

Eosinophilic Esophagitis and Gastroenteritis

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Abstract Eosinophilic gastrointestinal disease (EGID) can be classified as eosinophilic esophagitis (EoE) when the eosinophilia is limited to the esophagus or as eosinophilic gastritis (EG) if it is limited to the gastric tract, eosinophilic colitis (EC) if it is limited to the colon, and eosinophilic gastroenteritis (EGE) if the eosinophilia involves one or more parts of the gastrointestinal tract. EoE is by far the most common EGID. It is a well-defined chronic atopic disease due to a T helper type 2 (Th2) inflammation triggered often by food allergens. EoE diagnosis is done if an esophageal biopsy shows at least 15 eosinophils per high power field (eos/hpf). Globally accepted long-term therapies for EoE are the use of swallowed inhaled steroids or food antigen avoidance. The treatment of EoE is done not only to control symptoms but also to prevent complications such as esophageal stricture and food impaction. EGE cause non-specific gastrointestinal (GI) symptoms and are diagnosed if esophagogastroduodenoscopy (EGD)/colonoscopy show eosinophilia in one or more parts of the GI tract. They are rare diseases with an unclear pathogenesis, and they are poorly defined in terms of diagnostic criteria and treatment. Before initiating treatment of any EGE, it is imperative to conduct a differential diagnosis to exclude other causes of hypereosinophilia with GI localization. EGE are often poorly responsive to therapy and there is

no commonly accepted long-term treatment. EG has many characteristics similar to EoE, including the fact that it is often due to a food allergen-driven Th2 inflammation; transcriptome analysis however shows that it is more a systemic disease and has a different gene signature than EoE. EC is a benign form of delayed food allergy in infant and is instead a difficult-to-treat severe inflammatory condition in older children and adults. EC in the latter groups can be a manifestation of drug allergy or autoimmune disease. Overall EGE, EC, and EG are rare and are a diagnosis of exclusion until more common causes of eosinophilia have been excluded.

Keywords Eosinophilic esophagitis · EoE · Food allergy · Food impaction · Dysphagia

Abbreviations

EoE	Eosinophilic esophagitis
EGID	Eosinophilic gastrointestinal disease
EG	Eosinophilic gastritis
EGE	Eosinophilic gastroenteritis
EC	Eosinophilic colitis
GERD	Gastroesophageal reflux disease
PPI	Proton pump inhibitor
hpf	High power field
HES	Hypereosinophilic syndrome
TSLP	Thymic stromal lymphopoietin
PGD2	Prostaglandin D2
DSG-1	Desmoglein-1
PAMPs	Pathogen-associated molecular patterns
DAMPs	Danger-associated molecular patterns
DC	Dendritic cells

This article is part of the Topical Collection on *Food Allergy*

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Introduction

The eosinophilic disorders of the gastrointestinal tract (EGID) are a group of diseases characterized by an eosinophilic inflammation of the any part of the gastrointestinal (GI) tract [1, 2]. Based on clinical characteristics, pathogenesis, and response to therapy, EGID can be divided into four principal groups: eosinophilic esophagitis (EoE), eosinophilic gastroenteritis (EGE), eosinophilic gastritis (EG), and eosinophilic colitis (EC) [1–3].

EoE is by far the most common of the EGID with an incidence estimated to be similar to inflammatory bowel disease (i.e., 1/2000), at least in the Western developed countries such as the USA, North Europe, and Australia [4–7]. By definition, EoE is characterized by pathological eosinophilia limited to the esophagus driven by an allergic response to foods and likely environmental allergens [8, 9]. Diagnostic criteria and treatment modalities for EoE are well accepted among the global medical community [10–14, 15].

EGE, EG, and EC are, on the other hand, a group of heterogeneous, ill-defined diseases that are very rare. Even if they are characterized by eosinophilic infiltration in one or more part of the GI tract, there is no agreement on the level of eosinophils that constitutes disease, their pathogenesis is often unknown, and they appear to be poorly responsive to any anti-inflammatory therapy [2, 16–18]. Indeed EGE, EG, and EC should be a diagnosis of exclusion after other more common causes of eosinophilia have been excluded such as parasitic infections or drug allergy. Inflammatory diseases associated to GI eosinophilia (inflammatory bowel disease, Churg-Strauss, and lupus) should be also excluded [2, 16, 19, 20].

Eosinophilia in the GI tract can be found associated with moderate to severe peripheral hypereosinophilia (>1500 cell/ mm^3) in a group of premalignant and often debilitating disorders called hypereosinophilic syndrome (HES). HES are a multisystemic disorder involving GI and non-GI tract organs as well as peripheral blood; they are associated with debilitating symptoms such as anorexia, fever, and rapid weight loss, and if left untreated, they are often fatal [21, 22]. These diseases are often treated in conjunction with hematologist-oncologist with chemotherapy and will not be reviewed in this manuscript's present review. However, they should be part of the differential diagnosis of any EGE, EG, and EC associated with significant persistent peripheral eosinophilia.

Eosinophilic Esophagitis

Epidemiology

EoE was considered a rare disease, but its incidence appears to be rapidly escalating in highly developed countries such as the USA and Australia with an estimated 1/2000 similar to the one

of pediatric Crohn's disease [4–7]. Atopic, Caucasian males are disproportionally affected by EoE; indeed, the male/female ratio in both adults and children is 3:1 and up to 90 % of EoE patients has at least another atopic disease such as allergic rhinitis, asthma, and food allergy [23–25].

Members of the same family can be effected with a sibling risk ratio of 80, which is 40 times higher than for asthma, suggesting an important genetic component in EoE [26].

Diagnosis

EoE is a clinicopathological diagnosis. Symptoms due to EoE are stemming from dysfunctional esophageal motility and/or fibrosis with the former being more frequent in children and the latter in adults. Therefore, although any symptom can present at any age, typical symptoms are as follows (Fig. 1):

1. In infants and toddler: gagging, failure to progress in solid introduction and failure to thrive
2. In older children: abdominal pain and vomiting
3. In teenagers and adults: dysphagia and food impaction [14, 27, 28]

Symptoms of EoE can be very similar to gastroesophageal reflux disease (GERD), but differently from GERD, they are typically not responsive to maximal dose of proton pump inhibitors (PPI) [14, 27–29].

The diagnostic gold standard for EoE is the presence of at least 15 eos/high power field (hpf) in one esophageal biopsy obtained with esophagogastroduodenoscopy (EGD) after 8 weeks of maximum PPI dose. It is extremely important to have completed such therapy before the EGD. The esophagus is the only part of the GI tract naturally devoid of eosinophils [30]. The presence of eosinophils can be due to GERD, PPI-responsive esophageal eosinophilia (PPI-REE) or EoE or other rare diseases [31–33]. A proper treatment with PPI (20–40 mg twice a day or 1 mg/kg twice a day in children) for 8–12 weeks will exclude the first two diagnoses [31–33].

Feeding Disorder

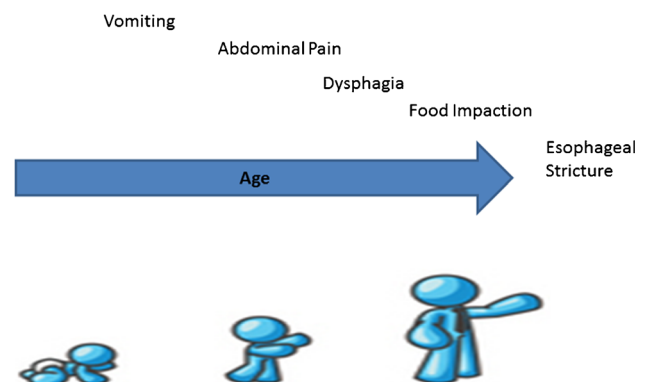


Fig. 1 EoE symptoms based on age

Macroscopically, an EGD can show in the esophagus signs of inflammation and or fibrosis (furrows, trachealization, edema, white plaques, tears, stenosis) or can be normal, so biopsies should be taken even from macroscopically normal epithelium. Moreover, the eosinophilia in EoE is often patchy; therefore, at least four biopsies should be obtained. Biopsies of the duodenum and stomach also need to be collected to rule out EGE [15•]. At the moment, there is no reliable biomarker that can substitute the EGD for the diagnosis and monitoring EoE progression and response to therapy [15•]. Future monitoring therapies include esophageal string test [34] or esophageal cytosponge [35].

Pathogenesis

EoE is a chronic, cell-mediated, food allergy-associated atopic disease characterized by esophageal eosinophilia and T helper type 2 (Th2) inflammation [8•, 36•, 37•, 38, 39•, 40, 41•]. It is also well established that genetics play a large role in susceptibility [23, 26•, 37•, 40, 41•, 42–44].

There are several lines of evidence that support EoE being an atopic disease:

1. The vast majority of patients with EoE (up to 80–90 % in some studies) are atopic [15•];
2. Several independent groups have shown that the inflammation associated with EoE is the typical atopic Th2 inflammation [45, 46•, 47–53]. The esophagus is normally devoid of eosinophils. Active EoE typically occurs in association with Th2 cytokines. IL-13, IL-5, and IL-4 expression in the esophagus and a mouse model that have been genetically modified to not express Th2 cytokines is less likely to develop EoE [28, 36•, 38, 50, 52–56, 57•].

Th2 cytokines cause the inflammation observed in EoE, as they (a) induce an increased Th2 response from T cells, basophils, invariant natural killer cells (iNKTs), and mast cells; (b) enhance survival and activation of eosinophils; and (c) are responsible for the fibrotic changes. However, the Th2 cytokines appear to exert redundant functions, as they have many similar effects; therefore, treatment strategies that are based on abolishing a single cytokine are probably not going to be sufficient to treat EoE [58•, 59].

Specifically IL-13 has been reported to play a major and essential role in EoE with a mechanism that depends on IL-5, STAT1, and STAT6 activation [50, 60]. IL-4 leads to Th2 lymphocyte survival and induces eotaxin-3 (a key chemoattractant for eosinophils) and the profibrotic factors periostin, collagen, and β -actin [28, 61]. IL-5 is the major cytokine responsible for the differentiation, recruitment, activation, and survival of eosinophils [62]. Mice genetically modified to not express IL-5 are resistant to EoE development,

whereas the ones that overexpress IL-5 have elevated levels of eosinophils in the esophagus [50, 51, 63, 64].

Inflammatory cells—the cells involved in EoE inflammation are all producers of Th2 cytokines and are part of the adaptive (Th2 T cells) or innate (eosinophils, basophils, mast cells, iNKTs) immunity.

Th2 lymphocytes are, together with the eosinophils, the most abundant infiltrating cell type in EoE and produce high levels of Th2 cytokines both at the site of inflammation and in the peripheral blood [65, 66]. They are most likely essential cells in EoE as mice deficient in T cells do not develop EoE [67].

Eosinophils are the major infiltrating cells in EoE biopsies and are pathognomonic for EoE inflammation. However, they appear to be recruited in the esophagus as a consequence of a Th2 inflammation and are not essential to maintain chronic esophageal inflammation typical of EoE. Indeed, treatment with anti-IL-5 has shown to be able to deplete eosinophils from the esophagus of EoE patients, but not to reduce symptoms or any other inflammatory manifestation in the tissue [58•, 59].

Basophils represent less than 1 % of leukocyte population and are able to secrete histamine when their high affinity receptor for IgE, Fc ϵ RI, is activated, and their role in type I (IgE-mediated) allergic responses is well established. However, recently, it is becoming apparent that they play also a major role in non-IgE-mediated allergic conditions such as EoE. Indeed a unique subpopulation of basophils that develops in the presence of thymic stromal lymphopoietin (TSLP), and expresses high levels of IL-4, is overexpressed in EoE [68]. In support of the importance of the TSLP-basophil axis in EoE pathogenesis, mice did not develop an EoE-like disorder if pretreated with antibodies against basophils and TSLP [39•]. Together, these studies show that TSLP-mediated basophil response might play an important role in the pathogenesis of EoE in humans.

Activated mast cells and mast cell products (TGF- β , prostaglandin D2 (PGD2)) have been described in the esophageal biopsies from active EoE subjects [69, 70]. They are good producers of Th2 cytokines and may play a central role in esophageal dysmotility observed in EoE given that they often are located in close proximity to nerves [71].

iNKTs specifically recognize self and foreign lipids, including food-derived ones, via their semi-invariant T cell receptor (TCR) [72, 73]. Jyonouchi et al. showed that iNKTs produce IL-4 and IL-13 upon stimulation with milk-derived lipids and are recruited at the esophagus via RANTES [38]. Therefore, they may play a role in the non-IgE-mediated allergy to milk commonly observed in EoE patients.

Epithelial Dysfunction

Epithelium-derived Th2 cytokines and chemokines appear to be essential to promote EoE inflammation, and a

dysfunctional epithelium is increasingly recognized as a central factor in EoE development.

Indeed, patients with active EoE have a significant epithelial barrier dysfunction, due to a downregulated expression of the cell adhesion protein desmoglein-1 (DSG-1) [74, 75]. This may be responsible for enhanced permeability of the epithelium to local food and environmental allergens, leading to increased access of antigens and activation of epithelial cell to produce cytokines and chemokines that ultimately induce the Th2 inflammation [76]. It is well established that the esophageal epithelium is more than a physical barrier, as it expresses Toll-like receptors [77, 78] and produces pro-inflammatory cytokines in response to both pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [77].

Upon activation with danger signals (PAMPs, DAMPs), activation of Toll-like receptors, atopic cytokines (IL-4, IL-13, TNF α), and environmental allergens, esophageal epithelial cells release in patients with EoE large quantities of TSLP, a cytokine that belongs to IL-7 family and is considered the master regulator of Th2-type allergic inflammation [39, 41, 68]. TSLP promotes the maturation and activation of dendritic cells (DC) permissive for the differentiation of naïve CD4⁺ T cells into Th2 cells [79] and also stimulates directly inflammatory cells (T cell, basophils, mast cells, iNKTs) to produce Th2 cytokines [39, 68]. Interestingly, in a mouse model of EoE, neutralizing antibodies against TSLP and basophils helped in ameliorating the EoE-like disease when administered after the onset of disease. This may suggest that targeting the TSLP-basophil axis may lead to potential therapeutic treatments for EoE.

Eotaxin-3 (CCL-26) is a potent eosinophil chemoattractant which signals through CCR3, a chemokine receptor expressed by activated eosinophils, iNKTs, and mast cells. In EoE subjects with active disease, eotaxin 3 is elevated in the esophageal epithelium and peripheral blood during active inflammation and plays key role in the migration of eosinophils to the esophageal tissue [37]. In vitro, esophageal epithelial cells secrete eotaxin-3 in response to IL-4 and IL-13 stimulation [80], and such activation can be suppressed by the proton pump inhibitor omeprazole cytokine mediated CCL-26 [81]. This observation suggested that proton pump therapy, a standard of care in the treatment of EoE, may play a role in reducing tissue eosinophilia through mechanisms independent of acid suppression alone, like in PPI-REE.

We and others have also demonstrated that EoE-derived epithelial cells can produce the eosinophilic and T cell chemokine, RANTES (CCL5), which may play a role in the migration and activation of IL-13 producing iNKT cells in EoE [38].

Mast cell-derived PGD₂, a prostanoid molecule specifically produced by mast cells in allergic responses, may also be another important chemoattractant by acting on the chemoattractant receptor expressed on Th2 cells (CRTH2),

which is a G protein-coupled receptor highly expressed on all cells (i.e., Th2 lymphocytes, eosinophils, and basophils) involved in a Th2 inflammation, and has been found to be elevated on eosinophils from patients with EoE [82].

Other regulatory molecules, such as micro-RNA (miRNA), have been shown to be playing a role in EoE pathogenesis and in particular in contributing to the Th2 inflammation. miRNA are single-stranded RNA molecules which are very conserved during the evolution and can regulate inflammation by silencing target genes [83]. In active EoE, miRNA implicated in the downregulation of the Th1 response such as miR-21, miR-146a, and miR-146b are upregulated and those associated with Th2 response such as miR-375 are downregulated. These data suggest that miRNA profile in EoE patient could promote their Th2 inflammation [83].

Allergen in EoE

Like in any other atopic disease, the vast majority of cases of EoE are triggered by allergens. In most children and adults, foods have been identified as the trigger of EoE Th2 inflammation with non-IgE-mediated mechanism [8, 84–86]. In addition, evidence suggests that aeroallergens may play a causative role in the development of EoE in select individuals [87].

Allergens seem to induce a Th2 inflammation in a non-IgE-mediated fashion. Indeed in a mouse model of EoE, IgE-depleted mice could still develop esophageal inflammation and consequent food impaction similarly to wild-type mice [39]. This is not surprising as testing for food allergy by skin prick testing or specific sera IgE has not proven successful in definitive identification of causative foods in EoE, in spite of the efficacy of targeted food diets in the treatment of EoE [8]. Rather, the addition of atopy patch testing, which represents a T lymphocyte-mediated allergen-specific response, increases the likelihood of identifying causative foods in EoE [8, 88–91]. Limited clinical trials have also shown that anti-IgE therapy with omalizumab has no effect on esophageal eosinophilia [92]. Finally, oral immunotherapy is used in research for desensitization to IgE-mediated food allergy, but 2–10 % of desensitized patients later develop EoE indicating a non-IgE mechanism [93, 94].

Fibrosis in EoE

There is general consensus that, if left untreated, EoE poses a significant risk of resulting in esophageal fibrosis; indeed, EoE is currently the leading cause of emergent endoscopy for esophageal food impaction in adults and over half of EoE patients report dysphagia [95, 96]. Interestingly, not only the incidence of esophageal food impaction has increased dramatically in the last 5–10 years [97], in parallel with the increased incidence of EoE, but also patients diagnosed with EoE and lost at follow-up tend to present initially with

GERD-like symptoms and return years later with dysphagia [8•]. All together, these data suggest that EoE is a risk factor to develop esophageal fibrosis.

Clinical presentation of fibrosis ranges from signs of progressive solid food dysphagia (excessive chewing and drinking with meals) to subtle changes in eating habits (meat avoidance) and to frequent episodes of food impaction. This underscores the importance of obtaining a thorough and targeted history in both established EoE patients as well as all new patients presenting with food allergy, atopy, and GERD-like symptoms.

Genetic Risks

EoE is a disease with a strong genetic component, and single nucleotide polymorphisms (SNPs) in several genes (eotaxin 3, TGF- β , TSLP, TSLPR, CAPN14, and EMSY) have been found to be associated with EoE (Table 1) [37•, 40, 41•, 42–44, 98]. Interestingly, these genes have also been found associated to other atopic diseases (albeit with a much weaker strength) (TSLP, EMSY) or have been found to be in genes regulated by Th2 cytokines (CAPN14) or important in Th2 inflammation (eotaxin 3, TSLP, TGF- β).

Treatment

The current clinically accepted EoE management is similar to all the atopic diseases and is based on allergen avoidance and corticosteroid treatment. The future treatments will be probably relying on induction of antigen tolerance and specific biological treatments (Table 2).

PPI are also integral part of treatment as they are used not only to rule out GERD and establishing the diagnosis but also to treat an emerging cause of eosinophilia in the esophagus called PPI-responsive esophageal eosinophilia (PPI-REE) whose pathogenesis is still not completely understood [33, 99–103]. PPI therapy (20–40 mg of available agents twice daily for adults or 1 mg/kg and 10–30 mg of available agents twice daily for pediatric subjects) is used to rule out GERD as a cause of esophageal eosinophilia, and consensus recommendation for the diagnosis of EoE requires an 8-week PPI trial before EoE diagnosis can be made [14, 15•].

Table 1 EoE genetic risk description of SNPs found in EoE

Variant [effect allele]	Chromosome	Gene
rs1438673 [T]	5q22	TSLP
rs55646091 [A]	11q13.5	c11orf30
rs74732520 [G]	2p23.1	CAPN14
rs36133495 [V]	Xp22.3; Yp11.3	TSLPR
rs2302009 [G]	7q11.23	Eotaxin

Steroid Treatment Steroids are a very effective treatment of EoE, like it happens in all other atopic diseases.

Oral steroids, even if they are very effective if used short-term (1–2 mg/kg max 60 mg/24 h, for 7–15 days) are not recommended as a long-term therapy for the well-known side effects [104–106].

Swallowed inhaled corticosteroids are effective and are considered “topical.” Fluticasone is given by mouth with a metered-dose inhaler without a spacer and swallowed twice daily [106, 107]. Budesonide is administered as an oral viscous preparation (slurry) mixed with Splenda or viscous foods (apple sauce, honey, maple syrup) [108, 109•].

Swallowed inhaled steroids are effective when used correctly in up to 80 % of patients and can be used as first-line therapy for initial and maintenance management of EoE. Even if swallowed inhaled corticosteroids appear to be safe as short term therapy (less than 1 year), they have potential long-term side effects, including growth suppression and osteopenia (low bone density) similar to the one observed in children treated for asthma at similar dosages [106, 109•]. Like in all other chronic atopic disease, while steroids are effective for treatment, clinical and histologic features of EoE return upon discontinuation [15•, 110–113].

Dietary Intervention The majority of patients with EoE are sensitized to both food allergens and aeroallergens [15•]. Foods are known triggers of EoE in nearly all adult and children [114]. Dietary elimination therapy is effective and should be considered in all children and motivated adults diagnosed with EoE (Table 2). There are three major clinically accepted dietary approaches that can be used in EoE: (1) an elemental diet, (2) specific antigen avoidance based on allergy testing, and (3) empiric food elimination based on the most common food antigens (also known as six-food elimination diet (SFED)) [15•]. The dietary regimen should be chosen based on the individual patient characteristics [85, 104, 105, 115].

Treatment with food avoidance is highly successful, with rates close to 100 % when amino acid-based formulas are used as the sole source of nutrition. However, prolonged elemental diet severely reduces quality of life and is not sustainable indefinitely [116].

Eliminating foods on the basis of allergy testing or empirically leads to resolution of esophageal eosinophilia in 50 to 80 % of patients, depending on the diet and the age of the patient. These diets are sustainable long-term, but may be difficult in some patients especially if multiple foods are eliminated. For additional details of dietary management, please see a recent review [116].

Esophageal Dilation Esophageal fibrosis and esophageal strictures are known complications of EoE and are common in untreated EoE. Endoscopic stricture dilation is sometime necessary for short-term symptomatic relief in patients that

Table 2 EoE therapies that have been tried in EoE

Type of treatment	Description	Effectiveness
Diet	Elemental Six-/four-food elimination diet Targeted diet	Elemental diet (90 %); six-/four-food elimination diet and targeted diet (70–80 %)
Pharmacological	Proton pump inhibitors Oral steroids Swallowed “topical” steroids	Proton pump inhibitors in PPI-responsive EoE only (20 %) Oral steroids (95 %) Swallowed “topical” steroids (70–80 %)
Biological	Anti-IL-5 (reslizumab, mepolizumab) Anti-IgE (omalizumab) Anti-CRTH2 (OC000459) Anti-TNF α (infliximab) Anti-IL-13 (QAX576)	Anti-IL-5 (reslizumab, mepolizumab) (not effective) Anti-IgE (omalizumab) (not effective) Anti-CRTH2 (OC000459) (40 %) Anti-TNF α (infliximab) (not effective) Anti-IL-13 (QAX576) (40 %)

have failed dietary and medical therapy. Importantly, esophageal mucosal fragility is a known feature of EoE raising the risk of complications including pain, bleeding, and esophageal perforation; therefore, they should not be used as the only therapy to manage EoE [15•, 117, 118].

Other Biological Treatments Other treatments that have been investigated including anti-IL-5, anti-IL-13, and CRTH2 antagonist [55, 56, 57•, 119–123]. These strategies have shown limited or no efficacy in controlling the disease suggesting that a broader inhibition of Th2 inflammation may be needed due the redundancy of its mediators. Future therapy may include anti-TSLP antibodies, which have been used for treatment of intractable asthma, but have never been tried in EoE [124].

Eosinophilic Gastroenteritis, Eosinophilic Gastritis, and Eosinophilic Colitis

Introduction

EGE, EG, and EC are a group of very rare, ill-defined diseases characterized by eosinophilia limited to the gastrointestinal tract (esophagus, stomach, duodenum, ileus, colon) [2, 16, 17].

EGE are characterized by involvement of multiple locations. When eosinophils are isolated to one part of the GI tract, it is called eosinophilic gastritis (EG) or eosinophilic colitis (EC). Eosinophilic ileitis exist but they are poorly characterized as biopsies of the ileum are rarely obtained [125, 126]. The diagnosis is based primarily on clinic pathological criteria [2, 16, 17]. Eosinophilic infiltration can be limited to the superficial layer of the GI mucosa (mucosal EGE, EG, EC), can involve only the serosal epithelium (serosal EGE, EG, EC), or can be deep and involve the muscular layer (mucularis EGE, EG, EC). The type of inflammation responsible for EGE, EG, and EC appears to be similar. It is not clear if EGE, EG, and

EC are different diseases or a spectrum of a same common pathological process [127].

EGE

EGE presents with chronic non-specific GI symptoms such as protracted or recurrent diarrhea, vomiting, and abdominal pain. Biopsies obtained with EGD show eosinophilia in one or more parts of the GI tract. Esophageal eosinophilia can be found in association with eosinophilia in other parts of the GI tract in EGE. Once EGE are suspected, other causes of eosinophilia have to be carefully ruled out before the diagnosis of EGE can be made (Table 3).

Epidemiology

EGE are extremely rare disorders with only a few hundred cases described in the literature since the first report in 1938. In general, their incidence is estimated to be 1–30/100,000, but this could be very underestimated. Indeed a recent study has found that 0.67 % of all the biopsies done in one center met the criteria for EGE [16, 128•, 129•]. EGE are more common in males, but the serosal subtype is typically found in women older than 40 years of age [2, 16, 17]. Children and adults can be affected with diseases of similar characteristics; the maximum incidence happens between 30 and 50 years of age [2, 16, 17, 129•].

Table 3 Differential diagnosis for EGE

- Infection (parasites)
- Drug allergy
- Chronic graft-versus-host disease
- Chronic inflammation (e.g., IBD)
- Autoimmune disease
- HES
- Lymphoma, leukemia

Diagnosis

EGE is suspected when there are chronic or recurrent GI symptoms such as vomiting, diarrhea, weight loss, or failure to thrive in children; low protein (malabsorption or protein-losing enteropathy), GI bleeding (macroscopic or occult); anemia; and icterus [16, 128•, 129•]. The involvement of serosal layers such as the peritoneum can lead to abdominal distension and ascites, whereas the involvement of the muscle can cause severe cramps or abdominal obstruction. Finally, an involvement of multiple layers of the GI epithelium can lead to rare abdominal perforation [16, 128•, 129•]. Hepatobiliary tree involvement can occur and may present as pancreatitis [130] or eosinophilic cholangitis [131].

Once EGE are suspected, the diagnosis is confirmed by EGD and colonoscopy, which reveal eosinophils present in one or more location in the GI tract [2, 16, 17]. EGE can be associated with mild to moderate eosinophilia in the blood ($<1500 \text{ mm}^3/\text{ml}$); however, rarely moderate to severe eosinophilia ($>1500 \text{ mm}^3/\text{ml}$) can be found [16, 128•, 129•]. If eosinophilia is $>1500 \text{ mm}^3/\text{ml}$, HES should be excluded [16, 128•, 129•]. EGE should be a diagnosis of exclusion after other more common causes of eosinophilia have been excluded [2, 16, 19, 20•]. A careful history should include a review of all drugs used (therapeutic recreational, alternative, dietary supplements) and travel history to rule out secondary causes of eosinophilia such as allergic or infectious. One of the major infectious causes of eosinophilia are parasitic infections, hence a stool sample should be analyzed for ova and parasite and serology for *Strongyloides stercoralis* or *Toxocara canis* should be obtained [2, 16, 19, 20•]. For patients with peripheral chronic moderate to severe eosinophilia ($>1500 \text{ eos/mm}^3$), additional studies need to be obtained to rule out HES: TCR clonality studies (T cell clonality in lymphocytic HES), FIP1-like 1/platelet-derived growth factor receptor α fusion gene studies (typical of myeloid HES), and cardiac echocardiogram (to rule out the endomyocardial fibrosis, heart dilation, or congestive heart failure that is seen in HES with cardiac involvement) [21, 22]. The diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA or Churg-Strauss syndrome) should be considered in patients with significant lung disease or presence of nasal polyps. These patients can present with dysphagia, anorexia, vomiting, abdominal pain, and bloody diarrhea. Chest X-ray may show migratory infiltrates common in EGPA, and serum anti-nuclear cytoplasmic antibodies can help with the diagnosis if positive.

Differently from the esophagus, eosinophils are normally present in the rest of the GI tract and the definition of pathological eosinophilia does not exist, with authors using as definition of pathological levels of eosinophils any level between 20 and 80 per hpf in one or more hpf [1, 126, 132, 133]. In a recent pediatric study, the authors defined as pathological $>50 \text{ eos/hpf}$ in the stomach or colon and $50/\text{hpf}$ for the

duodenum and ileum based on the fact that normal levels are between 10 and 50 eos/hpf (with the distal colon and stomach being the organ where the highest level of eosinophils is found in normal individuals and lower levels in the duodenum, ileum, and proximal colon) with a gradual distribution [134].

The natural history of the EGE is unknown; however, a small study on 43 patients followed for 13 years further subclassifies the EGE based on the duration of the disease. Most commonly, EGE are chronic or recurrent/chronic diseases, where active disease alternates with times of remission, others have a progressive worsening outcome, whereas others go in definitive remission spontaneously or after one round of treatment [126, 129•].

Pathogenesis

The GI tract, with the exception of the esophagus, is rich in eosinophils, and among the non-hematopoietic organs, it has the highest amount of eosinophil in a healthy state. Typically, eosinophils reside in the lamina propria at the level of the mucosa and with the highest concentration in the distal colon, appendix, and esophagus [3].

Like for EoE, a large proportion of patients with EGE have other atopic diseases and animals can develop EGE when appropriate stimulation with allergens is performed. Eosinophils and the typical Th2 inflammation have also been described in EGE [135, 136]. Differently from EoE, the majority of adult and pediatric patients with EGE do not respond to diet suggesting an autoimmune process [3, 19].

Therapy

Because EGE are rare diseases, most of the data we have about how to treat the disease are based on a single case report or small case series [2, 16, 17]. Differently from EoE, the EGE are often difficult to control with up to 65 % of patients who are not responsive or only partially responsive to any kind of treatment including oral steroids [126, 129•, 134, 137]. Even those patients that are responsive to treatment often require the use of multiple therapies to keep the disease under control. In one of the largest published study on 42 patients, Dellon et al. [129•] found that only a minority of patients responded to treatment (35 %; 15/42). Among those who responded, about 47 % responded to diet, 80 % to steroids, and 7 % to mast cell stabilizer or anti-leukotrienes. In another study [126], 40 % had spontaneous remission and the rest responded poorly to any treatment [126]. The oral steroids are the most effective treatment both in the short-term and in the long-term [126, 129•, 137]. The use of the topical steroid budesonide used in capsule has had some sporadic success [126, 129•, 137–142]. Patients with suspected predominantly ileal disease can use the Entocort capsules for optimal ileal activity. These capsules controlled release budesonide in the ileum with very

minimal gastric delivery. Case reports show that occasionally, PPI and mast cell stabilizers are effective in EGE treatment [43, 126, 129•, 137, 143]. However, it is hard to tell as patients can have spontaneous remission and the effects in case reports maybe due to medication or spontaneous remission.

The value of the diets both elemental and elimination ones is an object of some debate. In some studies, it has been shown to be effective, mainly in case reports [18, 144, 145]. A recent meta-analysis on the use of diet in EGE shows no efficacy in the majority of cases [18].

EG

EG is a chronic illness thought to affect approximately 0.02–0.03 % of the population. Even if it is more prevalent in adults, it can be found children. EG like EoE and EGE is characterized by tissue eosinophilic inflammation, peripheral eosinophilia, coexisting allergic diseases (e.g., allergic rhinitis and/or asthma), and sensitization to multiple food allergens. Also, EG, like EoE, is more prevalent in males [127, 134].

Diagnosis

Symptoms of EG vary depending if they involve the stomach or the duodenum. Involvement of gastric or duodenal tract can be associated with abdominal pain and bloating. Patients with gastric inflammation have nausea, vomiting, and early satiety, and those with duodenal have malabsorption and protein-losing enteropathy. Patients can have simultaneous duodenal and gastric disease. If eosinophils involve the muscularis layer, there can be obstruction (duodenum) or perforation (gastric/duodenum). Subserosal involvement is associated with eosinophilic ascites. It is unclear if these subtypes represent a spectrum of the same disease or different disease entities. EG can present with other manifestations, such as gastric ulcers that do not respond to PPI [146]. Eosinophilic inflammation can be associated with EG, but in this case, strictures occur in only 5–10 % which is quite different from EoE where there is a higher incidence of strictures [146]. EG is diagnosed when clinical symptoms suggestive of EG are corroborated by a positive biopsy showing eosinophilic inflammation. Biopsies should be obtained from five to six sites per affected segment (e.g. stomach, duodenum), and the gross appearance of the biopsies and tissue may be normal on endoscopy, both features similar to EoE. Eosinophils in ascites fluid can also be diagnostic of EG. Other etiologies for gastrointestinal eosinophilia need to be excluded (see “EGE”). The number of eosinophils considered pathogenic in EG is still an object of debate. The most widely used level is 30 eos/hpf in the stomach and 50 eos/hpf in the duodenum [127, 134]. The presence of pseudopolyps or eosinophils in particular tissue layers (i.e., intraglandular eosinophils, or in the muscularis layer) makes the diagnosis of EG more likely [147]. Pseudopolyps

are present in up to 25 % of EG and are distinguished from real polyps as they are constituted by a dense collagen deposit with overlying epithelium, without the hyperplastic glandular or epithelial components typical of true polyps [147]. Patients with EG may also have esophageal eosinophilia in up to 25 % of patients with concurrent esophageal eosinophilia (≥ 15 eos/hpf) [20•, 134]. Peripheral eosinophilia is present in the majority of patients with EG. Differential diagnosis with HES should be considered for moderate to severe HES (>1500 eos/mm³) [20•].

Pathogenesis

There is some evidence that differently from EGE, EG could be food allergen-driven since select patient improve with diet [134]. This food allergy appears to be Th2-mediated but with a different mechanism compared to IgE-mediated peanut allergy, and healthy controls are different. EG was associated with an IL-5⁺, IL-13⁺ T cell response to foods upon multiple stimulation, while those with peanut allergy showed an IL-5⁺, IL-13⁺ Th2 response upon one single stimulation [148, 149]. A recent study addressed the question if EoE and EG are a spectrum of the same disease or they are different. Indeed there are many similarities between EoE and EG (i.e., food allergen induced, Th2 inflammation, and male predominance) [127]. By analyzing genome-wide transcript profiles and eosinophilia (both in the tissue and in the peripheral blood), Caldwel et al. [127] concluded that EG is a systemic disorder associated with high levels of blood and gastrointestinal tract eosinophilia Th2 immunity and with a conserved gastric transcriptome signature. Such signature is very different from the one found in patients with EoE. Indeed, only 7 % of patients with EG had a transcriptome that overlapped with EoE one. More specifically, in EG there were increased IL-4, IL-5, IL-13, IL-17, CCL26, and mast cell-specific transcripts and decreased IL-33 transcripts observed compared to EoE. Therefore, EG is a different disease than EoE and not a spectrum of disease.

Treatment

In both pediatric and adult patients with EG, diet (both elemental and SFED) has been reported to be effective in the majority of patients [134, 150]. Surprisingly, in a pediatric study, SFED was more effective in EG than in associated eosinophilic infiltrates in the esophagus in those patient who had it suggesting that esophageal eosinophilia associated with EG may differ from EoE [134].

Diet often is effective after several days and often symptoms of EG require a more quickly effective treatment. Therefore, most patients are treated initially with systemic steroids (0.5–1 mg/kg/day, 5–14 days) which differently from EGE are very effective in inducing remissions. Once symptoms are

controlled, steroids are typically tapered over a few weeks [2–4]. Once remission is achieved, long-term therapy can be done with diet or with the use of topical or swallowed steroids. Swallowed budesonide is well studied in EG and has low oral bioavailability [142]. Entocort® is a widely available, commercial formulation of budesonide used for EG. These are controlled release of drug in the ileum with very minimal gastric delivery; hence, patients are instructed to open the Entocort capsule, crush the contents into a powder, and dissolve it in 15–30 mL of water and juice [142]. These capsules are taken once daily at bedtime on an empty stomach, with a starting dose is typically 9 mg once daily. Once a patient has been off systemic steroids for a few months, the budesonide dose can be tapered slowly over a few months to achieve a desired dosing range of 3–6 mg/day for long-term use in maintaining remission. Swallowed fluticasone has been used in EoE patients successfully, and in such a study, it was shown to also decrease gastric eosinophils [151].

Monoclonal anti-IL-5, reslizumab, has been used to treat EG in an open-label clinical trial of four patients and is very effective in decreasing peripheral and gastric eosinophilia [152]. Monoclonal antibody (anti-IgE) omalizumab was not effective in treating tissue eosinophilia in EG.

Other allergy drugs have been trialed in EG with varying results, i.e., montelukast and sodium cromolyn have shown inconsistent results on sustaining remission of EG [143, 153].

EC

Introduction

EC is due to a chronic eosinophilic inflammation of the colon. Like other EGID, EC occurs more frequently in atopic individuals. EC is often seen in young infants and is considered part of the food protein-induced enterocolitis spectrum [154]. EC very rarely can also occur in older children and adults [155]. EC can be more severe compared to other forms of EGID and often require hospitalization for acute management.

Diagnosis

Based on localization of the eosinophils, the symptoms vary:

Mucosa-predominant variant presents with protein-losing enteropathy, malabsorption, and diarrhea [156]:

- Muscularis-predominant disease presents with symptoms of intestinal obstruction, volvulus, intussusception, and intestinal perforation [157].
- Disease involving the serosa presents with eosinophilic ascites.

Once suspected, eosinophils in the colonic biopsies obtained with colonoscopy or from ascites confirm the diagnosis; a diagnostic cut-off of 20 eosinophils per high power field (hpf) or greater has been used.

In the differential diagnosis specific for EC

- Drug-induced EC has been described from various medications including clozapine [158], carbamazepine [159], rifampicin [160], non-steroidal anti-inflammatory drugs [161], tacrolimus [162], and gold [163].
- EC can also be a sign of early inflammatory bowel disease (IBD), in particular Crohn's disease [164], or autoimmune especially connective tissue diseases (scleroderma, lupus polymyositis, and dermatomyositis) [165, 166].
- EC has also been observed following bone marrow transplantation [167].

Pathogenesis

The pathogenesis of EC is not well-defined. Most infantile EC is food-driven forms of food protein-induced enterocolitis, with cow's milk and soy protein being the main causative foods. It can occur in breast-fed infants and infants on casein hydrolysate formulas, is poorly understood in older children and adults, and appears to be driven by a Th2 inflammation with no apparent trigger similar to the EGE [168, 169].

Treatment

Currently, the mainstay of treatment for EC is diet for infants, and mostly they respond to a milk- and soy-free diet [170, 171].

The older children and adult patient will respond to oral steroids within 2 weeks of treatment with a slow taper over weeks suggested after remission is reached. Relapse is frequent so recurrent systemic steroid courses are required in most patients [142]. Swallowed budesonide has been effective in case reports in treating right colon disease, but further studies need to be done to corroborate this effect and to define whether it is effective therapy for left-sided colonic disease. The anti-histamine ketotifen, an H1 antagonist, decreased symptoms as well as tissue eosinophilia in isolated cases. Anti-IL-5 (mepolizumab) and anti-IgE (omalizumab) have been used with some success [172].

Conclusions

EGID can be divided into EoE when the eosinophilia is limited to the esophagus and EGE when pathological

eosinophilia are found in other parts of the GI tract. EGE is further split based on the location of the eosinophils (EGE—throughout the GI tract, EG, and EC, increased eosinophils in stomach and the colon, respectively).

EoE is the most common of the EGID with a strong atopic pathogenesis with a genetic component.

- The diagnosis is made when at least 15 eos/hpf are found limited to the esophagus after 8 weeks of maximal PPI therapy.
- Food allergens have been shown to trigger the typical Th2 inflammation in both children and adult.
- Treatment is generally effective and relies on the use of steroids and dietary intervention.

EGE are a group of ill-defined clinical pathological disease that for the most part are difficult to treat.

- Eosinophilia can affect one or more parts of the GI tract.
- The diagnosis is made when pathological eosinophilia is found in biopsies, but there is no general consensus of the level of eosinophils that constitute pathology vs normal.
- Given the rarity of the EGE, other causes of eosinophilia need to be excluded.
- The response to therapy (mainly steroids and diet) is generally limited.

EG

- EG is characterized by eosinophilia limited to the esophagus.
- It affects most often an atopic man.
- It responds to diet and steroid treatment.
- EG is distinct in terms of pathogenesis from EoE.

EC

- EC is due to eosinophilia limited to the colon.
- EC symptoms can be severe and often require hospitalization.
- In infant is part of the FPIES and is treated with diet; steroids are rarely necessary.
- In older children and adult is typically unresponsive to diet and is treated with steroid.
- Differential diagnosis for drug allergy and inflammatory bowel diseases is essential as EC is a diagnosis of exclusion especially in older children and adults.

Acknowledgments Institutional Support from the Department of Pediatrics, The Children's Hospital of Philadelphia, and the Joint Center for Gastroenterology and Nutrition of CHOP-HUP and the CHOP Food Allergy Family Research Fund are gratefully acknowledged.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Spergel reports grants from the NIH and DBV Technology and personal fees from Dannone. In addition, he has a patent EPIT for treatment for EoE pending. Dr. Cianferoni declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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