervision, AB. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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