EXPERT REVIEWS

Eosinophilic gastroenteritis: an update

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Eosinophilic gastroenteritis (EGE) is characterized by dense eosinophilic inflammation of one or several digestive tract sections. The symptoms include abdominal pain, weight loss, vomiting and diarrhea. Biopsy samples taken during endoscopic examination allows the diagnosis of the disease. An infiltration of >30 eosinophils per high-power field in at least five high-power fields, exhibiting signs of eosinophilic degranulation and extending to the muscularis mucosa or submucosa are all histological indications of EGE. EGE is traditionally classified into three forms depending on the depth of inflammation in the wall (mucosal, muscular or serosal). This, together with the digestive tract segments involved, determines the clinical presentation. The natural history of EGE includes three different evolutionary patterns, since patients may suffer a single outbreak, a recurrent course or even chronic disease. Corticosteroids are the most frequently used therapy for EGE; dietary treatments should be also considered. Surgery has been limited to solving obstruction and small bowel perforation.

Keywords: allergic gastroenteropaty • eosinophilia • eosinophilic gastritis • eosinophilic gastroenteritis • eosinophilic gastrointestinal disorders • gastroenteritis

Eosinophilic gastrointestinal disorders (EGID) constitute a pathology characterized by eosinophilic infiltration of the GI tract, the symptoms of which vary depending on the affected digestive segments and the involvement of the different layers of the digestive wall.

In the case of eosinophilic gastroenteritis (EGE), the typically affected sites are the stomach and small bowel, although any area of the GI tract from the esophagus to the rectum can be also involved. First described in 1937 by Kaijser, interest in EGE has grown in recent years in parallel with an increasing number of case reports and case series from different continents [1].

The currently accepted diagnostic criteria for EGE were proposed by Klein *et al.* in 1970 [2] and updated by Talley *et al* in 1990 [3] and includes the presence of generally recurrent gastrointestinal symptoms, demonstration of a dense eosinophilic infiltrate in biopsies taken from the GI tract or high eosinophil content in peritoneal fluid and the absence of parasitic or extraintestinal diseases that could cause eosinophilia [4,5] such as vasculitis, drug reactions or neoplasms. Peripheral eosinophilia is currently not required for a positive diagnosis since it is not a universal finding.

Despite being still recognized as a rare disorder, nearly a fourth of all historical descriptions of EGE in the literature come from the last 5 years. However, many aspects of the disease remain unknown. Thus, no definitive epidemiological features have been established, physiopathological data are extremely limited and an established natural history for EGE is lacking and therapeutic options are mostly based on empirical experience. There is a complete lack of controlled and randomized studies that clearly establish definitive information regarding EGE. However, information provided by case reports over a wide range of years and geographical origins allow us to assume some common observations as characteristics for the disease. This article aims to comprehensively review the latest, most relevant published information regarding EGE to provide a guide for understanding this increasingly recognize disorder.

Epidemiology of EGE

Until few decades ago, EGID was not of particular interest to gastroenterologists. However, the wide recognition of eosinophilic esophagitis (EoE), the most frequent manifestation of this family of disorders that currently represents the most common cause of dysphagia and food impaction in young males and the second most common cause of chronic esophageal disturbance after gastroesophageal reflux disease [6], has increase

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the awareness and diagnosis of new cases of EGID. The disorder begins with a constellation of symptoms that depend on topography and the intensity of the inflammatory response, eventually leading to endoscopic evaluation of these patients.

This rise in the prevalence of EGID and immunoallergic diseases in general has occurred in parallel with a decrease in infectious diseases, a coincidence that has been explained through the hygienic hypothesis [7]. This hypothesis asserts that reduced exposure to microorganisms during childhood can modify the patterns of gut microflota, leading to a change in the fine tuning of Th1, Th2 and T-regulatory responses. This gives rise to an imbalance of the immune system and a predisposition for developing allergic and autoimmune disorders triggered by altered or missing innate immune cell activation. In fact, the influence of Th2 cells, which are important in the development of responses mediated by IgE, usually fades after the first 2 years of life in nonallergic individuals. This is possibly due to a secondary stimulation of Th1 responses after bacterial infections [8], a phenomenon which is limited in over-hygienic environments. Environmental exposure thus seems to be an important risk factor as genetic predisposition for developing EGID. For example, one US study recently demonstrated that the increased prevalence of EoE parallels that of bronchial asthma in common geographical areas, being higher in urban as compared with rural settings [9,10], as well as in cold climate zones compared with tropical and arid areas [11].

Except for EoE, available data about the epidemiology of EGID in general and EGE in particular are limited. Due to its low prevalence, most of accumulated knowledge on EGE comes from individual case reports and short case series. Because these methods lack systematization, it is impossible to establish well-based conclusions or even a consensus with regard to diagnostic criteria: the density of eosinophilic infiltration or its precise location in the layers of the wall of the digestive tract vary widely from one study to the other. Since a certain eosinophil count can form part of the normal histology of the stomach and small bowel walls, and because this can vary between different geographical areas [8], a commonly accepted diagnostic criteria for EGE has not yet been defined. Still, an increase in the prevalence of EGE could have existed in several settings during the last years. In fact, the number of studies on EGE referenced in PubMed in the last decade has doubled since the 1980s representing almost 40% of the overall available scientific information on the disease.

Reported cases of EGE show no predominance of individuals of any gender or race. Although it can affect all ages, the majority of cases occur in adults in the third to the fifth decades of life [12–15], with pediatric series also being described [16,17]. While no accurate epidemiological estimations for EGE exist to date, an incidence of approximately one case per 100,000 inhabitants has been traditionally proposed [3,14]. However, these figures have been recently updated after an American electronic survey which estimated an overall prevalence of 28 per 100,000 EGE or colitis [10]. Most patients are diagnosed during an endoscopic examination for a variety of symptoms, usually abdominal pain or diarrhea. An internet database has been set up recently in order to register cases and further clarify many of the unknowns of the disease [18].

Finally, it must be taken into account that a better awareness of EGID (and of EGE in particular) by clinicians and pathologists forms the cornerstone of accurate diagnosis of the disorder, which may subsequently contribute to the rise in its epidemiology, especially in different parts of Europe.

Pathophysiology of EGE

Eosinophil tissue accumulation above normal levels along with infiltration of the epithelium [19] is a common finding in several digestive disturbances, including IgE-mediated food allergy, EGID [5], gastroesophageal reflux [20,21] and inflammatory bowel disease, in which both findings may constitute a bad prognostic factor [22,23]. However, studies continue to debate what constitutes 'normal' and 'abnormal' numbers of eosinophils in the different sections of the GI tract, and how they vary with patient's age: since the esophageal epithelium lacks eosinophils under normal conditions, these form part of the resident cells in the remaining digestive tract organs, with an increasing gradient from the stomach to the right colon (Table 1) [24]. Thus, the histopathological diagnosis of some cases of EGID are based on finding 'more eosinophils than expected' in the gastrointestinal tissues [25].

It must be taken into account that resident eosinophils are integrated in the mucosal immune system, and have a specific role in the GI tract of healthy individuals [26]. The physiological functions of eosinophils include protection against parasites [27] and allergic-type reactions [28,29]. When their number increases in EGID, eosinophils contribute to tissue damage through their proinflammatory functions. Despite being widely considered as multifunctional proinflammatory cells, the biology of these functionally complex cells is not yet fully known. The effector function, which was the first recognized function of eosinophils, is exerted through cytotoxic proteins contained in their cytoplasm granules, which are capable of causing cell damage [30]. Eosinophils also release preformed proinflammatory mediators, which activate endothelial cells and may stimulate T lymphocytes, acting as antigen-presenting cells [19].

The physiopathological mechanism of EGID seems to be comprised of mixed disturbances, sharing characteristics of IgE-mediated disorders (e.g., oral allergy syndrome and food-triggered anaphylaxis) and exclusively cell-mediated disorders (e.g. celiac disease or food protein-induced colitis). EGE has been related to food allergies in that it originates from the interplay of environmental and individual genetic factors. Approximately three out of four EGE patients present various atopic manifestations (personal or familiar background of bronchial asthma, allergic rhinitis, dermatitis, hypersensitivity to food, inhalants or drugs, blood hypereosinophilia, elevated total and specific IgE serum levels and positive skin allergic test results), which reinforces the idea that eosinophils accumulate in the stomach and small bowel in response to exposure to food [12,31] or environmental [32] antigens. Clinical and histological responses to therapies used in other allergic diseases and dietary modifications are also observed in most EGE cases.

Limited research has been developed on the molecular basis of EGE and its pathophysiology is poorly known, with most of the available information coming form extrapolations of studies

Table 1. Summary of eosinophilic gastroenteritis symptoms and common findings, according to the classification proposed by Klein *et al*. in 1970.

Forms	Estimated frequency (%)	Maximal depth of digestive tissue involvement	Main organs affected	Main symptoms	Common findings
Mucosal	45–80	Mucosa and submucosa	Stomach and duodenum	Abdominal pain, weigh loss, diarrhea, nausea/ vomiting, iron deficiency, malabsortion, protein losing enteropathy	Mucosal hyperemia, ulcerations, aphthe, thickness of folders
Muscular	12–30	Muscle layer	Stomach and duodenum	Nausea/vomiting, gastric outlet or small bowel obstruction	Strictures, rigidity, dysmotility and obstruction
Serosal	12.5–39	Subserosal and serosal layers	Any segment of the GI tract	Ascitis and peritonitis	Eosinophilic ascitis, intense peripheral eosinophilia Small bowel perforation

Data taken from [2].

on EoE, the high prevalence of which has allowed more specific research. However, it should be adverted that extrapolating information from other EGIDs may not be adequate.

A Th2-type immune response seems to be involved in both EoE and EGE [33–36]. In fact, IL-5 and IL-13, together with granulocyte–macrophage colony-stimulating factor and especially eotaxins, may play a central role in the recruitment of eosinophils from circulating blood into tissues [37]. The frequent family association of EGID cases (~10% of patients have affected relatives) [5] points to the role of immune response regulatory genes in these diseases, which in the particular case of EoE show a preserved transcriptome among patients [38,39]. The genes involved include eotaxin-3/CCL26, mast cell carboxipeptidase-A3 (*CPA3*) and tryptase (*TPSAB1*) and high-affinity IgE receptor (FCεRI). Timic stromal lymhopoyetine, a master regulating factor of Th2 responses [40], is also upregulated in these patients.

Fibrous remodeling in EGID and EGE

Eosinophilic inflammation of the airways leads to structural changes known as remodeling. The most clinically relevant components of this phenomenon are smooth muscle hypertrophy and collagen subepithelial deposition because they can lead to narrowing of the bronchial diameter and impairment of respiratory function. Fibrous remodeling has also been demonstrated in pediatric [41] and adult EoE patients [42,43]; it is a reversible phenomenon in the former [44], but tends to persist in the latter [42,43]. In addition to digestive motor disturbances [45], fibrous remodeling also explains strictures commonly associated with EoE and obstructive symptoms found in many reported cases of EGE affecting the pylorus and small bowel [46]. These often require resection of the affected area [47].

Fibrosis in EGID is directly related to eosinophil activation, as evaluated through immunohistochemistry against major basic protein [48]. Eosinophil-released major basic protein increases gene expression of FGF-9, a cytokine implicated in the proliferative response after tissue damage [49]. Eosinophils also produce and secrete high amounts of CCL18, a type-2 chemokine implied in fibrous remodeling of the lungs through fibroblast proliferation and collagen deposition, whose expression levels have been shown to be increased in EoE [42]. However, the most widely studied cytokine in promoting fibrous remodeling in EGID is TGF-β1,the expression of which has been found to be upregulated in both children [41] and adults [42,50] with EoE, but which can be reduced with the aid of steroid treatment [42,44,50,51].

Histopathology of EGE

There is no established consensus on a diagnostic threshold with regard to eosinophil count for most of EGID. This is due to several reasons, including inconsistencies in definitions of what constitutes an eosinophil (e.g., the presence of a cell defined by a nucleus or an aggregate of granule proteins) and the size of a high power field (hpf); (the nonstandardized area of tissue covered by a 40× light microscope objective), along with variability in analysis between pathologists and gastrointestinal/allergy clinicians [9,25]. EGE diagnostic criteria have thus been based on tissue infiltration by sheets of eosinophils, along with edema that generally involves the submucosa or any layer of the gut, the presence of digestive symptoms and the exclusion of parasitic infections or other causes of eosinophilia [52]. With the exception of the esophageal squamous epithelium, which normally contains no eosinophils, their presence in the remainder of the luminal gut is poorly defined [24,53]. Information regarding the quantity and location of eosinophils in the GI tract has been provided for healthy children [24]; examination of the antrum, fundus and small intestine revealed none or minimal eosinophils in the surface epithelium, while an average of two to ten cells/hpf was documented in lamina propria of the stomach and duodenum, respectively. Additionally, atopic and nonatopic patients had comparable numbers of eosinophils. Likewise, there is only limited histopathological information on the additional features in EGE.

In contrast to EoE, where a histopathological diagnostic threshold of ≥15/hpf has been consensually defined, such a threshold has not been established for EGE; however, the limit of ≥20/hpf

is the most commonly agreed upon [13,16]. A recent study evaluating EGE-associated histopathological findings included sheets of eosinophils, frequent involvement of the muscularis mucosa or submucosa and a density of ≥30 eosinophils/hpf in at least 5 hpf as diagnostic criteria of 'histological eosinophilic gastritis' in the absence of known causes of eosinophilia [54]. Eosinophilic degranulation or cryptitis has also been recognized as a typical criterion [13], but epithelial infiltration may not be a constant feature [54]. These proposed criteria seem robust as they exhibited no differences between gastric antrum and corpus, and no significant seasonal, age or geographic variations [54].

A lack of association between *Helicobacter pylori* infection and EGE has been reported [54]. Likewise, superinfection by the protozoa *Isospora belli*, a common opportunistic parasite in inmmunodepressed patients, is considered to be an exceptional association in EGE [55].

Clinical manifestations

From descriptions of EGE, the authors can infer that it is a heterogeneous disease with respect to its clinical presentation. Clinical findings may reflect the extent, location and depth of the eosinophil infiltration in the digestive organs [3]. Following the proposals of Klein *et al.* in 1970 [2], several studies have established a classification of EGE into three different arbitrary patterns based on clinical manifestations and depth of inflammation into the GI tract wall (Table 2).

Mucosal form: the most common presentation (45% of cases, although in a recent series it reached over 80%) [14], characterized by mucosal and submucosal involvement. Symptoms include abdominal pain, diarrhea, weight loss and malabsorption-related findings, including iron deficiency and losing protein enteropathy [56]. It has been suggested that EGE in the mucosal layer has become predominant in recent years [10].

Muscular form: appearing in 12–30% of cases [3,13]. In these patients, the inflammation extends deeper into the muscle layers, leading to digestive wall thickening and typical obstructive symptoms. Although any section of the digestive tract can be involved, the stomach and duodenum are the most commonly affected segments [46,47,57].

Serosal form or eosinophilic ascitis: the rarest presentation of EGE (but reaching up to 12.5–39% of cases in certain series) [3,13] is the serosal manifestation of the disease, in which eosinophil-rich inflammatory infiltrate permeates all layers of the digestive wall, reaching the serosal cover and causing the appearance of eosinophilic ascitis. A white blood cell count of at least 10% characterizes eosinophilic ascitis [58], but it can reach up to more than 80% [59]. Interestingly, eosinophilic ascitis and the underlying transmural EGE form has been predominantly described in women, occasionally trigger during pregnancy or after delivery [60–62].

There are reports of some EGE patients presenting with intestinal perforation [63–67]. This complication usually requires surgical repair and represents a transmural involvement of the disease different from that eosinophilic ascitis, but not recognized in the Klein classification. The cytotoxic effector function exerted by eosinophilic granule proteins may be the underlying cause of tissue damage in these patients [30]. It can affect any small bowel segment, from the duodenum to the ileum.

Several aspects of EGE are intriguing, although the lack of large case series prevents us from establishing these assertions with certainty. For example, peripheral blood eosinophilia is a frequent finding, being found in up to 90% of patients [15]. It is more intense and frequent in patients exhibiting mucosal and serosal (with ascitis) types than in those affected only up to the muscle layers [3,13,57]. At same time, 80% of cases have a personal background of allergies, with 50–62% of these being food allergies [10]. By contrast, only 27% of adult patients reported a family history of allergy; this was limited to those with mucosal involvement [14]. Furthermore, 16% of patients had or currently have a relative also suffering EGE [10].

More than a half of patients had increased IgE serum levels [15]. All these atopic manifestations seem to be more common in mucosal and serosal forms [12,13], but are also present in a high proportion of muscular EGE forms [14].

Regarding the topographical distribution of EGE, the stomach and duodenum have been proposed as the most frequently involved digestive organs. However, it should be noted that these are also the most prevalent examined digestive segments by means of endoscopy, so it remains uncertain whether this represents a bias. Nevertheless, virtually any segment of the GI tract may be affected. In fact, 50% of patients present concomitant involvement of the rectum and/or colon [15], while simultaneous esophageal eosinophilic infiltration is present in between 30 and 50% of patients with EGE. Large bowel-derived symptoms including bloody diarrhea (which can mimic inflammatory bowel disease) and symptoms of esophageal dysfunction (e.g., dysphagia) may coexist together with stomach and small bowel-derived symptoms. Interestingly, infiltration of the lamina propria by eosinophils and their presence in the crypts of rectal mucosal biopsies of young children with constipation due to intolerance to cow's milk has been described [68], as an alternative to EGE-associated diarrhea.

Biliopancreatic involvement has also been described for EGE [13,69–71]. These patients present with cholecystopancreatitis with bile duct dilation, obstruction or jaundice, together with symptoms derived from gut inflammation.

Together with EGE, hypereosinophilic syndrome and immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome are two additional systemic disorders that can also include eosinophilic inflammation in the digestive tract walls between its components. Hypereosinophilic syndrome are a heterogeneous group of rare systemic diseases of idiopathic origin, characterized by marked blood eosinophilia (at least 1500 cells/mm^3) persisting for more than 6 months. Signs or symptoms of organic affectation [72] with eosinophils in the GI tract can be found. Patients show high levels of mast cell tryptase in serum and bone marrow analyzes show a high number of dysplastic mast cells which decrease after treatment with the tyrosine kinase inhibitor imatinib mesylate [73]. IPEX syndrome constitutes an autoimmune-allergic disorder caused by germ-line mutations in the *FOXP3* gene, a master transcriptional

Table 2. Eosinophilic infiltration in different gastrointestinal organs in eosinophilic gastroenteritis; eosinophil count, histopathological findings and derived symptoms.

Involved organ	Mean eosinophil density in normal conditions	Minimum eosinophil count required for diagnosis	Histopathologic features	Clinical manifestations	Ref.
Esophagus	<5/hpf	15/hpf in the epithelial layer	Elongated papillae and basal zone hyperplasia of the epithelial layer with eosinophilic infiltration of the lamina propria and muscularis mucosae Eosinophilic microabscesses	Esophageal dysfunction, including dyspagia, food impaction and GERD-related symptoms	[101,102]
Stomach	2/hpf in lamina propria† No intraepithelial eosinophils†	>20–30/hpf	Sheets of eosinophils, edema, eosinophilic degranulation and cryptitis	Dyspepsia, nausea/vomiting, epigastric pain, gastric outlet obstruction and ascitis	[13,17,24,54]
Duodenum	10/hpf in lamina propria Minimal intraepithelial eosinophils	>20–30/hpf	Sheets of eosinophils, edema, eosinophilic degranulation, cryptitis Eosinophilic infiltration of lamina propria, muscle fibers and serosal layer Hypertrophic muscle layer	Gastric outlet obstruction, abdominal pain, diarrhea, weigh loss, malabsortion findings, perforation and ascitis	[16,24,46]
Ileum	13/hpf in lamina propria† Minimal intraepithelial eosinophils†	>20–30/hpf	Sheets of eosinophils, edema, eosinophilic degranulation, cryptitis Eosinophilic infiltration of lamina propria, muscle fibers and serosal layer Hypertrophic muscle layer	Abdominal pain, small bowel perforation, small bowel obstruction and ascitis	[14,24]
Large bowel	8–30/hpf†	>20–50/hpf (depending on location)	Eosinophil and lymphocyte infiltration of the lamina propria and the presence of intraepithelial eosinophils in the crypts	Diarrhea, bloody diarrhea, abdominal pain and constipation	[24,68,103,104]
Bile ducts/pancreas	Unknown	Unknown	No data available	Jaundice, cholestasis, epiastralgia, altered liver function tests and dilated bile ducts	[69–71]

†Reported for pediatric control patients.
GERD: Gastroesophageal reflux disease; hpf: High-power field.

regulator for the development of CD4 regulatory T cells [74,75]. IPEX syndrome includes enteropathy among its clinical picture, but digestive affection is only one more manifestation of this multisystemic disorder, together with immune dysregulation, polyendocrinopathy and other organ-specific diseases such as anemia, thrombocytopenia, hepatitis and nephritis. In both syndromes, EGE would only be a manifestation of the general disease and a differential diagnosis should be warranted.

Image diagnostic techniques in EGE

Recent reports have described the endoscopic and radiological findings typical in EGE. Most endoscopic findings tend to be nonspecific, with mucosal hyperemia and thickened gastric folds [14] being the most common. Areas of rough or nodular appearance, erosions, aphthae and ulcers have also been described in EGE. In some cases, the endoscopic findings were described as normal [13]. Findings from capsule endoscopy include multiple erythematous lesions, loss of villi [15], incomplete strictures with ulcerated mucosa alternating with preserved areas [76] or a mimicking of mucosal diaphragms with complete retention of the capsule [77]. One patient with eosinophilic ascitis showed a bluish discoloration of the deep layers of the intestinal wall without mucosal changes; the authors hypothesized that in this case, eosinophilic infiltration had not affected the mucosa [78].

Radiological findings in EGE are equally unspecific in two thirds of patient [14]; double contrast radiology findings are usually

normal [14], but may occasionally show thickened folds, irregular or serrated edges in the small intestine walls, nodular contrast defects or slow contrast progression indicative of gastrointestinal hypomotility.

Treatment of EGE

Heterogeneity in the clinical presentation, severity, and evolution of EGE, together with its low prevalence, has made it difficult to establish ideal treatment strategies for these patients. As in the case with other EGID, including EoE, no drugs have been approved specifically for the treatment of EGE and comparative studies between different therapeutic modalities are lacking. To make matters more confusing, patient age (children or adults) and the medical specialty area in which they are attended tend to determine which treatments are administered.

Dietary treatment

In some pediatric patients the disease appears before the age of 1 year and resolves after the elimination of cow's milk from the diet [79]; similar results have also been reported for adult patients [80]. Complete resolution of eosinophilic infiltrate in EGE can also be achieved by exclusive feeding with an amino acid-based elemental diet. However, the elimination of these foods after skin prick tests or radioallergosorbent test has shown variable results [5,13,81]. Thus, a series of pediatric EGE patients showed remission of symptoms in 40% of cases after dietary treatment, which consisted of an elemental diet in children under 6 months and hypoallergenic feeding in older children [17]. Once the remission of EGE is achieved, specific foods should be reintroduced gradually, identifying problem foods by the reappearance of symptoms or through bioptic monitoring. Evidence of further tolerance to offending foods has not been clearly assessed. In the case of adult patients, allergic sensitization test results did not correlate with foods responsible for the disease. Generally speaking, from the literature we can infer that the later EGE appears during childhood, the worse it responds to dietary modification [13]. No agreement exists in the literature as to which allergic evaluations or tests should be carried out on EGE patients.

Drug therapy

Corticosteroids have by far been the most widely used drugs for treating EGE in both children and adults [14,16]. Corticosteroids also constitute the main treatment for patients in whom dietary therapy is not feasible or after failing to achieve improvement [5]. Prednisone, used at doses of 0.5–1 mg/kg/daily, has proven highly effective in the initial control of symptoms [14], eosinophilic tissue infiltration, blood hypereosinophilia and also for controlling ascitis, as described in various studies and case reports. Usually, after an initial treatment period of 7–10 days, the dose is gradually reduced until the drug is withdrawn after a period of up to 4 months. Response to steroids in EGE is significantly superior to the mere control of symptoms [15].

Different series have described steroid-dependent patients in whom symptoms reappeared during steroids tapering [15]. These patients had to either resume taking previous doses, maintain remission by using low doses, substitute prednisone for budesonide [17], or maintain remission with other antiallergic or immunosuppressant drugs. Approximately 20% of patients require maintenance therapy over time [17]. Budesonide has a better safety profile than prednisone and is especially useful in EGE affecting the distal small bowel and right colon [82], although it is also helpful in more proximal disease [57].

Disease recurrence is more likely in those patients requiring treatment at the moment of diagnosis as compared with those who exhibit spontaneous remission; patients with recurrent disease may also present a higher blood eosinophil count at diagnosis than those who show spontaneous remission [13].

Steroid-dependent or refractory patients can be also managed with thiopurins (azathoprine or 6-mercaptopurin), similar to the treatment of inflammatory bowel disease [83,84].

Unfortunately, with regard to the utility of other antiallergic drugs in treating EGE, most of the available information comes from isolated cases or small series, which limits our ability to ensure its real usefulness. Some EGE patients have obtained benefit from mast cells stabilizers [13,85,86] such as sodium cromolyn or nedocromil, contrary to what has been observed in EoE, in which they have not demonstrated efficacy [87]. Ketotifen and histamine-1 blockers have shown efficacy in reducing tissue eosinophilia and symptoms in patients with EGE [88,89]; suplatast tosylate was effective in the only case in which it was used [90]. Information regarding the leukotriene inhibitor montelukast is contradictory, since it showed no efficacy in some cases [91–93] while it successfully acted as a steroid-sparing agent in isolated steroid-dependent patients [16,94].

Finally, biological therapies with the anti-IL-5 monoclonal antibodies mepolizumab and reslizumab to treat hypereosinophilic syndrome have provided only limited data to date. A pilot study in which four EGE patients were treated with a single dose of mepolizumab showed an average drop in blood eosinophilia of 75 and 50–70% in tissue eosinophilia, but with minimal symptoms improvement [95]. In addition, one patient experienced a noticeable increase in gastrointestinal tissue eosinophil count 4 weeks after treatment, while two additional patients underwent an increase in their peripheral eosinophilia, with a worsening of baseline gastrointestinal symptoms after 7–8 weeks of treatment [96]. Intravenous immunoglobulin was successfully used in a patient with erythematous lupus associated with steroid-refractory EGE [97].

Surgical treatment

While the muscular form of EGE may cause obstructive symptoms [98] due to bowel wall thickening and narrowing of the lumen, some cases of EGE have been diagnosed after intestinal resection of the affected area after acute abdomen [47], intestinal obstruction or perforation [64,65,99]. Note that these complications occur more often in the duodenum or the distal ileum. Unfortunately, data on the long-term outcome and possible recurrence of cases after resection of the affected segment is lacking.

Natural history of EGE

In spite of the approximately 400 EGE cases described in the literature, very few series have focused on elucidating its natural

history. A recently published French study analyzed the clinical characteristics and evolution of 43 adult patients with EGE who were followed for a mean period of 13 years [13]. The authors described three different evolutionary patterns (Figure 1): 42% of patients suffered a single outbreak of EGE lasting <3 months; 37% of patients exhibited a recurrent pattern of disease, with an average of 5.2 flare-ups during extremely variable intervals and finally 21% of patients had a continuous disease course with persistent symptoms. No additional studies have determined the global relapse rate after the first flare. High eosinophil blood counts at the time of diagnosis were associated with an increased risk of disease recurrence [13]. There was no tumor or myeloproliferative transformation in any patient during follow-up. In fact, an association between EGE and malignancy has only been described once in the literature in a case study of a 69-year-old Japanese man with multiple gastric cancer and EGE who responded well to a total gastrectomy and prednisolone treatment [100].

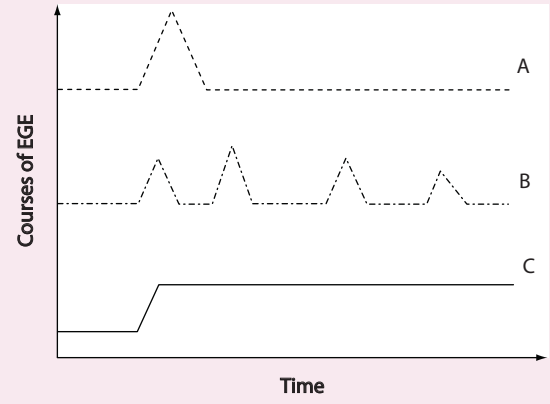

Figure 1. Types of evolution of eosinophilic gastroenteritis. After a mean follow-up period of 13 years, de Chambrun *et al.* identified different types of evolution of EGE [13]. **(A)** Patients with a single outbreak of disease without recurrence (42% of cases). **(B)** Patients with a recurrent course characterized by multiple outbreaks and periods of complete remission lasting from 2 months to several years (37% of cases) and **(C)** patients with a continuous course (21% of cases).
EGE: Eosinophilic gastroenteritis.
Reproduced with permission from [13].

Expert commentary

EGIDs constitutes an increasingly common heterogeneous group of intestinal diseases with assorted clinical manifestations depending on the organ involved and the extent of inflammation into the digestive walls. As such, they should be considered as a diagnostic possibility for patients with common gastrointestinal symptoms. The study of these complex disorders, which share an eosinophil-rich infiltration as a common hallmark, has focused on the similarities they usually share, mainly their association with allergic manifestations, especially Th2-driven bronchial disorders, and a common response to corticosteroids. Both the symptoms and molecular basis of EoE, the most widely studied form of EGID, has been well defined, but the small number of diagnosed EGE cases (due to epidemiological reasons) has limited the primary knowledge of this disease, which manifests with extremely heterogeneous symptoms. Researchers, through systematic registries of whole cases that exhaustively include clinical and immunological characteristics of patients, type, response to therapy, evolution of the disease and even molecular data, should now have access to enough information to broaden our knowledge about EGE. Theses registries should constitute the pillars for subsequent multicenter studies, which should seek to delimit the etiology, pathogenesis, and best therapeutic alternatives in order to prevent and even modify the outcomes of these relevant disorders.

Five-year view

Over the next 5 years, investigators should focus on clarifying several important aspects of EGE that still remain unclear. First of all, clinical presentation, allergic diatheses association, and response to therapies (especially dietary therapies) vary widely from case to case. We should keep in mind that an eosinophil-rich infiltration of the gastrointestinal wall structures and its derived symptoms may represent the ultimate common phenotype resulting from the convergence of different activation forms of inflammation, which cannot be identical in each case [26]. Molecular analysis of heterogeneous patients will thus shed light on whether EGE should be considered as a unique disease or several disorders sharing common features.

Similarly, the natural history of the disease should be clearly defined. We do not know whether the disease in children and adults is equivalent, nor whether the pediatric forms tend to last into adulthood. There is also a shortage of data concerning the ability of different therapeutic modalities to change the natural history of the disease. Scant, but important, studies have defined different behavioral patterns in EGE patients treated with corticosteroids, but data on dietary interventions and their sustained effects are lacking. Moreover, neither the long-term outcome of patients requiring surgery after obstruction or perforation, nor the increase in reports of labor-associated EGE have been reported.

Only long-term follow-up reports can clarify this point, with the available case series reports being further analyzed after several years in order to define the real outcome and significance of EGE. Results from the recently established online database case registry are also awaited in order to gain insight into the current unknowns of this disease.

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Key issues

- Eosinophilic gastroenteritis (EGE) is defined by the presence of gastrointestinal symptoms, biopsies showing predominant eosinophilic infiltration with sheets of eosinophils, and the absence of parasitic or extraintestinal diseases that may cause eosinophilia.
- Despite being a rare disorder with a proposed incidence of approximately 1 and up to 28 per 100,000 individuals, its epidemiology could be on the rise in parallel with other gastrointestinal immune-mediated diseases.
- The natural history of EGE may include three different evolutionary patterns: there are patients who present with a single outbreak, others with a remittent and recurrent course, and patients with continuous disease. High blood eosinophil levels and the need for corticosteroids at the moment of diagnosis are associated with a recurrent course of EGE.
- The stomach and duodenum are the most frequently involved digestive organs; up to 50% of patients also present large bowel or esophageal-associated involvement.
- EGE has been found to have a myriad clinical manifestations because symptoms appear to depend on both the section of the GI tract involved (including biliopancreatic disease), as well as on the depth of involvement of the gut wall (as reflected in the classic classification into mucosal, muscular and serosal forms).
- Endoscopic (including capsule endoscopy) and radiologic findings in EGE are unspecific and frequently reveal a normal appearance. Histopathologic evaluation of biopsy samples remains essential for diagnosis; a density of ≥30 eosinophils/hpf mainly distributed in sheets, exhibiting signs of eosinophilic degranulation or cryptitis, and infiltration into the muscularis mucosa or submucosa have all been characterized as typical features.
- Systemic corticosteroids (mainly prednisone) remain the most frequently used therapy for EGE in children and adults and are efficient in almost all cases. Budesonide presents a better safety profile and is useful as a maintenance therapy. Data on other antiallergic, immunomodulatory or biological drugs are mostly restricted to isolated reports and show contradictory outcomes.
- Dietary management should be always considered, especially for younger patients. Surgery has been limited to resolving obstructive disease and small bowel perforation. Data regarding the long-term evolution of operated cases are lacking.

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