



Diagnosis, Natural History and Treatment of Eosinophilic Enteritis: a Review

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Abstract

Purpose of Review To review recent findings regarding eosinophilic enteritis, including epidemiology, pathogenesis, natural history, and treatment.

Recent Findings A 2017 population-based study using a US healthcare system database identified 1820 patients with a diagnosis of eosinophilic enteritis among 35,826,830 individuals. The majority of patients with eosinophilic enteritis in this study were women (57.7%), Caucasian (77.5%), and adults (> 18 years of age) (83.5%). The overall prevalence of eosinophilic enteritis was estimated at 5.1/100,000 persons.

Summary Eosinophilic enteritis, also known as eosinophilic gastroenteritis, is a rare primary eosinophilic gastrointestinal disorder (EGID) of unknown etiology characterized by the presence of an intense eosinophilic infiltrate on histopathological examination of the intestinal mucosa. The etiology of eosinophilic enteritis remains unknown. However, there is evidence to support the role of allergens in the pathogenesis of this disorder, as children and adults with EGIDs often have positive skin testing to food allergens and a family history of allergic diseases. Recent studies unraveling the role of IgE-mediated but also delayed Th2-type responses have provided insight into the pathogenesis of this disease. Eosinophilic enteritis causes a wide array of gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, bloating, or ascites, and its diagnosis requires a high degree of clinical likelihood, given the nonspecific clinical presentation and physical examination findings. Oral corticosteroids are considered to be the mainstay of treatment and are generally used for a short period with good response rates. Antihistamine drugs and sodium cromoglycate have also been used to treat patients with eosinophilic enteritis. Preliminary studies have demonstrated the potential benefit of biological therapies targeting the eosinophilic pathway such as mepolizumab, an anti-IL5 antibody, or omalizumab, an anti-IgE monoclonal antibody. Eosinophilic enteritis is generally considered to be a benign disease without relapse, but up to 50% of patients may present a more complex natural history characterized by unpredictable relapses and a chronic course.

Keywords Eosinophils · Gastroenteritis · Natural history · Allergy · Treatment · Corticosteroids

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Introduction

Eosinophilic enteritis (EE), also known as eosinophilic gastroenteritis, is a rare primary eosinophilic gastrointestinal disorder (EGID) of unknown etiology characterized by the presence of an intense eosinophilic infiltrate on histopathological examination of the intestinal mucosa [1•, 2, 3] (Table 1). Eosinophilic enteritis causes a wide array of gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, bloating, or ascites, and its diagnosis requires a high degree of clinical likelihood, given the nonspecific clinical presentation and physical examination findings. As it was firstly described by Kaiser et al. [5] in 1937, diagnosis of EE requires the identification of a

Table 1 Primary eosinophilic gastrointestinal disorders

Eosinophilic esophagitis	Eosinophilic gastro-enteritis	Eosinophilic colitis
Forms		
Atopic	Mucosal	Atopic
Non-atopic	Muscular	Non-atopic
Familial	Subserosal	
Definition		
Eosinophilic infiltration of the esophageal mucosa without other intestinal segment involved	Gastrointestinal symptoms + Eosinophilic infiltration of one or more intestinal segment	Children Eosinophilic infiltration of the colon Atopy or cow milk protein allergy
Main clinical characteristics		
Dysphagia	Abdominal pain	Diarrhea
Vomiting	Diarrhea	Rectal bleeding
Food impaction	Obstruction	
	Ascites	

Adapted from Pineton de Chambrun et al. [4]

pathologic eosinophilic infiltration of at least on part of the intestinal wall and the exclusion of secondary causes of intestinal eosinophilia [6]. Eosinophilic infiltration could be seen in any segment of the intestine with frequent involvement of the duodenum and the stomach. Also, eosinophils could involve the different layer of the intestinal wall, and Klein et al. described three anatomical forms of EE according to predominant involvement of the mucosa, the intestinal muscle, or the serosal [2]. Treatment of EE is challenging, as there are very little evidence regarding drug efficacy in patients with EE [7]. Dietary restriction in patents with food allergy, Leukotriene inhibitors, mast cells stabilizers, and corticosteroids have been used in patients with EE with conflicting results [8••]. Recent studies unraveling the role of IgE-mediated but also delayed Th2-type responses have provided insight into the pathogenesis of this disease [9]. Preliminary studies have demonstrated the potential benefit of biological therapies targeting the eosinophilic pathway such as mepolizumab, an anti-IL5 antibody, or omalizumab, an anti-IgE monoclonal antibody [10]. We will hereby review recent findings regarding EE epidemiology, pathogenesis, clinical characteristics, and treatment.

How to Diagnose Eosinophilic Enteritis

Patients with EE mostly present nonspecific gastrointestinal symptoms, and the confirmation of the diagnosis requires the demonstration of a pathological eosinophilic infiltration of at least one intestinal segment. It is important to note that eosinophils are immune cells which normally reside within the lamina propria of the intestinal mucosa except in the esophagus. The eosinophil count in the lamina propria increases from the duodenum to caecum and then decreases from the right colon to the rectum [11]. Thus, cut-offs to define a pathological eosinophilic infiltration should take into account the localization

of intestinal biopsies. In the duodenum, most studies have used a threshold of 20 eosinophils per high power field ($\times 400$) for the diagnosis of EE [6, 12]. Apart from eosinophils in the lamina propria, other signs on histology in favor of EE are eosinophils in the epithelial or muscular layers, degranulation of eosinophils (extracellular deposition of the eosinophil major basic protein due to eosinophil activation), villous atrophy, crypt hyperplasia or abscesses, and epithelial degenerative/regenerative changes (Fig. 1). Analysis of ascites fluid when present, or surgical specimens when available, may also play an important role in demonstrating an abnormal presence of eosinophils. Thus, the diagnosis of EE requires the presence of gastrointestinal symptoms associated with a pathological eosinophilic infiltration of the intestine and exclusion of secondary causes of intestinal eosinophilia [6] (Fig. 2 and Table 2).

Aside from primary eosinophilic gastrointestinal disorders including EE, numerous conditions are responsible for intestinal eosinophilia and should be considered in patients with eosinophilia and gastrointestinal symptoms [13]. Table 2 summarizes the secondary causes of intestinal eosinophilia. Intestinal parasites and medications are two frequent causes of peripheral blood and tissue eosinophilia [14]. In patients suspected to have EE, parasitic infection should be ruled out by direct stool examination, intestinal biopsies, and serological markers. Systematic antiparasitic treatment could also be used in patients with gastrointestinal eosinophilia due to the lack of sensitivity of parasite detection methods. Other gastrointestinal disorders with eosinophilic mucosal infiltration are gastrointestinal vasculitis, gastroesophageal reflux disease, celiac disease, inflammatory bowel disease, and *Helicobacter pylori* gastritis [15]. Of note, specific bone marrow disorders are responsible for an hypereosinophilic syndrome defined by peripheral blood eosinophilia > 1500 eosinophils/mm³ for more than 6 months, with signs and symptoms of organ involvement. In this case, the diagnosis of EE is excluded and

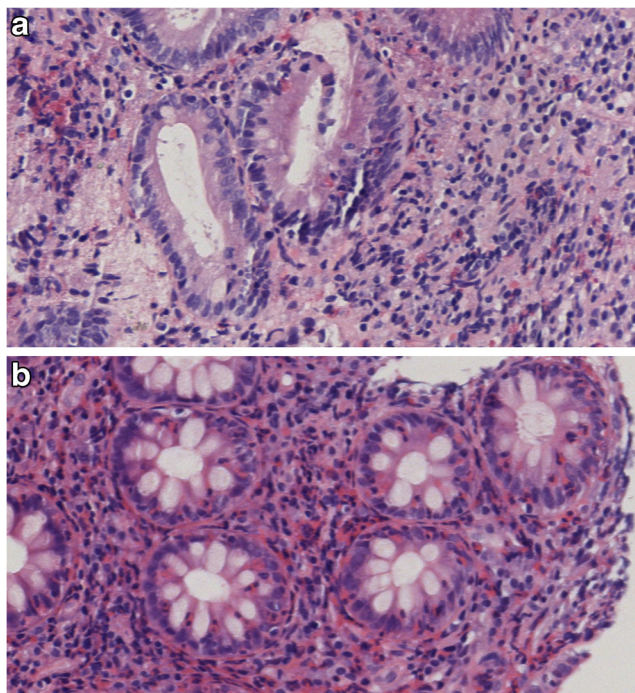
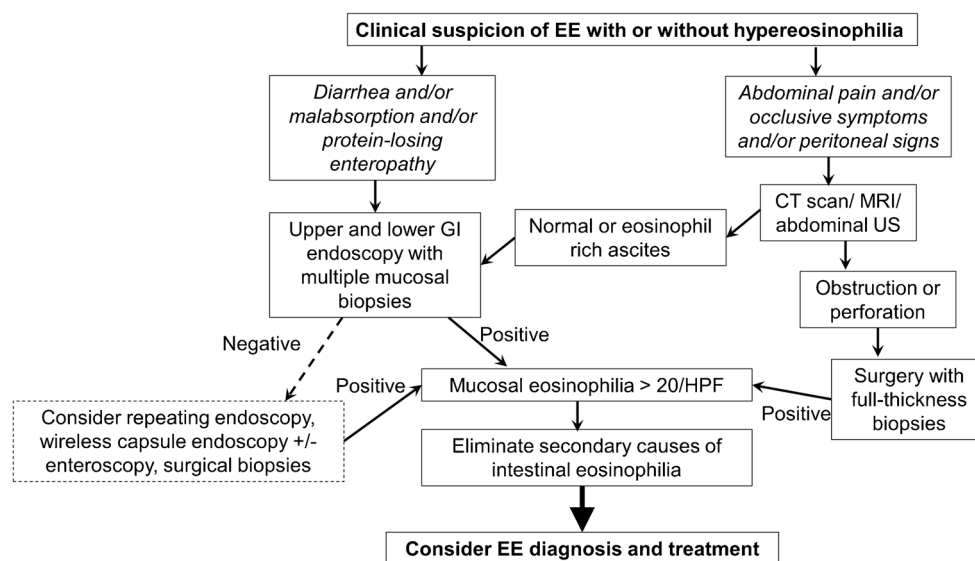


Fig. 1 Histological findings in patients with eosinophilic enteritis. **a** Eosinophilic infiltration of the duodenum in a female patient with eosinophilic enteritis. Dense infiltration of the lamina propria by eosinophils, signs of degranulation, and invasion of the duodenal epithelium by eosinophils. Hematoxylin-eosin coloration. Magnification $\times 40$. **b** Eosinophilic infiltration of the colon in a male patient with eosinophilic enteritis. Eosinophils are seen in red with lobulated nucleus. On this picture, there is not only an increased number of eosinophils in the lamina propria, but also the abnormal presence of eosinophils in the colonic epithelium and signs of degranulation (red coloration outside cells). Hematoxylin-eosin coloration. Magnification $\times 40$

specific analyses should be done with bone marrow aspiration, lymphocyte phenotyping, and testing for a FIP1L1-PDGFR fusion transcript [16].

Fig. 2 Diagnostic algorithm for eosinophilic enteritis (adapted from Abou Rached et al.) [8•]



Epidemiology of Eosinophilic Enteritis

Since the first description of eosinophilic enteritis in 1937 by Kaiser et al., only less than 400 cases have been published as case reports or retrospective monocenter studies [2, 6, 7, 12, 17–20]. Reports of subsequent cases have revealed a widely variable and heterogeneous profile of physical manifestations. Interestingly, a recent population-based study [1•] using a US healthcare system database identified 1820 patients with a diagnosis of EE among 35,826,830 individuals in the database from 2012 to 2017. The majority of patients with EE in this study were women (57.7%), Caucasian (77.5%), and adults (> 18 years of age) (83.5%). The overall prevalence was estimated at 5.1/100,000 persons. The prevalence in female patients was slightly higher than in male patients. Also, the prevalence was higher in children compared with adults [1•]. Other studies from North America have described a prevalence ranging between 8.4 and 28 per 100,000 [21•, 22]. The incidence of the disease has slightly increased over the past 50 years [23]. The age at diagnosis of EE varies widely, and many cases have been described in the pediatric population. In adults, the disease typically arises between the third and fifth decade of life [6]. Higher socioeconomic status, Caucasian race, and excess weight may be risk factors for EE [23]. The diagnosis of EGE is elusive due to nonspecific gastrointestinal symptoms leading to a missed diagnosis in many patients, as well as an extended delay between the onset of first symptoms and diagnosis (more than 2 years in some case series).

Pathogenesis of Eosinophilic Enteritis

Eosinophils are produced in the bone marrow. After a maturation step with differentiation and proliferation under the

Table 2 Secondary causes of intestinal eosinophilia

Diagnoses	How to investigate
Hypereosinophilic syndrome Persistently elevated blood eosinophil count ≥ 1500 eosinophils/mm ³ for at least 6 months	Clinical observation with testing for involvement of either the heart, nervous system, or bone marrow Testing for mutations involving the PDGFRA and FIP1L1 genes T cell clonality
Gut infections Intestinal parasitosis Ascariasis, toxocariasis, trichinosis, schistosomiasis, teniasis, ankylostomiasis, trichuriasis, strongyloidiasis, enterobiasis <i>Helicobacter pylori</i> , <i>Escherichia coli</i> , <i>Shigella</i>	Patient medical history, stool parasitological exam, serologies (teniasis, schistosomiasis, toxocariasis, trichuriasis), antiparasitic treatment Gastric biopsies, stool and blood cultures
Drugs and toxic substances Gold therapy, oral hypoglycemic agents, psychotropic drugs, antibiotics, NSAIDs Inflammatory bowel disease Crohn's disease and ulcerative colitis	Patient medical history Upper and lower GI endoscopies Anti- <i>Saccharomyces cerevisiae</i> antibodies and ANCA
Celiac disease	Anti-transglutaminase antibodies, duodenal villous atrophy
Vasculitis et autoimmune diseases Periarteritis nodosa, eosinophilic granulomatosis with polyangiitis, scleroderma Neoplasia	ANCA, anti-nuclear antibodies, vascular biopsies, clinical examination Imaging studies, histology (solid tumors, lymph nodes, myelogram, osteomedullary biopsy)

ANCA anti-neutrophilic cytoplasmic antibodies, GI gastrointestinal, NSAIDs non-steroidal anti-inflammatory drugs

control of cytokines such as GM-CSF, IL-3, and IL-5, eosinophils are released in the bloodstream in order to reach targeted organs [24]. Eosinophils are immune cells which normally reside within various organs including the gastrointestinal tract, uterus, thymus, and mammary glands. Eotaxin-1, an eosinophil-specific chemoattractant cytokine, is responsible for the migration and the homing of eosinophils in tissues [24]. In the intestine, eosinophils remain in the lamina propria and serve as part of the innate immune system to protect against parasites [3].

Eosinophils are characterized by a lobulated nucleus and specific intra-cytoplasmic granules with high affinity for acid dyes such as eosin. Eosinophil granules contain several acidophilic cationic proteins such as the major basic protein (MBP), the eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN) [25]. When activated, eosinophils secrete their granules containing the cationic proteins which are able to disrupt helminth and bacteria membranes and neutralize viruses with their RNase activity [26]. Cationic proteins are also able to disrupt cell membranes and act as cytokines with the activation of eosinophils themselves, basophils, neutrophils, and mast cells.

Numerous signals are responsible for the activation of eosinophils. Indeed, non-specific tissue damage, parasitic infection, bacterial infection, or allergens are able to activate eosinophils. Activation of eosinophils in the gastrointestinal tract will lead to tissue damage and is responsible for the symptoms

observed in patients with EE [27, 28]. Several mechanisms contribute to the effect of eosinophils on the intestinal mucosa. Eosinophil degranulation triggers cytotoxicity from cationic proteins and leads to the secretion of IgE [3]. Activated eosinophils are able to secrete a large number of pro-inflammatory cytokines such as IL-4, IL-5, IL-13, and RANTES [29]. These cytokines recruit and activate other adaptive immune cells to the site of inflammation. Initially, the eosinophil was considered as a terminal effector of innate immunity with the secretion of cationic proteins in tissues. Recent advances in eosinophil pathophysiology clearly demonstrate that the eosinophil is a multifunctional leucocyte expressing a wide array of surface markers which is able to interact with other immune cells at the frontier between innate and adaptive immunity [29].

Interestingly, a recent study analyzing the sera of 13 infants with EE demonstrated increased levels of thymic stromal lymphopoietin and IL-33, which are recognized as key cytokines in allergic disorders [30•]. Another study investigated the role of CCR-3 which acts as the receptor of eotaxin-1 in the development of eosinophilic gastrointestinal disease [31•]. In this experimental study, the authors demonstrated that anti-CCR3 antibodies significantly reduce the severity of eosinophilic inflammation, mucosal injury, and diarrhea in a mouse model of food allergen-induced GI eosinophilic inflammation. Thus, not only delayed Th2 adaptive response but also direct IgE-mediated response may be involved in the pathogenesis of EE [9].

Allergy has long been suspected to be the trigger of the gastrointestinal eosinophilic infiltration in patients with EE. Indeed, 64% of patients with EE have a family history of atopic disease [32••]. Patients with EE also frequently have other allergic manifestations such as rhinitis, eczema, asthma, or food intolerance [8••]. In addition to eosinophilia, elevated IgE levels in the blood are also in favor of an allergic reaction. However, identification of a specific allergen in patients with EE is rare. Dietary questionnaires may be useful, as well as skin tests for food allergens in patients with EE. In cases without a history of atopia or increased IgE, sequential exclusion of food allergens potentially incriminated is not recommended and has not shown to be useful for obtaining sustained clinical improvement [6].

Clinical Characteristics of Patients with Eosinophilic Enteritis

Patients with EE have nonspecific gastrointestinal symptoms such as abdominal pain, diarrhea, bloating, and nausea [6, 7, 20]. Other less frequent symptoms described in patients with EE are vomiting, ascites, rectal bleeding, and jaundice. Moreover, patients with EE may present with a complication of their disease as a first clinical manifestation (obstruction, stenosis, peritonitis) [33]. Clinical presentation depends on the depth of the eosinophilic infiltration within the intestinal wall. EE was initially classified by Klein et al. [2] into three different forms according to the predominant intestinal layer involved: (1) the mucosal form characterized by a predominant mucosal inflammation with diarrhea, abdominal pain, and signs of malabsorption or protein losing enteropathy; (2) the muscular form characterized by intestinal strictures with abdominal pain, nausea, and vomiting which can lead to intestinal occlusion; and (3) the subserosal form characterized by an eosinophilic-rich ascites with bloating and abdominal pain [2]. Our data indicated that 44% of patients with EE had a mucosal form, 12% a muscular disease, and 49% a subserosal form [7]. In the study from Talley et al. [6], the mucosal form was reported in 57.5% of the patients, the muscular form in 30%, and the subserosal form in only 12.5% [6]. Variation in the proportion of different forms of the disease in the literature and over time is probably due to the decrease in surgical specimens which are often necessary to diagnose the predominantly muscular disease.

Patients with EE may also differ in clinical presentation due to the distribution of the eosinophilic infiltration along the intestinal tract. Indeed, all segments of the intestine can be involved with specific symptoms for each segment. The most frequent localization of digestive eosinophilia is the stomach and the proximal small intestine, reported in around 40–80% of patients with EE [6, 7, 23, 34]. When the eosinophilic infiltration is spread along the small intestine, it may be responsible for protein-losing enteropathy, malabsorption, and iron deficiency

anemia. Esophageal and colonic localizations of eosinophilic infiltration are less frequently described. Of note, an isolated infiltration of the esophagus is considered to be eosinophilic esophagitis, and not EE. In EE, these two localizations are probably underestimated due to the lack of systematic biopsies in the majority of reported case series of EE. Indeed, colonic infiltration was reported in up to 80% of patients with EE in a study where systematic colonic biopsies were performed [7] (Table 3). It is important to mention that the nonspecific presentation of EE requires systematic biopsies of all intestinal segments in patients in whom the diagnosis is suspected.

The main abnormal finding in the blood of patients with EE is an elevated eosinophil count [7]. More than 70% of the patients with EE have peripheral blood eosinophilia (eosinophils $> 500/\text{mm}^3$) which is transient and concomitant with EE flares. Very high levels of eosinophils in the blood ($> 3000/\text{mm}^3$) can be observed in patients with EE, especially in patients with a predominantly subserosal disease. The other biological marker of EE is abnormal elevation of serum IgE levels, observed in more than 50% of the patients with EE. These IgE do not show any specificity. In EE patients with protein losing enteropathy, malabsorption, or intestinal inflammation, several other biologic abnormalities can be seen such as hypoalbuminemia, iron deficiency, steatorrhea, and an increase in C-reactive protein [33]. Of note, the absence of peripheral blood eosinophilia observed in 25% of the patients should not exclude the diagnosis of EE.

Findings of imaging studies in patients with EE are non-specific. Only intestinal biopsies will lead to the confirmation of the diagnosis. Upper gastrointestinal endoscopy and ileocolonoscopy may be macroscopically normal, or show only slight mucosal abnormalities such as erythema, erosions, edema, or nodules [35]. Wireless capsule endoscopy is useful to explore the entire small intestine and to reveal lesions not seen by conventional endoscopy, although biopsies cannot be performed with this exam [36]. Thus, in patients with

Table 3 Distribution of biopsy specimens and eosinophilic infiltration in patients with EE ($n = 43$)

Intestinal segments	Number of patients biopsied at each intestinal segment	Patients with eosinophilic infiltration (%)
Esophagus	20	6 (30)
Stomach	37	14 (37.8)
Duodenum	39	24 (61.5)
Ileum	25	18 (72)
Colon	34	30 (88.2)
Pancreas	2	2
Gall bladder	2	2

From [7]

EE eosinophilic enteritis

eosinophilic infiltration of the distal jejunum or proximal ileum, enteroscopy would be required to obtain biopsies and confirm EE [37]. New radiological exams such as CT-scan and MRI are useful in patients with EE in order to characterize the depth of eosinophilic infiltration within the intestinal wall and the presence of an ascites.

Treatment of Eosinophilic Enteritis

Treatment of EE is challenging, as there are no clear recommendations and very little evidence-based data in the literature [8•]. Treatments which have been already used and evaluated in patients with EE are summarized in Table 4. It is important to note that approximately 40% of patients with EE will have a spontaneous remission of their disease [7].

Diet

With regard to food allergy, several dietary strategies have been proposed for the treatment of patients with EE. When a limited number of food allergens are detected, patients with EE should be maintained on a targeted elimination diet. When many or no allergens are identified, a more aggressive empiric elimination diet or an elemental diet can be tested. To date, the overall data in the literature are insufficient to recommend empiric and total elimination diets in routine management.

Corticosteroids

The use of systemic corticosteroids is one of the main treatments of patients with EE [3, 15]. Most case series have reported good efficacy of corticosteroids with clinical remission obtained in 50 to 90% of patients with EE [23, 32•]. Treatment should be started at 0.5 to 1 mg/kg for few weeks before tapering the dose over a 6- to 8-week period [8•]. Subsequently, about 20% of patients with EE will have corticosteroid dependency requiring low-dose prednisone to maintain clinical remission. To avoid the side effects of corticosteroids, budesonide, which has a low systemic absorption, could also be used. Indeed, it was demonstrated that budesonide is effective at a dose of 9 mg/day for the induction and the maintenance of clinical remission in patients with EE [38–45]. The initial dose of 9 mg/day can be tapered to 6 mg/day and then 3 mg/day for maintenance therapy if needed.

Azathioprine

Azathioprine has been used with efficacy in patients with EE refractory to or dependent on corticosteroids. The usual dose for EE patients is similar to that used in patients with IBD (2–2.5 mg/kg) [46].

Biologics

Biologic agents have also been reported in some case studies of EE [8•]. Mepolizumab, an anti-IL-5 monoclonal antibody

Table 4 Treatments used in EE

Drugs	Mechanisms of action	Treatment indication
Dietary strategies	Targeted elimination diet or elemental diet	First-line treatment based on food allergy tests
Prednisone	Systemic corticosteroid	First-line treatment for induction of remission and Maintenance for steroid dependent disease (low dose)
Budesonide	Corticosteroid with low absorption	First-line treatment for induction of remission and Maintenance for steroid dependent disease (low dose)
Montelukast	Selective leukotriene inhibitor	First-line treatment or Steroid sparing agent
Sodium cromoglycate	Mast cell stabilizer	First-line treatment or Steroid sparing agent
Ketotifen	2nd-generation H1-antihistamine agent	First-line treatment or Steroid sparing agent
Azathioprine	Apoptosis of T and B cells	Steroid sparing agent
Mepolizumab	Anti-IL5 monoclonal antibody	In case of refractory disease
Omalizumab	Anti-IgE monoclonal antibody	In case of refractory disease
Infliximab/adalimumab	Anti-TNF monoclonal antibodies	In case of refractory disease

EE eosinophilic enteritis

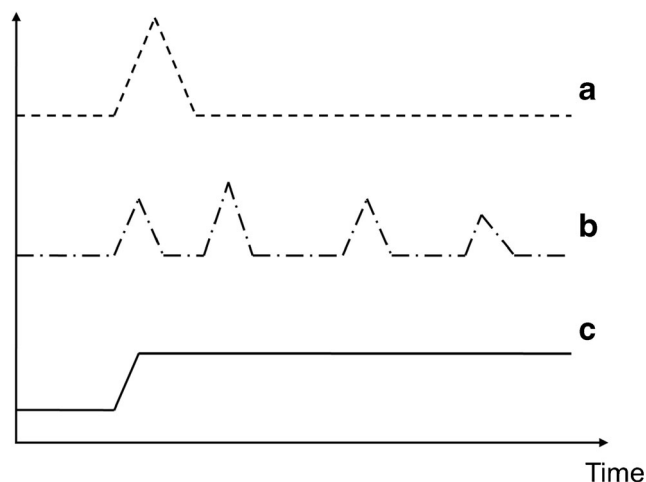


Fig. 3 Course of eosinophilic enteritis [7]. After a median follow-up of 13 years, we identified three different disease courses of eosinophilic gastroenteritis. Forty-two percent of patients presented a single flare with no relapse (A), 37% a recurring course with multiple flares and period of full remission (from 2 months to several years) (B), and 21% a continuous course (C). Seven out of 9 patients with a continuous course, 12 out of 16 patients with a recurring course, and 8 out of 18 patients with a single flare were treated

which was previously tested in eosinophilic esophagitis, may be an interesting alternative in patients with a complicated course of EE [47]. Indeed, mepolizumab (anti-IL5) was reported to have improved tissue and peripheral eosinophilia in four patients with EE [8•], but without relieving symptoms. Omalizumab, an anti-IgE monoclonal antibody, has also been tested for the treatment of EE with improvement in histologic lesions [48]. Infliximab and adalimumab, two anti-TNF monoclonal antibodies (anti-TNF), were reported as effective for inducing remission in refractory EE in some case reports [49].

Other Treatments

Other treatments used in patients with EE include antihistaminic drugs, montelukast, and sodium cromoglycate [15]. Ketotifen, a second-generation H1-antihistamine agent, is used to inhibit the release of mast cell mediators [50]. Montelukast is a selective leukotriene (LTD4) inhibitor, commonly used to treat asthma, which is used at the dose of 5–10 mg/day in patients with EE [51–56]. Sodium cromoglycate is a mast cell stabilizer that blocks the release of immune mediators and the subsequent activation of eosinophils. It has been used for the treatment of EE with some efficacy in several case reports [57]. The results of these drugs in patients with EE are conflicting and need further prospective studies.

Natural History of Eosinophilic Enteritis

The natural history of patients with eosinophilic enteritis has been described in our cohort of patients with EE in the North

of France [7]. In this study, three clinical courses of the disease were identified after a median follow-up of 15 years (IQR 1–27). A single flare without recurrence was observed in 44% of patients with EE, 36% of patients had a recurring course of their disease with multiple flares separated by periods of remission, and 21% had a chronic course without remission (Fig. 3). In our study, a predominant mucosal disease accounted for approximately 80% of the patients with a continuous course. Patients with a single flare without any recurrence had a subserosal forms in more than 50% of the cases [7]. Long-term follow-up of our patients does not demonstrate any occurrence of myeloproliferative disorders [7]. Another study with long-term follow-up of patients with EE demonstrated that only one third of patients remained in long-term remission, with many patients presenting a persistent or progressive disease course [32•].

Conclusion

EE is a rare disease characterized by a pathologic infiltration of the intestine by eosinophils. Patients with EE have very nonspecific gastrointestinal symptoms which depend on the localization of the eosinophilic infiltration along the intestine and through the intestinal wall. It is recommended to perform systematic intestinal biopsies in each intestinal segment in patients with unspecific gastrointestinal symptoms or elevated eosinophil blood count in order to avoid misdiagnosis of EE. Even if allergy is suspected to play a role in the development of EE, exact pathophysiological mechanisms leading to EE are still unknown. Corticosteroid therapy is the most common treatment of EE flares with good efficacy in the majority of patients. Food exclusion and elemental diet should be restricted to patients with identified food allergens. Most of the patients with EE will present a benign course of their disease with only few recurrences. However, natural history of EE could be more complex with frequent relapses or chronic continuous course requiring maintenance therapy with corticosteroids or immunosuppressants.

Compliance with Ethical Standards

Conflict of Interest Guillaume Pineton de Chambrun reports personal fees from MSD, Abbvie, Takeda, Ferring Pharmaceuticals, and Hospira as a lecturer and consultant, outside the submitted work.

Gaspard Dufour, Barbara Tassy, Benjamin Rivière, Najima Bouta, Michael Bismuth, Fabrizio Panaro, Natalie Funakoshi, Jeanne Ramos, Jean-Christophe Valats, and Pierre Blanc declare 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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