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Eosinophilic gastroenteritis: A state-of-the-art review

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Abstract

Eosinophilic gastrointestinal disorders are a series of diseases which include eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis. Among these disorders, eosinophilic gastroenteritis is an uncommon and heterogeneous disease characterized by eosinophilic infiltration of the gastrointestinal tract in the absence of secondary causes, presenting with a variety of gastrointestinal manifestations. Up to now, epidemiology and pathophysiology of eosinophilic gastroenteritis are still unclear. Based on clinical manifestations and depth of eosinophilic infiltration into the gastrointestinal tract wall, eosinophilic gastroenteritis is classified into three different patterns including predominantly mucosal pattern, predominantly muscular pattern and predominantly serosal pattern. For diagnosing eosinophilic gastroenteritis, it is necessary for clinicians to have a high degree of clinical suspicion. In addition to the gastrointestinal symptoms, other evidences such as laboratory results, radiological findings and endoscopy can also provide important diagnostic evidences for eosinophilic gastroenteritis. And these indirect information together with histological results will lead to a definitive diagnosis of eosinophilic gastroenteritis. To avoid specific allergen, dietary treatments can be considered

as initial treatment strategy before drug treatment. Corticosteroids are the main medication for eosinophilic gastroenteritis, and have a dramatic therapeutic efficacy. Yet others medications need further verify their effects in clinical practice, and surgery should be avoided as far as possible.

Key words: eosinophilic gastroenteritis, eosinophilia, eosinophil

Introduction

Eosinophilic gastrointestinal disorders are a series of diseases which selectively affect the segments of gastrointestinal (GI) tract with eosinophilic inflammation in the absence of secondary causes for eosinophilia [1]. These disorders can be divided into five principal groups: eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis (EG), eosinophilic enteritis, and eosinophilic colitis [1]. Among these disorders, EG is an uncommon and heterogeneous disease characterized by eosinophilic infiltration of the gastrointestinal (GI) tract, presenting with a variety of GI manifestations which depend on the site of affected GI tract and the layer of the GI wall involved [2, 3]. In 1937, Kaijser described this disorder for the first time [2]. Then in 1970, Klein *et al* [3] defined three types of this disorder based on the clinical manifestations and the depth of involvement including predominantly mucosal disease, predominantly muscular disease, and predominantly serosal disease. Although stomach and duodenum are the most commonly affected organs, it might involve any segment of the GI tract from the esophagus to the rectum [4, 5]. There are hundreds of cases reported in the medical literatures, most of them are just single case reports or rather small case series [6-8]. Thus we have only a limited understanding of this disease

until now. The underlying molecular mechanisms of this disease are still unknown, and definitive epidemiological features have also not been established. Moreover, the etiology has yet to be fully elucidated, and its diagnosis requires a high degree of clinical suspicion. Fortunately, good therapeutic efficacy has been achieved by oral corticosteroids for a short period based on empirical experience and it is used as the main therapeutic options for EG patients [6].

Although there is a complete lack of a large, randomized, controlled trial to clearly establish definitive information referring to EG, information provided by single case reports or small case series over several decades and from different countries could also allow us to assume some common observations as characteristics for this disease. Therefore, our review aims to completely summarize the latest, most relevant published information referring to EG and provide a more comprehensive understanding.

Epidemiology of EG

Eosinophilic gastroenteritis is an uncommon and heterogeneous disease, so there is no large survey to investigate its incidence. Although hundreds of cases or small case series have been reported worldwide, the exact incidence of eosinophilic gastroenteritis is still difficult to estimate. The current case reports suggest that EG can affect any age group from infancy to the aged, however, most commonly between thirties to forties years of age, with a slightly male predominance [2, 3, 6-8]. Though no accurate epidemiological estimation for EG exists up to now, some previous studies have also provided population-based prevalence estimates. Guajardo *et al* [9] reported that the prevalence in the USA is approximately 2.5/100,000 for EG with a male: female ratio of 1.2:1. However, extrapolating responses from US samples,

Spergel *et al* [10] recently estimated an overall prevalence of 28/100,000 for EG. Kinoshita *et al*. [11] concluded that the prevalence of EG in Japan is approximately 5.5 times higher than that of USA and the male/female ratio for EG was also 1.2:1. However, the exact prevalence of EG is unclear. Reed *et al* [12] conducted a retrospective cohort study in 2014 and calculated that EG was seen in approximately 30/100,000 procedures. The prevalence is basically coincided with a published prevalence estimate of 28/100,000 by Spergel *et al* [10]. However, they found that EG may be more prevalent in male children and female adults, which is quite different from those have been reported [2, 3, 6-9, 11]. Considering the relatively small amount of patients with EG, the results may be underpowered to conclude differences between subgroups. With the increased awareness of EG by clinicians and pathologists, this disease will be diagnosed more accuracy, and further contributing to the rise in its epidemiology. In addition, it must be taken into account that the larger series in future will provide a more comprehensive analyzes of EG's epidemiology.

Pathophysiology of EG

Though eosinophils are normally present in the lamina propria except esophagus, the number of eosinophils along the GI tract is various and the highest concentrations are found in the cecum and appendix [13, 14]. It is involved in the mucosal immune system of GI tract, and has a role in host defense for healthy individuals [15]. The number of eosinophils increases in the pathogenesis of numerous inflammatory processes, including parasitic infections and allergic diseases. Then, the activated eosinophils produce and release highly bioactive inflammatory mediators like eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), eosinophil peroxidase (EPO) and major basic protein (MBP). These

cationic proteins possessing ribonuclease and antiviral activity are cytotoxic to the GI epithelium. This could trigger degranulation of mast cells and release of cytokines (*e.g.*, IL-1, IL-3, IL4, IL5, IL13, transforming growth factors), chemokines (*e.g.*, eotaxin, Regulation upon Activation Normal T-cell Expressed and Secreted (RANTES)), lipid mediators (*e.g.*, leukotrienes, platelet activating factor), and neuromediators (*e.g.*, substance P, vasoactive intestinal polypeptide) [14, 16, 17].

Moreover, the Th2-type immune response seems to be involved in EG [18-22]. Recent studies also strongly support that Th-2 cytokines (*e.g.*, IL-4, IL-5 and IL-13) and chemokines such as eotaxin (*e.g.*, CCL26) play a critical role in the pathogenesis of eosinophilic gastroenteritis. It was found that levels of TH2 cytokines (*e.g.*, IL4, IL5, and IL13) and the eosinophil-related chemokine eotaxin-3 (CCL26) are upregulated [22]. But different from eosinophilic esophagus, EG has a prominent and conserved transcriptome that has minimal overlap with that of EE, the respective transcriptome of which provides a rationale for shared and unique therapeutic intervention strategies.

Histopathology of EG

Except for the squamous mucosa of the esophagus, the lamina propria of the remaining GI tract contains constitutive eosinophils. And intramucosal eosinophils counts vary widely among normal individuals, depending on region, climate, age, exposure to food allergens and infectious agents, etc. Furthermore, the number of eosinophil in the same individual is believed to vary within different segments of GI tract.

Up to now, there are relatively limited information available regarding normal counts or distribution of eosinophils in GI tract. In 19 children from Ohio, DeBrosse *et al* [23] found

peak eosinophil counts of 8 eosinophils/HPF in antral and 11 in oxyntic mucosal biopsies. Talley *et al* [24] found a mean eosinophil count of 12 eosinophils in 5 HPF in biopsies from the cardia, body, and antrum of asymptomatic adult volunteers from Northern Sweden. Recently, Lwin *et al* [25] noted that the mean eosinophil count for the 135 normal controls was 4 eosinophils/HPF (± 4 SD), equivalent to 15 ± 17 SD eosinophils/mm² (range, 0 to 110). And there were no significant differences between the counts in biopsies from the antrum and corpus. These results are in agreement with those of DeBrosse [23] and Tally [24]. Moreover, these studies also confirms that, in the population of the United States, the normal gastric eosinophilic counts are usually < 38 eosinophils/mm², equivalent to 9 eosinophils/HPF. In 2015, Matsushita T *et al* [26] first elucidated the number and distribution of eosinophils in the mucosa throughout GI tract in a Japanese adult population. The results showed a significant increase in the number of eosinophils from the esophagus to the right colon (mean $\pm$ SD/mm²: 0.07 ± 0.43 for the esophagus, 12.18 ± 11.39 for the stomach, and 36.59 ± 15.50 for the right colon), compared with a decrease in the left colon (8.53 ± 7.83). They also found race and environmental factors seem to have only a little effect on eosinophil densities and distributions. However, based on current available data, there is no established consensus on a diagnostic threshold with regard to eosinophil count for EG. However, based on current available data, there is no established consensus on a diagnostic threshold with regard to eosinophil count for EG. Due to eosinophilic patchy infiltrates, eosinophilia was potentially missed in these patients. And the diagnostic threshold number of gastric eosinophils required in EG varies among investigators, ranging from 20 eosinophils in one HPF to 30 eosinophils per HPF in at least five HPFs [27, 28]. In clinic practice, a benchmark of more than 20

eosinophils/HPF has been suggested when EG is a high degree of suspicion [29]. In a review, Collins *et al* [30] tactfully suggested less emphasis on eosinophil quantity and focusing more on additional pathologic changes and also proposed using the term “mucosal eosinophilia” to describe increased numbers of mucosal eosinophils without other histologic alterations, and reserving the term “EG/colitis” for cases with additional pathologic changes. A recent study [25] recommend that the term ‘histological eosinophilic gastritis’ be used for the diagnosis in patients who: (1) have gastric biopsies that show an average density >127 eosinophils/mm² (or >30 eosinophils/HPF on microscopes equipped with wide-lens oculars) in at least five separate HPFs; (2) have no known associated causes of eosinophilia (e.g., *Helicobacter pylori* infection, Crohn’s disease, parasitic infections, and hematological or lymphoid disorders).

Clinical manifestations of EG

EG is an uncommon and heterogeneous disease characterized by eosinophilic infiltration of the GI tract, presenting with a variety of GI manifestations which depend on the site of affected GI tract and the layer of the GI wall involved [2, 3]. And many patients had a history of atopic conditions including asthma, allergic rhinitis or atopic dermatitis, and allergy to medicine food or pollen [12, 31]. Although symptoms of EG were non-specific and various, abdominal pain and nausea/vomiting were the most frequent presenting symptoms in children and adults [12, 27, 31, 32]. Especially, children and adolescents maybe present with growth retardation, failure to thrive, delayed puberty or amenorrhea.

Based on clinical manifestations and depth of eosinophilic infiltration into the GI tract wall, Klein *et al.* [3] proposed a classification of EG into three different patterns, including

predominantly mucosal pattern, predominantly muscular pattern and predominantly serosal pattern. Predominantly mucosal pattern is the most common presentation, characterized by mucosal and submucosal involvement [33]. These patients present mainly with abdominal pain, nausea, vomiting, diarrhea, bleeding, anemia, protein-losing enteropathy, malabsorption, and weight loss. Predominantly muscular pattern is the second common presentation, characterized by muscle layers involvement [33]. Patients present more with bowel thickening and symptoms of pyloric or intestinal obstruction. And the stomach and duodenum are the most commonly affected segments. Predominantly serosal pattern is the rarest presentation of EG, in which eosinophil-rich inflammatory infiltrate permeates all layers of the digestive wall and reaches the serosal cover [33]. And eosinophilic ascites are regarded as the special feature of this pattern, which has favorable response to corticosteroid treatment [34]. Interestingly, according to Klein *et al* classification, a French study [27] found that predominantly serosal pattern of EG seemed to have a relatively good prognosis presenting a majority of single flare and no continuous chronic course. On the contrary, predominantly mucosal pattern presented mostly a chronic continuous course, and predominantly muscular pattern was more likely to relapse.

Though there is classification of EG, the layers involved are still not easy to find in a real clinical practice. This was caused by that only mucosal and submucosal biopsies were taken in almost all cases and clinical and pathologic features often overlap. Recently studies [32] debated that it was necessary to focus more on the correlation of the layers of GI wall predominately affected and symptoms.

In addition to the common presentations noted above, there are single case reports or case

series of patients with EG presenting with a variety of unusual complications. Pancreatitis secondary to EG was the common complication caused by mechanical obstruction of the pancreatic duct secondary to eosinophilic infiltration of the duodenum [27, 34]. It was reported that eosinophilic infiltration could lead to edema, fibrosis and distortion in the ampulla and periampullary duodenum, resulting in pancreatitis [35]. Some cases will typically present as an acute bowel obstruction which is a combination of both mechanical obstruction due to stricture and functional obstruction due to inflammation, edema, and decreased GI motility [36]. In most cases, these obstructions are reversible with corticosteroid treatment, avoiding the unnecessary surgery treatment. Several studies also had reported patients presenting with duodenal ulcer or perforation [37, 38]. Only treatment with proton pump inhibitor therapy is ineffective for duodenal ulcer of EG, suggesting an etiology for the ulcer other than acid peptic disease. In stark contrast, duodenal ulcer does respond well to corticosteroid treatment. Perforation usually requires surgical repair immediately and represents a transmural involvement of eosinophilic infiltration. Other complications, such as cystitis, hepatic dysfunction, had also been reported as single case report [39-41].

Diagnosis of EG

Though there is no standard guideline for the diagnosis of EG, a high degree of clinical suspicion is especially necessary [20]. Definitive diagnosis requires typical GI symptoms coupled with increased eosinophils in biopsy specimens from the GI tract wall. Moreover, exclusion of other potential causes for the intestinal eosinophilia including parasitic infections, side effects of drugs, inflammatory bowel disease (IBD), connective tissue diseases, and lymphoproliferative malignancies [42] (Table 1). Thus, the clinical history,

laboratory results, endoscopy and radiological findings are essential before the final diagnosis of EG (Figure 1).

Laboratory results

Peripheral eosinophilia in the context of GI symptoms is a useful clue to EG, but this test is not a reliable diagnostic criterion. Many studies found that peripheral eosinophilia was absent in some EG patients [11, 31, 43]. Therefore, absence of peripheral eosinophilia should not be a deterrent from performing an endoscopy with biopsies when EG is clinically suspected. Furthermore, it was [31] found that peripheral eosinophil count was not a reliable observational index to estimate disease activity. Therefore it was not reliable for following up patients after therapy, because patients continued to have similarly elevated eosinophil counts regardless of their histological response to therapy. Allergy evaluation includes total IgE level and the use of commonly available tests including skin prick tests (SPT) and radioallergosorbent tests (RAST) detecting IgE antibody specific to inhaled and ingested allergens [14]. Although positive skin prick tests and/or elevated serum total IgE levels had been detected indeed in some of patients [1], they also could be found in parasitic infection, food allergy etc., resulting in being not a special indicator for EG. Moreover, it was reported that higher levels of fecal eosinophilic cationic protein (ECP), serum ECP and eosinophil-derived neurotoxin (EDN) were found in EG compared with other inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease [44]. Zhang *et al* [32] reported that 92.8% of patients in their study had an elevated a 2-macroglobulin level, which maybe a useful clue to EG.

Radiological findings and endoscopy

The radiological findings in only about two thirds patients with EG are variable and unspecific [6]. In most of patients with EG, radiological findings are normal. Moreover, nonspecific diffuse or local mucosal fold thickening may be the common manifestation in predominantly mucosal pattern of EG, and other manifestations include polyps, ulcerations, luminal narrowing. Stenosis or obstruction, rigidity and dysmotility may be found in patients with predominantly muscular pattern. Radiological findings show that the present of ascites is regarded as the feature of predominantly serosal pattern. Given multiple layers of the GI wall can be involved, radiological findings often coexist. If patents with EG present with pancreatitis, radiological findings may reveal the sign of pancreatitis, diffuse wall thickening in the duodenum, and/or ascites [34]. If patents present with cystitis, diffuse wall thickening of the bladder wall may exist [40]. Several reports had shown endoscopic exams were normal in about half of patients. The most common gastric and duodenal finding was mucosal erythema [12, 32]. In addition to mucosal erythema, other signs include mucosal hyperemia, thickening of folds, friability, areas of roughening, whitish specks, erosions, superficial ulcers, or nodularity. Some studies reported that eosinophilic infiltration was found in biopsies from areas of relatively normal endoscopic appearance or radiological findings, but such infiltration was absent in some areas with abnormalities as described above in [2, 32]. This apparent inconsistency may result from the characteristically patchy involvement of eosinophilic infiltration as noted in previous studies [7, 31, 32]. Therefore, multiple biopsies in both abnormal and relative normal appearing mucosa, particularly in the second part of duodenum, are strongly suggested.

Furthermore, if eosinophilic infiltrations are restrictive mainly to the submucosa or serosa, mucosal biopsies may be negative. In the circumstances, a full-thickness surgical biopsy may be necessary if confirmed by a high degree of suspicion derived from clinical manifestations and radiologic findings [8, 45, 46]. Because of the inherent limitations of endoscopically obtained biopsies, it is likely that intestinal eosinophilia was potentially missed. Capsule endoscopy is a good selection to find intestinal abnormalities including multiple erythema, villous atrophy [2], incomplete obstruction with ulcerated mucosa alternating with preserved areas [47] or a mimicking of mucosal diaphragms with complete capsule retention [48].

Treatment of EG

Up to now, there is no consensus optimal treatment strategy of EG. On account of heterogeneous presentations and extremely low incidence of EG, there is a complete lack of the large, randomized, controlled trials to clearly establish standard treatment guideline. Current treatment of EG is based mainly on evidence in case reports and case series for a variety of agents, including dietary treatment, corticosteroid therapy and other drugs. If patients with EG appear to perforation or obstructive manifestation, it should be necessary to consider undergoing surgery to repair damages or relieve obstruction. One study [49] proposed a therapeutic strategy. First, they recommended avoiding specific allergen (airborne and food allergen). If this is not feasible or failed to achieve improvement, then they recommended glucocorticoid therapy, including starting with topical delivery and then considering systemic delivery (Table 2).

Dietary treatment

A high proportion of cases of EG are associated with food allergy [7, 9]. As a result, use of

elimination or elemental diets is recommended. And the use of dietary treatment not only has been effective in reducing the dose for corticosteroids, but also has improved the poor growth associated with the disease [50]. However, in clinical practice, the elimination of these foods based on the results of skin prick tests or radioallergosorbent test has shown variable results [1, 7, 27]. The response to elimination diet not correlate with the patients' food sensitization profile [31]. Thus, it is difficult to identify the causative foods, resulting in limiting the efficacy and application of elimination diet. Now, an empiric diet, preferentially devoid of the 6 most common food-allergens, milk, soy, eggs, wheat, peanuts/tree nuts, and shellfish/fish (6-FED), has also been used for EG. And the reintroduction process was helpful to identify the causative foods. Some studies had also reported EG in children and adults showed remission of symptoms after this elimination diet [31, 51]. Except for elimination diet, elemental diet has often been chosen for the treatment of EG, aimed at avoiding all protein antigen exposure. Good efficacy in EG can also be achieved by exclusively amino acid-based elemental diet [50]. However, elemental diet can lead to reduce quality of life [52] due to the restricted nature of the diet, poor palatability and relatively high expense. As a result, the application may be limited.

In addition, dietary treatment for EG is used in combination with other interventions in most cases. Its efficacy need to be further confirmed in large and prospective trials.

Drug treatment

Corticosteroids

If dietary treatment is not feasible or failed to achieve improvement, corticosteroids would be

the optimum therapeutic drugs [1, 17]. A number of uncontrolled studies and case series have demonstrated that corticosteroids as main drugs have an important role for treating EG in children and adults [6, 53]. Among the patients with EG, those with predominantly serosal pattern seem to have the greatest response to corticosteroids [8].

Prednisone, budesonide, fluticasone were the main therapeutic drugs in corticosteroid treatment. Doses of prednisone of 0.5 to 1 mg/kg typically achieve a markedly symptomatic remission in 2 to 14 days. The results indicated that short-term systemic corticosteroids treatment is a fantastic therapeutic strategy to achieve clinical remission. Once clinical symptoms are controlled, dose of prednisone is tapered over the next 2 or more weeks until prednisone is stopped. But some steroid-dependent patients relapse during steroids tapering or after withdrawal of corticosteroid treatment [27]. These patients should resume taking initial doses, maintain remission by the minimum required dose. Meanwhile, budesonide can be used as an alternative drug of Prednisone for maintenance therapy and successful treatment with budesonide has been reported. The major advantage of budesonide is its high metabolism rate, leading to a lower risk of long-term treatment's side effects [54]. Most patients achieve a symptomatic remission improvement of symptoms at 9 mg/d doses of budesonide, and the dose of 3 to 6 mg/d long term is preferable [42]. Compared with prednisone, budesonide has a similar efficacy and even a better safety profile. Fluticasone is a fluorinated corticosteroid with an extremely low oral bioavailability of less than or equal to 1% [55]. This low oral bioavailability makes it potentially an optimum drug for topical delivery in EG. Unfortunately, fluticasone is the only available commercial formulation in pulmonary and nasal inhalers, neither of which contain sufficient dose to treat EG.

Despite their dramatic efficacy, the long-term use of corticosteroids is not desirable due to serious side effects, such as adrenocortical suppression, fluid and electrolyte disturbances, hyperglycemia, cushingoid state. Hence, we still need to drill down into other therapeutic strategies.

Other drugs

With regard to the efficacy of other therapeutic drugs in treating EG, most of the available evidence comes from single cases or small case series and this limits us to verify its real application value. Nevertheless, these evidence points out the new thoughts on future treatment. Nowadays, other drugs used with some success include mast cell inhibitors, leukotriene receptor antagonists, antihistamines, anti-interleukin-5.

Mast cell inhibitors

Disodium cromoglycate is a mast cell stabilizer that prevents release of toxic mediators like histamine, platelet activating factors and leukotrienes from mast cells. There have been sporadic case reports of a beneficial response to the drug [35, 56, 57]. Some studies reported that disodium cromoglycate might result in a positive response at a dose of 200 mg four times a day [35, 56]. Ketotifen, an antihistaminic agent and mast cell membrane stabilizer, also produced a clinical improvement with a dose of 2–4 mg per day in some cases [58, 59].

Leukotriene receptor antagonists

Montelukast, a selective and competitive leukotriene receptor antagonist, may be considered as a relatively safe and effective steroid-sparing therapy for EG [60, 61]. Some studies suggested that montelukast treatment for several months at a dose range of 10–40 mg orally per day achieved a beneficial improvement in both peripheral eosinophilia and symptoms

[61-63]. Therefore, montelukast seems promising to be an effective long-term treatment in patients with EG, in particular when they are steroid-dependent.

Anti-interleukin-5

In regard with anti-interleukin-5, the information is contradictory in some cases. Despite a humanized anti-IL-5 monoclonal antibody (mepolizumab) had been found to be effective in a small, open-label, uncontrolled study in which had four patients with hypereosinophilia syndrome (HES) [64], the rebound eosinophilia was seen after anti-IL-5 treatment in patients with HES and EG in a small clinic trial [65]. Thus, further randomized, controlled trials must be conducted to verify the potential therapeutic value of anti-IL-5 antibody in patients with EG.

Antihistamines

Antihistamines cannot probably become the first-line therapy in the current circumstance, because evidence for application of antihistamines (H-1 receptor antagonists) in EG is based merely on the murine model of aeroallergen induced EE, and several reports of EG in association with seasonal allergies [66-68]. In consequence, a comprehensive understanding of the mechanisms underlying idiopathic EG is need in the future.

Fecal microbiota transplantation (FMT)

Intestinal microbiota constitute a microbial organ that is indispensable to overall host physiological function, including pivotal roles in metabolism and immune system function [69], resulting in attracting more and more attention. Recently, a case report first found fast therapeutic efficacy of FMT in EG cases presenting as long-term diarrhea [70]. But it remains unclear whether FMT could cure EG or maintain long-term clinical remission. If sufficient

evidence in support of FMT efficacy is confirmed in the future, it will be served as more effective, safer and promising therapeutic strategies against EG.

Surgery

Predominantly muscular pattern of EG can present obstructive symptoms, due to bowel wall thickening and narrowing of the lumen caused by eosinophilic infiltration. In most cases, these obstructions can be reversible with corticosteroid treatment [37, 38]. Nevertheless, some cases of EG had been diagnosed only after resection of the obstructing segment after laparotomy or laparoscopic full thickness biopsy [36]. Thus, it is necessary for clinicians to have a high degree of suspicion for EG. If EG can be diagnosed in time and obstructions can be reversible with treatment, an unnecessary surgery treatment is avoided as far as possible.

But patients with EG presenting with GI perforation need to be considered to undergo surgery for repairing damage. Notably, these complications may persist or often occur, warranting close follow-up and dietary therapy and appropriate medical treatment [71-73].

Natural history of EG

With regard to natural history of EG, many questions remain largely unknown. Indeed, only single case reports or small cases series reported follow-up survey after treatment with limited and shot in detail [6-8]. Recently, a published French study analyzed the data on clinical presentation and long-term outcomes of 43 adult patients with EG who were followed up for a median period of 13 years [27]. They identified three different patterns of disease course: (1) a single flare of EG, defined by GI symptoms present for less than 6 months associated with the absence of any relapse after initial flare; (2) a recurring course of EG, defined by at least 2 flares of the disease separated by a period without GI symptoms and

without peripheral blood eosinophilia; (3) a continuous course of the disease, defined by chronic persistent GI symptoms for more than 6 months without period of remission. They also found that absence of spontaneous remission and high blood eosinophil counts at diagnosis were significantly associated with a high risk of clinic relapse [27] (Figure 2). Unfortunately, very few studies continue to focus on elucidating natural history of EG. Further research from large studies is needed to validate the three different patterns of disease course.

Conclusion

Eosinophilic gastroenteritis is an uncommon and heterogeneous disease, and many problems still left to be answered. Up to now, there is no standard guideline for the diagnosis of EG, and a high degree of clinical suspicion is especially necessary. Although corticosteroids as main medication have a dramatic efficacy for treating EG, the serious side effects of long-term application cannot be ignored. In the future, large and high-quality studies are needed to further investigate the epidemiology and pathophysiology of EG, make the consensus diagnostic criteria, evaluate optimal treatment strategy, and verify its natural history.

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Table 1: Differential diagnosis of eosinophilic gastroenteritis

Systemic disorders: vasculitis, connective tissue disease, hyper-eosinophilic syndrome, graft-versus-host disease, systemic mastocytosis, tuberculosis, etc.

Gastrointestinal diseases: Crohn's disease, ulcerative colitis, celiac disease, acute abdomen, intestinal perforation, pyloric narrowing and obstruction, malabsorption syndrome, etc.

Food/drug allergy: food (milk, soy, egg, wheat, peanuts tree nuts, and shellfish_fish, etc);
drug (penicillin, cephalosporin, aspirin, sulfonamides, etc.)

Tumor: carcinomas, lymphomas, etc.

Parasitic infection: ascaris, trichuris, schistosomiasis, ancylostoma caninum, enterobius vermicularis, giardia lamblia, anisakis, trichinella spiralis, etc.

Table 2: The treatment of eosinophilic gastroenteritis

Treatment	Classification	Application
Dietary treatment	elimination diet	initial therapy
	elemental diet	initial therapy
Drug treatment	corticosteroids	main therapy
	mast cell inhibitors	often combined with corticosteroids
	leukotriene receptor antagonists	often combined with corticosteroids
	anti-interleukin-5	need further verify efficacy
	antihistamines	need further verify efficacy
	fecal microbiota transplantation	need further verify efficacy
Surgery treatment	—	avoid unnecessary surgery treatment

Figure Legends

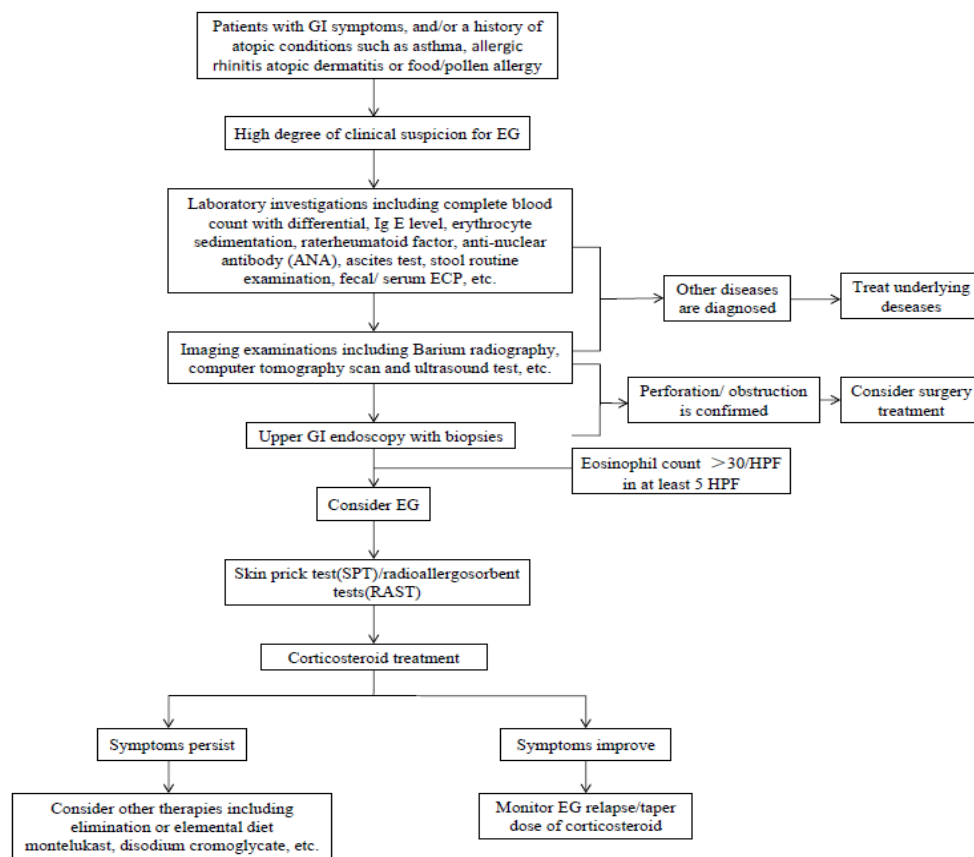


Figure 1: Flowcharts for diagnosis and treatment of eosinophilic gastroenteritis (EG).

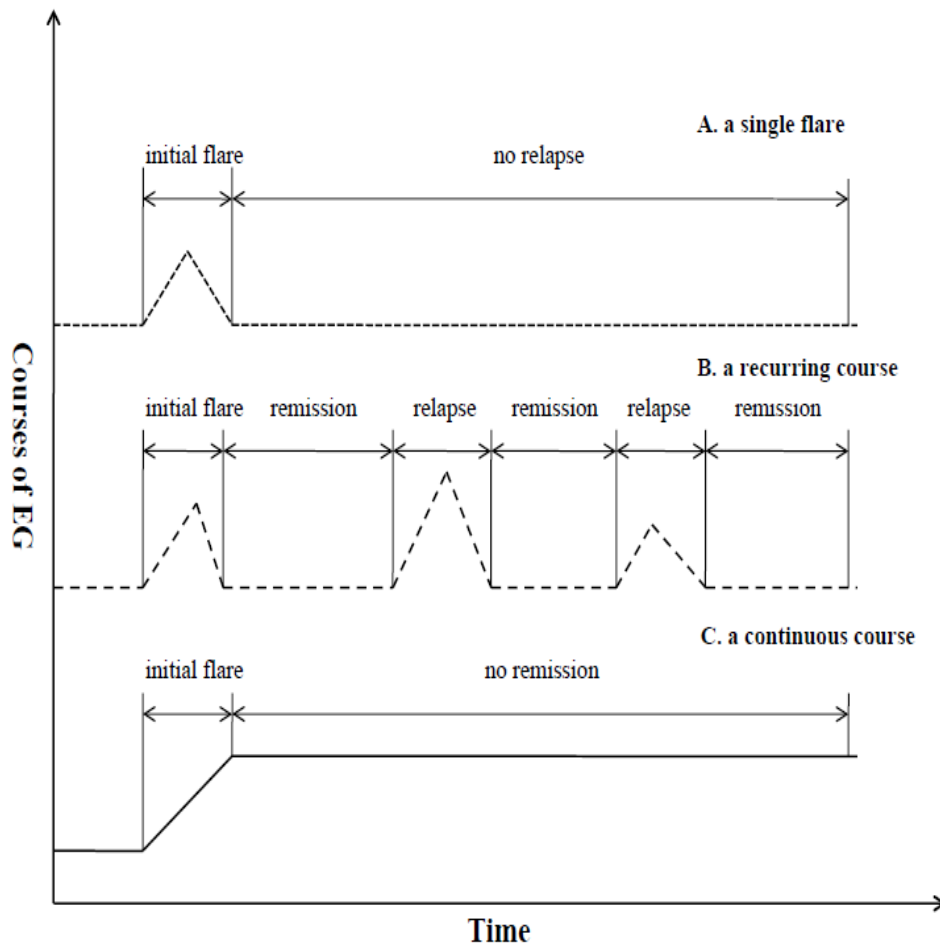


Figure 2: Three types of eosinophilic gastroenteritis. (A) a single flare of EG, defined by GI symptoms present for less than 6 months associated with the absence of any relapse after initial flare; (B) a recurring course of EG, defined by at least 2 flares of the disease separated by a period without GI symptoms and without peripheral blood eosinophilia; (C) a continuous course of the disease, defined by chronic persistent GI symptoms for more than 6 months without period of remission of EG (modified, based on de Chambrun *et al.* [27]).