Review Article

Eosinophilic gastrointestinal disorders: a narrative review on clinical perspectives and research gaps in the Asian context

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Background and Objective: Eosinophilic gastrointestinal disorders (EGID) are a heterogeneous group of conditions, comprising eosinophilic esophagitis (EoE) and non-EoE EGID which have gained considerable research interest. There are likely to be differences in disease characteristics between populations with distinct dietary, environmental and cultural backgrounds. However much of our understanding on EGID have come from studies from Europe and North America. The aim of this review is to summarize the recent developments and updates in EGID focusing on disease phenotype specifically in Asian patients, and identify opportunities for future research pertaining to disease profile in the Asian population.

Methods: Original studies, systematic reviews, meta-analyses and review articles up to March 2024 were systematically searched on PubMed, with specific focus on newer studies published in the past 10 years. Case reports, conference abstracts and articles that were not published in the English language were excluded.

Key Content and Findings: Prevalence and incidence of EoE and non-EoE EGID have reportedly increased globally over time, but population-based studies are lacking in Asia. Based on heterogeneous data from a limited number of studies from Asia, there are features in epidemiology, clinical phenotype, and treatment response that may be appreciably distinct in Asian patients with EoE and non-EoE EGID, as compared to the Western patient population. Moreover, the efficacy of novel biologic therapies such as dupilumab in the Asian population has not been well-defined.

Conclusions: There is a lack of robust data on many basic aspects of EGID in Asia. There is a pressing need to bridge this gap by building research networks and collaborations across wider regions in Asia, to gather high-quality, multicenter data using standardized and uniform criteria and build a more accurate understanding of EGID in Asian patients.

Keywords: Eosinophilic gastrointestinal disorders (EGID); eosinophilic esophagitis (EoE); food allergy

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Introduction

Eosinophilic gastrointestinal disorders (EGID) are emerging as an increasingly important disease entity affecting adults and children, and gaining considerable research interest over the past 2 decades. EGID is a heterogeneous group of conditions characterized by gastrointestinal (GI) dysfunction and symptoms, and increased eosinophilic infiltration in the GI tract with the exclusion of other causes of GI eosinophilia (1). While diagnostic criteria and treatment of eosinophilic esophagitis (EoE) are well-established, there remains a lack of consensus on the clinical definition and management of non-EoE EGID (2,3). The prevalence of both EoE and non-EoE EGID is reportedly on the rise worldwide, and approaching similar figures as chronic inflammatory bowel diseases (IBD) in the United States (4,5).

While the exact pathophysiologic mechanisms in EGID remains to be fully elucidated, the manifestation of EGID is predominantly the effect of a T-helper cell type 2 (TH2) inflammatory response to an interplay of genetic, dietary and environmental factors and triggers (6). EoE and non-EoE EGID are often associated with food allergies and atopic disorders, and response to elimination diet therapy particularly in EoE lends proof that food triggers have an important role to play in disease pathogenesis in EGID (3). For a condition that is so closely associated with food antigen and environmental triggers, it is reasonable to postulate that inherent differences in disease phenotype and triggering factors should exist between different populations with distinct genetic, dietary, and cultural backgrounds. In this respect, it is an interesting observation that the majority of studies on EoE and non-EoE EGID have been from Europe and North America.

In this article, we aimed to present a review that summarizes the recent developments and updates in EGID with a specific focus on epidemiology and clinical characteristics in Asian patients in comparison with Western patients, and identify gaps and opportunities for future research pertaining to disease profile in the Asian population. We present this article in accordance with the Narrative Review reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-34/rc).

Methods

For the purpose of this narrative review, original studies, systematic reviews, meta-analyses and review articles were searched on PubMed using combination of MeSH terms and search criteria: “eosinophilic esophagitis”, “eosinophilic gastrointestinal diseases/disorders OR eosinophilic gastritis OR eosinophilic gastroenteritis OR eosinophilic colitis”, “Asia OR Asian”, “racial groups”, “epidemiology OR prevalence OR incidence”, “drug therapy”, “diet therapy”. Literature search was conducted for studies up to March 2024, with specific focus on newer studies published in the past 10 years since 2014 (*Table 1*). Case reports, conference abstracts and articles that were not published in the English language were excluded.

Definition and histopathologic diagnosis

Diagnosis of EoE is based on clinical symptoms of esophageal dysfunction and esophageal eosinophilia of at least 15 eosinophils per high power field (eos/hpf) with the exclusion of other causes of esophageal eosinophilia (2). Notably in the updated 2018 international consensus, proton pump inhibitor (PPI) trial was removed from the diagnostic criteria as it was increasingly recognized that EoE and gastroesophageal reflux disease (GERD) were not mutually exclusive: EoE can cause secondary reflux due to gastroesophageal dysmotility, and GERD can result in epithelial barrier dysfunction and pathologic response to antigen exposure (2).

Unlike EoE, there is no consensus or guidelines for the diagnosis of non-EoE EGIDs at present. Non-EoE EGID can involve the stomach, small bowel, colon or combination of these, and can be further classified into mucosal, muscular or serosal involvement. Just recently in 2022, a consensus was developed for the standardized nomenclature for the different categories of non-EoE EGID (7). It is agreed upon that EGID is the umbrella term for eosinophilic inflammation of the GI tract in the absence of secondary causes. EGID involving the stomach, small intestine and colon are named eosinophilic gastritis (EoG), eosinophilic enteritis (EoN, which can be classified into duodenitis, jejunitis or ileitis if segment of involvement is known), and eosinophilic colitis (EoC) respectively.

Establishing diagnostic criteria for non-EoE EGID is challenging because a normal resident population of eosinophils exists in the stomach, intestinal and colonic mucosa, ranging up to 26–28 eos/hpf in the small intestine, to maximum of 50 eos/hpf in the colon (8). Investigators have used varying diagnostic thresholds to define EoG which limits the comparability of data across studies (9). Moreover, standard endoscopic mucosal biopsies do not provide information on eosinophilic infiltration in the

Table 1 The search strategy summary

Items	Specifications
Date of search	15 March 2024
Databases searched	PubMed
Search terms used	"eosinophilic esophagitis", "eosinophilic gastrointestinal diseases/disorders OR eosinophilic gastritis OR eosinophilic gastroenteritis OR eosinophilic colitis", "Asia OR Asian", "racial groups", "epidemiology OR prevalence OR incidence", "drug therapy", "diet therapy"
Timeframe	Up to March 2024 with specific focus on newer studies published since 2014
Inclusion and exclusion criteria	Inclusion: original studies, systematic reviews, meta-analyses and review articles
	Exclusion: case reports, conference abstracts, articles not published in the English language
Selection process	All authors (F.K.C., L.Q.N., W.L.) conducted the search independently. Selection of articles for the review was by consensus from all three authors based on relevance, type of articles and study methodology where applicable

deeper layers, and in most cases tissue biopsies are limited to only the proximal small bowel as the entire length of the small intestine is rarely examined. Therefore, negative mucosal biopsies may not completely rule out EGID (10). Nonetheless, it has been proposed that a histopathologic threshold of ≥30 eos/hpf in at least 5 hpf, or ≥70 eos/hpf in at least 3 hpf forms the basis for the diagnosis of EoG together with relevant clinical and endoscopic features (11,12). For EoN, the proposed threshold is >52 eos/hpf in the duodenum and >56 eos/hpf in the ileum. The threshold varies in the large bowel with a higher cut-off of >100 eos/hpf in the cecum and ascending colon, and a lower cut-off of >84 in the transverse/descending colon, and >64 eos/hpf in the rectosigmoid colon (12). In addition to the eosinophilic count, other pathologic features such as altered eosinophilic activity and distribution and reactive epithelial alterations may provide further support to the diagnosis of EGID (10). Odetola *et al.* have proposed that studying the eosinophil degranulation ratio (degranulated eosinophils/granulated and degranulated eosinophils) in tissue biopsies may provide critical information on disease activity in EoE, and may identify potential biomarkers of eosinophilic activity and inflammation in EoE as well as non-EoE EGID (13).

Pathogenesis

With the exception of the esophagus, there is a baseline population of eosinophils in the GI tract. This normal population of GI eosinophils not only helps to defend the host against parasitic helminths, but may also play important roles in immune regulation of T-cells and possibly in tissue and organ development (14). Evidence on pathogenesis of EoE points towards an underlying genetic susceptibility to heightened pro-inflammatory, Th2-mediated response, for example in gain-of-function mutation or over-expression of thymic stromal lymphopoietin (TSLP) or C-C motif chemokine ligand-26 (CCL-26) (which encodes eotaxin-3, a potent recruiter of eosinophils), in combination with down-regulation of proteins associated with epithelial integrity and barrier function such as filaggrin and desmoglein-1 (6). Impaired barrier function permits abnormal allergen exposure and antigen presentation leading to activation of Th2 lymphocytes and expression of type 2 cytokines including interleukin (IL)-4, IL-5 and IL-13 which promote differentiation of T cells into Th2 cells, expression of eotaxin and proliferation and maturation of eosinophils. Eosinophils facilitate further inflammation in turn by triggering the activation of mast cells and basophils (6,15). Chronic esophageal inflammation eventually leads to dysmotility, fibrosis and stricture formation (6).

One interesting observation has been the inverse correlation between Helicobacter pylori (HP) infection and EoE. In a systematic review by Shah *et al.*, HP exposure was associated with 37% reduction in odds of EoE, based on 11 observational studies including 2 from East Asia (China and Japan), which recorded the highest prevalence of HP (47–72%) among the other studies with overall prevalence of 8.9% (16). A more recent case-control study from South Korea published in 2023 also demonstrated that EoE was inversely associated with HP infection with odds ratio of 0.2 (17). It has been postulated that this association may be related to the 'hygiene hypothesis' which explains the rise

in allergic and atopic diseases being possible consequence to improved sanitation and reduced childhood infections including HP (15). Another postulation is the immune-regulatory effect of HP which protects against an allergic Th2 inflammatory process seen in EoE (15). The global prevalence of HP is declining particularly in Asian populations (18,19), but it remains unproven whether the simultaneous global rise in the incidence of EGID is coincidental or one of the many surrogate outcomes associated with the 'hygiene hypothesis'.

Similar to EoE, a common understanding in the pathophysiology of non-EoE EGID is that the Th2-mediated inflammatory process, mediated by IL-4 and IL-5, seems to be central to the disease (3,20,21). In addition, there are other similarities in features between EoE and non-EoE, including high prevalence of atopy, sensitization to food allergens, therapeutic response to dietary therapy, as well as the co-existence of EoE and non-EoE EGID in a substantial proportion of patients (3). However, despite these similarities, it remains uncertain whether EoE and non-EoE EGID truly share the same pathogenesis. Response to dietary therapy is observed to be less successful in non-EoE EGID compared to EoE (3). Moreover, a study by Caldwell *et al.* showed distinct gastric transcriptome in EoG with very little overlap with EoE biopsies, supporting the theory of possible distinct molecular pathways in the pathogenesis of both conditions (22).

Epidemiology

Based on recent meta-analyses of population studies, the overall prevalence of EoE was 34–40 per 100,000 inhabitants, and pooled incidence was 6.6 new cases per 100,000 person-years in children and 7.7/100,000 person-years in adults (4,23). Incidence was highest in high-income countries, particularly North America (23). Male gender is associated with at least 2 times the risk of EoE as compared to females (4). These data however were limited by high level of heterogeneity between studies, and nearly all the studies came from North America and Europe, with only one paper from Asia included in the meta-analysis by Hahn *et al.* (23,24). While EoE is still considered a rare condition in Asia, there is an appreciable increase in diagnosis and incidence rate in the past 10 years mirroring similar trends in Western populations (25). Recent Asian publications in 2015 from Japan and China in patients undergoing endoscopy for GI symptoms or health-check have estimated the overall prevalence of EoE to be 0.4% (24,26), whereas a meta-analysis consisting of 9 older Asian studies [2011–2014] reported a prevalence of 0.06% of patients undergoing endoscopy (27). A recent nationwide multicenter study in Korea reported that the prevalence of EoE in the pediatric population who had symptoms of esophageal dysfunction and underwent endoscopy was 1.5% while the prevalence of non-EoE EGID was 1.3% (28). The different methodology used in these studies in assessing prevalence does not allow for direct comparison with population-based data from Western countries. Till date there has been no proper population-based study to estimate the true prevalence or incidence of EoE in Asian countries. Demographically, EoE affects patients of all ages, and a similar male preponderance has been observed in Asian patients (27,29).

With regard to epidemiology of non-EoE EGID, the pooled overall prevalence, inclusive of adult and pediatrics, is reported to be 1.9% of patients presenting with GI symptoms, and the prevalence was higher in developed countries as compared to developing countries (2.4% *vs.* 1.5%) (5). These data were derived from a meta-analysis comprising ten studies of which five were derived from Asian cohorts. Analyzing studies from India, China, Japan and Malaysia, the prevalence of non-EoE EGID in symptomatic patients ranged between 1.2% to 5.7% (5). Based on International Classification of Diseases (ICD) codes from a national database on insurance claims in the United States, the estimated prevalence of EoG, eosinophilic gastroenteritis (EoGE) and EoC were 6.3, 8.4 and 3.3 per 100,000 respectively, much lower than EoE (30). A separate population-based study also from the United States using data derived from an aggregated electronic health record database, estimated the overall prevalence rate of EoGE to be 5.1 per 100,000 persons, and prevalence rate of EoC to be 2.1 per 100,000 (31). Both of these studies reported Caucasian majority and female predominance in non-EoE EGID, and higher prevalence in the pediatric age group (30,31). A more recent multicenter study of 373 patients comprising mostly children (n=317) with non-EoE EGID showed no significant gender predilection and also concluded that the frequency of diagnosis of non-EoE EGID has been increasing over time (32). Population studies on the true prevalence and incidence of non-EoE EGID in Asian countries are also lacking at present (33). Interestingly, Ito *et al.* found in their systematic review of 121 studies that while EoE accounted for the large majority (>90%) of EGID in Caucasian patients, EoE was much rarer and non-EoE EGID was the more predominant (72%) EGID subtype in Asian patients (34). *Table 2* summarizes

Table 2 Summary of epidemiology of EoE and non-EoE EGID in Western and Asian populations

EGID sub-type	Western				Asian			
	Publication (country, year) (ref)	Study design	Patients	Data	Publication (country, year) (ref)	Study design	Patients	Data
EoE	Navarro (International, 2019) (4)	Meta-analysis of 29 population-based studies, mostly North America and Europe, none in Asia	65,382 (adults and children)	Prevalence: 34.2/100,000	Kinoshita (Asian countries, 2015) (27)	Meta-analysis of 9 studies (2011–2014)	77 (adults and children)	Prevalence 0.06% of patients undergoing endoscopy
	Hahn (International, 2023) (23)	Meta-analysis of 40 population studies, only 1 study from Asia (China)	147,668 (adults and children)	Prevalence: 40.04/100,000 Incidence 5.31/100,000 person-years	Ma (China, 2015) (24)	Single-centre, prospective	4 (adults)	Prevalence: 0.4% of patients undergoing endoscopy
					Adachi (Japan, 2016) (26)	Single-centre, prospective	20 (adults)	Prevalence 0.4% of patients underdoing endoscopy
					Lee (South Korea, 2020) (28)	Multicentre, retrospective	14 (children)	Prevalence 1.5% of patients with esophageal symptoms
Non-EoE EGID	Jensen (US, 2016) (30)	Retrospective, population-based	774 (EoG), 954 (EoGE), 404, (EoC), adults and children	Prevalence: 6.3/100,000 (EoG), 8.4/100,000 (EoGE), 3.3/100,000 (EoC)	Licari (International, 2020) (5)	Meta-analysis of 10 studies (4 studies from North America and Europe, 6 studies from Asia)	156 (adults and children) in India, China, Japan, Malaysia	Prevalence 1.95% of symptomatic patients
	Mansoor (US, 2017) (31)	Retrospective, population based	1,820 (EoGE), 770 (EoC), adults and children	Prevalence: 5.1/100,000 (EoGE), 2.1/100,000 (EoC)				
	Licari (International, 2020) (5)	Meta-analysis of 10 studies (4 studies from North America and Europe, 6 studies from Asia)	36 (adults and children), in United States, Denmark, Italy	Prevalence 1.1% of symptomatic patients				

EoE, eosinophilic esophagitis; EGID, eosinophilic gastrointestinal disease; EoG, eosinophilic gastritis; EoGE, eosinophilic gastroenteritis; EoC, eosinophilic colitis.

the recent epidemiologic data of EoE and non-EoE EGID in Western and Asian populations.

Clinical presentation and associations

It is well-recognized that symptoms of EoE vary according to age group. Children may present with non-specific symptoms such as feeding difficulties, vomiting and faltering growth, whereas adolescent and adult patients are more likely to present with the cardinal symptoms of dysphagia or food impaction, although subtle behavioral adaptations such as over-chewing, over-cutting or lubricating foods with sauces and liquids might be easily overlooked (35-37). Chronic GERD symptoms are common across age groups (6). The difference in clinical presentation in children and adults may be related to long-term esophageal tissue remodeling from chronic inflammation, and the resultant progression from a 'subclinical' inflammatory phenotype in childhood to a fibrostenotic phenotype with stricture formation in adults (15). Interestingly, a study from the United States have also reported that a significantly larger proportion of white persons as compared to African Americans or other races had dysphagia (74%, 56% and 53% respectively) and food impaction (35%, 13% and 13% respectively) (38). This observation was also highlighted in a systematic review by Ito *et al.* which reported that Asians with EoE were less likely to have dysphagia (47.9% *vs.* 77.2%) and heartburn (16.9% *vs.* 38.9%), but more likely to present with vomiting (5.6% *vs.* 1.1%) and abdominal pain (18.3% *vs.* 1.8%) as compared to Caucasian patients with EoE (34) (*Table 3*). In Ito's paper, the authors postulated that clinical presentation might be influenced by different dietary habits as well as background prevalence of HP and its specific genotypes, all of which may affect the distribution of eosinophilia and inflammation in the GI tract, and presence of co-existing GERD symptoms. A Korean study comprising 72 adult patients with EoE similarly found epigastric pain and/or dyspepsia (54.2%) to be the most common symptoms, followed by heartburn (30.6%), while dysphagia/food impaction was less common (15.3%) (25). By contrast, 2 recent studies from Japan, both published in 2021, with relatively larger patient cohorts have shown that dysphagia was the predominant symptom affecting 66.9–82% of patients with EoE, whereas abdominal pain was reported only in 6.1–24% (29,39) (*Table 3*). Authors in both papers have acknowledged the recent sharp increase in prevalence and incidence of EoE in Japan, possibly related to the coincident decline in HP prevalence as well as increase in disease awareness and other environmental and dietary factors. However, it remains unclear if the contrasting findings in clinical symptomatology reflects a true change in disease characteristics in the Asian population, or possibly the result of reporting bias in the context of increasing disease recognition and diagnosis over time. As for Asian children with EoE, consistent with international data, a multicenter study on pediatric EoE in Korea showed that non-specific symptoms such as vomiting (57.1%), abdominal pain (42.9%) and weight loss (42.9%) were the most common symptoms, whereas dysphagia was less common, observed in only 14.3% of patients (28).

In non-EoE EGID, symptoms are related to the region of the GI tract that is involved. Abdominal pain is commonly encountered across all non-EoE EGID (30,32,40). Specifically, EoG can present with dyspepsia, nausea/vomiting, early satiety, peptic ulcer disorder which may be non-responsive to standard treatment with PPIs, small bowel involvement can lead to malabsorption, protein-losing enteropathy and diarrhea, and patients with EoC are more likely to present with diarrhea and hematochezia (3). Complications of ascites and bowel obstruction may occur in cases of muscular or serosal involvement (5). Studies on Asian patients have also reported abdominal pain as the most common symptom affecting up to three-quarters of patients with non-EoE EGID, and diarrhea was observed to affect nearly half of these patients (29,34,39,41-43). Yamamoto *et al.* has also highlighted an interesting observation that restriction in activities of daily living was reported for 51% of patients with non-EoE EGID, as compared to only 12% of patients with EoE (29). This may signify more severe symptoms and disease course, and possibly lack of standardized treatment in non-EoE EGID. Symptoms were similar in Asian children with non-EoE EGID, with abdominal pain, diarrhea and vomiting being the most common clinical symptoms based on pediatric studies from Japan and China (44,45). Interestingly, the majority (>70%) of our cohort of children with EoG from Singapore presented with vomiting and hematemesis, with patients being notably younger (median age of 15 months) than in other pediatric studies (46) (*Table 4*).

There is a strong association between EoE and atopic and allergic disorders, with high frequencies of allergic rhinitis (57–70%), asthma (27–60%), atopic dermatitis (6–46%) and IgE-mediated food allergy (24–68%) in the EoE population (47). A systematic review on EoE in Asian countries reported that bronchial asthma was the most frequent comorbid allergic disease occurring in 24% in

Table 3 Summary of presenting symptoms in Western and Asian patients with EoE

Publication (country, year) (ref)	Study design	Patients	Symptoms				
			Dysphagia	Heartburn	Food impaction	Vomiting	Abdominal pain
Western data							
Ito (International, 2015) (34)	Systematic review of 121 studies	2,193 (1,873 Caucasian, 105 Asian), adults and children	77.2%	38.9%	–	1.1%	1.8%
Moawad (US, 2016) (38)	Retrospective, multicenter	793, adults and children	74% (White), 56% (African American), 53% (other races)	33% (White), 36% (African American), 38% (other races)	35% (White), 13% (African American), 13% (other races)	28% (White), 28% (African American), 23% (other races)	–
Shaheen (International, 2018) (36)	Systematic review of 27 studies on natural history from US, Europe, Australia and 1 study from Japan (26 patients)	20,905, adults and children	4.8–60.9% (children), 46.2–94.5% (adults)	7.7–54.5% (adults)	6.7–21.7% (children), 16.9–65.7% adults)	16.7–59.6% (children), 4.5–38.2% (adults)	15.7–56.6% (children)
Asian data							
Ito (International, 2015) (34)	Systematic review of 121 studies	2,193 (1,873 Caucasian, 105 Asian), adults and children	47.9%	16.9%	–	5.6%	18.3%
Kinoshita (International, 2015) (27)	Systematic review of 25 studies from Asia, mostly from Japan	217, adults and children	43.7%	22.1%	4.2%	6.1%	14.1%
Kim (South Korea, 2019) (25)	Retrospective, single center	72, adults	15.3%	30.6%	–	–	54.2%
Lee (South Korea, 2020) (28)	Retrospective, multicenter	14, children	14.3%	–	–	57.1%	42.9%
Yamamoto (Japan, 2021) (29)	Retrospective, multicenter	153, adults and children	82%	–	–	30%	24%
Okimoto (Japan, 2021) (39)	Retrospective, single-center	181, adults	66.9%	43.1%	–	–	6.1%

EoE, eosinophilic esophagitis.

Asian patients with EoE, followed by allergic rhinitis (22%), food allergies (13%) and atopic dermatitis (11%) (27). More than 50% of Asian patients with EoE had at least 1 allergic/atopic disorder (27). Other Asian single and multi-center studies have further reported rates of concomitant allergic disorders in 35–80% of patients with EoE (25,28,48). A single-center study on race-specific characteristics in pediatric EoE showed no difference in atopic history or food allergies between black/African American, Hispanic or Latin, Asian, and patients of other races (49).

Equally high rates of allergic disorders (50–70%) were observed in non-EoE EGID, most commonly asthma and allergic rhinitis, and this was universal among Western and Asian populations (32,39,44,46). Food allergies were common and have been reported to affect as many as 24–38% of patients in non-EoE EGID (32,39,40). In addition, patients with non-EoE EGID may be more likely to have increased serum eosinophil counts (29–63% *vs.* 22–33%), and low serum protein/albumin (21% *vs.* 0%) as compared to EoE, but these parameters are not consistent or reliable enough to correlate with diagnosis or disease activity (27,29,39).

Table 4 Summary of presenting symptoms in Western and Asian patients with non-EoE EGID

Publication (country, year) (ref)	Study design	Patients	Symptoms						
			Abdominal pain	Vomiting	Bleeding	Edema/ ascites	Weight loss, faltering growth	Diarrhea	Dysphagia
Western data									
Ko (US, 2014) (40)	Retrospective, single-center	30 (EoG), children	43%	36%	11%	4%	7%	–	–
Ito (International, 2015) (34)	Systematic review of 121 studies	2,193 (1,873 Caucasian, 105 Asian), adults and children	66.3%	47.8%	–	–	–	47.8%	5.4%
Jensen (US, 2016) (30)	Retrospective, national insurance database	774 (EoG), 954 (EoGE), 404 (EoC). Adults and children	51.9% (EoG), 49.7% (EoGE), 59.2% (EoC)	25.2% (EoG), 28.9% (EoGE), 28.0% (EoC)	8.9% (EoG), 6.9% (EoGE), 14.4% (EoC)	–	1.7% (EoG), 2.6% (EoGE), 3.5% (EoC)	16.9% (EoG), 30.7% (EoGE), 40.8% (EoC)	0%
Pesek (US, 2019) (32)	Retrospective, multicenter	376, adults and children	51%	49%	11%	–	9%	30%	11%
Asian data									
Ito (International, 2015) (34)	Systematic review of 121 studies	2,193 (1,873 Caucasian, 105 Asian), adults and children	64.9%	22.5%	–	–	–	50.0%	5.4%
Abassa (China, 2017) (41)	Retrospective, single-center	20, adults	70%	35%	–	–	–	20%	–
Hui (Malaysia, 2018) (42)	Retrospective, single-center	64, adults	35.9%	–	–	–	–	46.9%	–
Yamamoto (Japan, 2021) (29)	Retrospective, multicenter	151, adults and children	74%	34%	15%	13%	–	44%	18%
Okimoto (Japan, 2021) (39)	Retrospective, single-center	34, adults	61.8%	–	–	–	–	47.1%	14.7%
Kobayashi (Japan, 2022) (44)	Retrospective, single-center	109, children	76.1%	14.7%	10.1%	–	0.9%	23.9%	0.9%
Chen (China, 2022) (45)	Retrospective, single-center	22, children	77.3%	40.1%	–	–	–	13.6%	–
Ng (Singapore, 2022) (46)	Retrospective, single-center	21, children	28.6%	76.2%	71.4%	19%	23.8%	14.3%	–

EoE, eosinophilic esophagitis; EGID, eosinophilic gastrointestinal disease; EoG, eosinophilic gastritis; EoGE, eosinophilic gastroenteritis; EoC, eosinophilic colitis.

Endoscopy

Endoscopic findings of EoE have been well-described in the literature. The endoscopic reference score (EREFS) is a grading system which is based on the presence and severity of endoscopic findings such as edema, rings, exudates, furrows and stricture (15). Based on Asian data, linear furrows were the most frequently reported finding in 52–69% (25,27). Shimura *et al.* found that rings and strictures were not frequent in Japanese patients with EoE, and that linear furrows on endoscopy were the most reliable endoscopic finding to predict esophageal eosinophilia (50).

Normal endoscopy findings may be seen in 18–40% of cases (27,51).

A recent study from North America using the EoG Endoscopic Reference System (EG-REFS) that was modeled after the EoE EREFS found that erythema (72%) was the most common finding, followed by raised lesions (49%), erosions (46%) and granularity (35%) (52). A Japanese study also found erythema to be the most frequent gastric finding (72%), followed by ulcers (39%), discoloration (33%), erosions (28%), nodularity (28%) and polyps (28%) (53). Endoscopic findings were not predictive of the density of gastric eosinophilic infiltrates (53).

Management

The management of EoE and non-EoE EGID can be divided into the following categories: (I) pharmacologic therapy; (II) dietary therapy; (III) endoscopic or surgical intervention (for esophageal strictures, GI bleeding or surgical complications associated with non-EoE EGID). We will focus the discussion on the first two categories of treatment.

Pharmacologic therapy

PPI and swallowed topical corticosteroids (STC) are established pharmacologic options for EoE (54). STC, in the form of swallowed fluticasone or oral viscous budesonide adapted from inhaled formulations for asthma, have been shown to be effective in inducing histologic remission in 70–90% of patients (55). Recent and ongoing research in specific oral formulations of STC for EoE, such as oral dispersible tablets and oral suspensions, have shown promising results and may be standard therapy in the near future (56-58). The basis for the use of PPI comes from the coexistence and reciprocal provocation between GERD and EoE, the hypothesis that PPI may have an anti-inflammatory effect in down-regulating allergic Th2 inflammation, and observational evidence showing symptom response in up to 30–60% of patients (54,59). Additionally, studies on Japanese patients with EoE have also documented high response rate with PPI therapy of over 70% (39,48), although it is not known if similar high response rates are seen in other Asian populations.

An exciting development in EoE therapy is dupilumab, a human monoclonal anti-IL-4/13 antibody which has recently been approved by the Food and Drug Administration (FDA) in the United States for the indication of EoE. Phase 3 data showed that weekly or 2-weekly dupilumab achieved histologic remission in around 60% of patients at 24 weeks and 74–85% of patients at 52 weeks in patients 12 years and older (60,61). This is indeed a promising breakthrough in contrast to the relative lack of clinical benefit in previously studied biologic agents such as anti-IL-5 (mepolizumab, reslizumab) and anti-IgE (omalizumab) (15). Further progress may be expected in targeted therapies in EoE, with ongoing trials using novel drugs such as cendakimab, dectrekumab (both inhibitors of IL-4/IL-13 pathway), losartan (inhibition of transforming growth factor-β), IL-15 inhibitor (CALY-002), antolimab and lirentelimab (Siglec inhibition), and barzolvolimab (mast cell inhibitor) (62). As many of these trials are conducted in North America and Europe, it will be interesting to see if these therapies respond similarly in Asian patients considering the genetic, dietary and environmental differences.

For non-EoE EGID, no randomized controlled trials are available to provide definitive guidance on treatment. Observational data have shown that corticosteroids, in various formulations such as oral systemic steroids and viscous or enteric-release budesonide were useful in improving clinical symptoms (63,64). Similar retrospective studies from Asia have also documented efficacy specifically with systemic corticosteroids (prednisolone) though relapses were observed when steroids were tapered off (39,43,45,65). Other pharmacologic agents such as PPI, leukotriene receptor antagonists, mast cell inhibitors, antihistamines and biologic agents have been documented in case reports and small series but at present there is little evidence of significant clinical benefit to make any recommendations for their use.

Dietary therapy

As food allergens are known to play a significant contributory factor to the pathogenesis of EoE, food elimination diet (FED) is an accepted first-line treatment strategy (54). While complete elimination of food proteins using elemental, amino-based formula feed has been associated with successful response rate of >90%, it is challenging to sustain such a dietary therapy because of poor palatability, high cost and negative quality of life (15). Empiric FED removing the most common food triggers is a more widely-accepted approach. Six-FED (cow's milk, wheat, egg, soy/legumes, peanut/tree nut, fish/seafood), 4-FED (cow's milk, wheat, egg, soy/legumes) and 1-FED

(cow's milk) have been found to achieve pooled histologic remission rates of 61.3%, 49.4%, 51.4% respectively (66). Based on meta-analysis of studies in which patients received step-wise food re-introduction and re-evaluation, the most common causative food triggers were cow's milk (70.5%), followed by wheat (48.0%), eggs (27.6%) and legumes (20.7%) (66). The 'step-up' strategy starting with 2-FED (cow's milk and wheat) and escalating to 4- and 6-FED only in non-responders may offer benefits in reduced diagnostic time, reduced endoscopic procedures and less unnecessary dietary restrictions (67). There is low concordance between identified food triggers and food-specific IgE or skin prick test, hence allergy-test directed elimination diet is not recommended (68). It is worth highlighting that in the management of children with EoE, nutritional skills and optimal growth are important considerations which can be impaired with extensive food elimination (35). Hence a multidisciplinary approach involving the pediatric dietician is important to ensure adequate caloric intake and appropriate nutritional milestones. Surprisingly there is scarcity of data on the efficacy of FED in Asian patients with EoE. This is an area that definitely warrants research as there are distinct dietary, cultural and environmental differences between Asian and Western populations that may influence the role of food triggers in EoE in Asian patients.

In non-EoE EGID, there is some evidence that shows that dietary therapy may have a role in inducing disease remission. In a systematic review of 30 studies (mostly case reports/series), elemental diet and extensive empiric FED have been shown to result in clinical remission in 76% and 85% respectively of patients with non-EoE EGID (69). Ko *et al.* found that dietary therapy, ranging from elemental to empiric 1- to 7-FED led to clinical response in 82% and histologic response in 78% of children with EoG in North America (40). Similarly to what has been found in EoE, response to dietary therapy did not correlate to patient's food-specific IgE or skin prick test results (40). In Kobayashi's study from Japan, 23 out of 24 (95.8%) pediatric patients on FED experienced improvement or resolution of symptoms (44). Our study has also documented clinical and histologic remission rates of 94.7% and 68.8% with combined FED and PPI therapy in 21 children with EoG in Singapore, with younger patients more likely to respond to treatment as compared to older children (46). Yamamoto *et al.* found in a nation-wide study in Japan that patients with non-EoE EGID, comprising adults and children. who were managed with dietary therapy (29 out of 151 patients) had symptom resolution rate of 52%, comparable with systemic corticosteroids (29). The heterogeneity in diagnostic criteria, treatment approach and outcome definitions between studies limits the generalizability of these results. Nonetheless, there seems to be preliminary observational data that food trigger may play an important role in the pathophysiology of non-EoE EGID especially in pediatrics, and FED may be an effective strategy as first-line treatment similar to EoE.

Table 5 summarizes recent studies on EoE and non-EoE EGID from Asia that reported defined outcomes based on various treatment modalities.

Outcome and prognosis

EoE is a chronic disorder which gradually progresses from an inflammatory phenotype in childhood, eventually to a fibrostenotic phenotype in adulthood (70). The time interval in the delay in diagnosis or untreated EoE has been shown to increase the odds of fibrosis and stricture (71,72). As disease progression is gradual, patients may not report worsening symptoms but instead adopt compensatory eating behavior to minimize dysphagia or discomfort from progressive esophageal fibrosis (70). A review of past endoscopies in 10 patients diagnosed with esophageal eosinophilia in a study conducted in Japan found that endoscopic findings of EoE could be observed at a mean of 6.1 years prior to diagnosis, with no significant progression over time and only three patients developing mild symptoms of dysphagia or heartburn (48). The study is limited by small patient number but the authors did postulate that EoE in Japanese patients could be milder in severity, with high rate of PPI-response. Nonetheless, recent studies have supported long-term treatment to maintain disease remission and prevent relapse and progression to fibrostenotic disease (73,74). To date there has been no report of malignancy associated with EoE (75).

The natural history and disease course of non-EoE EGID are less clearly understood. Pineton *et al.* summarized that patients could follow 3 different courses of disease progression: (I) an initial disease flare without relapse; (II) multiple flares separated by periods of remission; and (III) chronic disease (64). Reed *et al.* found that only one third of patients with non-EoE EGID remained in long-term remission, majority having a persistent or progressive disease course (63). Li *et al.* found that 56.4% out of 55 patients with non-EoE EGID from China, majority treated with corticosteroids, developed disease relapse with median

Table 5 Studies on EoE and non-EoE EGID from Asia with defined treatment outcomes

Publication (country, year) (ref)	Study design	Patients	Diagnostic criteria (tissue eosinophil count)	Treatment	Outcome
EoE					
Sato (Japan, 2018) (48)	Retrospective, single-center	17, adults	Esophagus ≥15 eos/hpf	PPI (100%) STC, FED not reported	HR: 70.6% (<5 eos/hpf)
Kim (South Korea, 2019) (25)	Retrospective, single-center	72, adults	Esophagus ≥15 eos/hpf	PPI (77.8%) STC (5.6%) FED (not reported)	CR: 93.2% ER: 66.7% HR (n=18): 66.7% (<15 eos/hpf)
Yamamoto (Japan, 2021) (29)	Retrospective, multi-center	153, adults and children	Esophagus ≥15 eos/hpf	PPI (84%) STC (24%) FED (3%)	CR: 40% with PPI, 57% with STC, 25% with FED ER/HR: not reported
Okimoto (Japan, 2021) (39)	Retrospective, single center	181 adults	Esophagus ≥15 eos/hpf	PPI (92.3%) STC (12.7%) FED (not reported)	CR/HR (not defined): 73.2% with PPI, 100% with STC
Non-EoE EGID					
Wong (Singapore, 2015) (65)	Retrospective, single-center	18, adults	Stomach ≥30 eos/hpf	SC (50%) STC (5.6%)	CR: 88.9% with SC ER/HR: not reported
Hui (Malaysia, 2018) (42)	Retrospective, single-center	64, adults	Ileum/colon ≥20 eos/hpf	AH/LRA (100%) SC (10.9%)	CR: 89.1% with AH/LRA, 100% with SC ER/HR: not reported
Yamamoto (Japan, 2021) (29)	Retrospective, multi-center	151, adults and children	Stomach ≥30 eos/hpf Small intestine ≥50 eos/hpf Colon ≥60 eos/hpf	PPI (42%) SC (40%) AH/LRA (44%) FED (19%, all children)	CR: 55% with SC, 52% with FED ER/HR: not reported
Kobayashi (Japan, 2022) (44)	Retrospective, single-center	109, children	Any region except esophagus ≥20 eos/hpf	PPI (21.1%) FED (22.0%) AH/LRA (18.3%) FED and AH/LRA (45.9%) FED, AH/LRA, SC (4.6%)	CR: 39.4% ER/HR: not reported
Ng (Singapore, 2022) (46)	Retrospective, single-center	21, children	Stomach ≥30 eos/hpf	PPI and FED (95.2%) STC (19.0%)	CR: 94.7% with PPI/FED ER (n=16): 81.3% with PPI/FED HR (n=16): 68.8% (<20 eos/hpf) with PPI/FED

EoE, eosinophilic esophagitis; EGID; eosinophilic gastrointestinal disease; eos/hpf, eosinophils per high power film; PPI, proton pump inhibitor; STC, swallowed topical steroids; FED, food elimination diet; HR, histologic response; CR, clinical response; ER, endoscopic response; SC, systemic corticosteroids; AH, anti-histamine; LRA, leukotriene receptor antagonist.

Table 6 Research opportunities to improve our understanding of clinical characteristics and manage of EGID in Asian patients

Data	Research gaps specific to EGID in Asia
Epidemiology	(I) Prevalence and incidence of EGID using standardized definitions, with wider diversity of populations in Asia
	(II) Environmental, dietary, genetic risk factors associated with development of EGID, with distinction between EoE and non-EoE EGID
	(III) Role of Helicobacter pylori in incidence and clinical manifestation and phenotype of EGID
Phenotype	(I) Clinical presentation, and characterization of disease phenotype of EoE and non-EoE EGID
Treatment	(I) Efficacy of food elimination diet and potential causative food triggers specific to Asian patients
	(II) Response rate with standard pharmacologic therapy, PPI and corticosteroids
	(III) High-quality randomized controlled trials of novel treatment, including biologic therapy
Outcome	(I) Disease progression and long-term prognosis, including incidence of stricture formation
	(II) Malignancy risk
	(III) Impact of disease on quality of life

EGID, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; PPI, proton pump inhibitor.

relapse-free interval of 12 months (76). In Japan, non-EoE EGID followed a continuous chronic course in 64% of patients, single-flare type in 19% (predominant in the younger age group 0–4 years), and intermittent relapsing course in 7% of patients (29).

Conclusions

EGID is still a relatively new group of conditions with many clinical and research questions that remain to be answered. Much of our current understanding of EGID have come from studies from Europe and North America. There are likely to be differences in disease characteristics between populations with distinct dietary, environmental and cultural backgrounds, however there remains a considerable scarcity of robust data on many basic aspects of EGID in Asia (*Table 6*). There is a pressing need to bridge this gap by building research networks and collaborations across wider regions in Asia through regional/international societies and registries, to gather high-quality, multicenter data using standardized and uniform criteria. It is through such collaborations that we can then pool data across studies meaningfully and have a more accurate understanding of EGID in Asian patients.

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Footnote

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