Eosinophilic Colitis: clinical review and update 2020

Journal: Minerva Gastroenterologica e Dietologica
Paper code: Minerva Gastroenterol Dietol-2656
Submission date: December 4, 2019
Article type: Review Article

Files:

1. Manuscript
   Version: 1
   Description: Manoscritto originale
   File format: application/msword

2. Figures 1
   Version: 1
   Description: Figura 1
   File format: application/pdf
Eosinophilic Colitis: clinical review and update 2020

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Abstract

Eosinophilic colitis (EC) is a rare inflammatory disease included in the chapter of eosinophilic gastrointestinal disorders (EGIDs), diagnosed by the presence of primary eosinophilic infiltrate in the colon wall in symptomatic patients. While the aetiology of primary colonic eosinophilia is unknown, several conditions are involved in the pathogenesis of secondary eosinophilic colonic infiltrate (food allergens, parasitic infections, drugs), which have to be excluded in order to correctly diagnose the primary form of the disease. Up to now, EC is lacking of codified guidelines regarding diagnostic criteria (especially eosinophil threshold values) and treatment, thus a correct approach to EC remains very challenging. Imaging, laboratory tests and endoscopy might be helpful in ruling out other mimic conditions, but EC is still a diagnosis of exclusion. Several treatment options are feasible, but most of the evidences are drawn from case reports and small case series, thus limiting their value. We carried out a review of the current literature to evaluate the more appropriate and modern clinical strategy for diagnosis and management of EC.
Introduction

Eosinophilic colitis (EC) is a rare inflammatory disease, included in the chapter of eosinophilic gastrointestinal disorders (EGIDs), and characterized by a high eosinophilic infiltrate in the colonic wall, with unknown causes.\textsuperscript{1,2,48,56} The definition of EC is still disputed. On the basis of the recent international literature, the term “eosinophilic colitis” should be reserved to symptomatic patients, whereas asymptomatic patients with a significant increase in colonic eosinophils should receive a diagnosis of “primary colonic eosinophilia” (PCE).\textsuperscript{3} Nevertheless, PCE remains a poorly characterized condition, even less than EC itself, that pathologists may consider when “greater than normal” numbers of eosinophils are found in colonic mucosa.\textsuperscript{2} For EC, there are no clear threshold values for eosinophils at this moment; matter of fact, even the normal number of eosinophils in colonic mucosa has not been clearly defined yet.\textsuperscript{34}

In this narrative review we report the updated evidence from literature, so to deeply examine etiology, pathophysiology, diagnostic criteria and therapeutic strategies of this condition.

Epidemiology

Primary eosinophilic colitis is considered to be a rare disease. Since there are no standardized diagnostic criteria, it is unclear the real frequency in the general population.\textsuperscript{1,5} A US database review performed on about 35 million people reported a prevalence of 2,1/100,000 persons. EC seems to be more common in adults (2,3/100 000) than in children (1,6/100 000) with a slightly higher ratio in women and in caucasian individuals.\textsuperscript{5} Other studies seem to show a bimodal age distribution, firstly in neonates and secondly in adulthood.\textsuperscript{6,7} It is known that EC, such as other EGIDs, is more common in urban and suburban areas versus rural areas and in patients with a higher level of education.\textsuperscript{8} It has been shown that EC is associated with a wide spectrum of allergic disorders, such as drug allergy, rhinitis, asthma, sinusitis, dermatitis, food allergy, eczema, and urticaria.\textsuperscript{5}
**Pathophysiology**

Today all the physiologic functions of eosinophils are still not completely known,\textsuperscript{10} making the pathogenesis of EC poorly understood.\textsuperscript{4} Eosinophils are by far more common in tissue than in blood and in the GI tract usually reside in the lamina propria of the small intestine, except the squamous epithelium of the esophagus.\textsuperscript{11} They are involved in several functions, especially in protection against bacterial and parasites, regulation of the intestinal microbiome and tissue homeostasis. Eosinophils are activated by several stimuli including allergens, bacterial and parasites infections and they are regulated by variety of cytokines, such as interleukin (IL)-5, IL-13, IL-4 and tumor necrosis factor (TNF), mostly produced by activated Th2 T-lymphocytes and mast cells.\textsuperscript{12,13} Once activated, eosinophils release cytotoxic proteins, Leukotriene C4 (LTC4) and several other cytokines that modulate the immune system by activating dendritic cells, inducing immunoglobulin (Ig)A-class switching in B cells and promoting their survival.\textsuperscript{10} It is general thought that several factors such as genetic predisposition, dysbiosis, and the environment (i.e. allergens) play a pivotal role in EGIDs, but the clear understanding of their relationship is still unknown.\textsuperscript{4} EC pathophysiology is related to age of onset: in infants, it seems to be an IgE-associated disorder since it has been reported in association with breast-feeding protein hydrolysate formula-feeding. Instead, in adults it is more likely due to a Th2 T-lymphocyte driven response.\textsuperscript{1} Studies have found association with autoimmune disorders such as inflammatory bowel diseases (IBD),\textsuperscript{14} celiac disease,\textsuperscript{15} rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and inflammatory myositis.\textsuperscript{16,17} This suggest a possible role of allergen-related immune dysregulation.\textsuperscript{18}

**Clinical features**

The clinical presentation of EC is heterogeneous and usually non-specific. An acute presentation is more common in infants as a self-limited bloody diarrhea, whereas the chronic presentation is more
common in adults and it is usually associated with abdominal pain and/or chronic watery diarrhea.\textsuperscript{1} Several other symptoms are commonly associated with EC, such as heartburn, dysphagia, nausea and vomiting, abdominal pain, unjustified weight loss, ascites, volvulus/intussusception, GI perforation, obstruction or haemorrhage.\textsuperscript{5} Since EC is frequently associated with history of atopy, other symptoms or diseases might be present, including asthma, food sensitivities, rhinitis or eczema.\textsuperscript{21, 22}

The eosinophilic infiltration can be located in various layers and depth of bowel wall. Three patterns have been described, that can be simultaneously present in the same patient.\textsuperscript{19} Mucosal disease (Type 1) is the most common and is usually associated with diarrhea, bleeding (which can lead to iron-deficiency anaemia) and protein losing enteropathy. Transmural disease (Type 2), much rarer, in which the eosinophilic infiltrations is widespread along the wall and usually associated with wall thickening and/or strictures that can lead to GI obstructions, volvulus and perforations.\textsuperscript{21} Subserosal disease (Type 3) is limited to external part of the bowel wall and is usually associated with eosinophilic ascites and/or bloating.\textsuperscript{26}

Type 1 EC clinical course is typically continuous, defined by chronic persistent GI symptoms for more than 6 months, without period of remission. Type 2 EC is associated with recurring course, defined by at least 2 flares of the disease, separated by a period without digestive symptoms. Type 3 EC is the most benign since it is usually associated to a single flare, defined by clinical symptoms present for <6 months associated with the absence of any relapse after initial flare.\textsuperscript{23} EC in infants is mostly benign, since it is widely associated with food-related allergy and the elimination of the allergen is enough to resolve the disease within few days. In adolescent or older onset, the course tends to be more aggressive and requires more advanced medical management.\textsuperscript{1}
**Diagnosis**

Since EC is part of EGIDs, diagnosis of EC should match the same criteria, namely: (1) presence of GI symptoms; (2) histologic evidence of eosinophilic infiltration; and (3) ruling out other causes of tissue eosinophilia (Secondary EC).\(^\text{23}\)

Laboratory findings might be helpful to suspect EC along the clinic, but typically they are not adequate for EC diagnosis alone. Peripheral eosinophilia (defined as an absolute count of > 500 eosinophils/µL) can be present up to 80% of patients.\(^\text{24}\) Moreover, Type 3 EC is more frequently associated to hypereosinophilia and is also considered as risk factor for frequent relapse phenotype.\(^\text{22}\) As in EGIDs, an increase in serum IgE is common in about 75% of cases.\(^\text{25}\) Since EC has a strong correlation with IgE-mediated pathological responses, allergic skin testing (AST) and radioallergosorbent tests (RAST) might be useful in allergic-EC forms (both ingested or inhaled allergens), although AST shows a high false-positive rate (i.e. low specificity) and low sensitivity.\(^\text{1}\)

Non-IgE Th2 dependent allergy tests (skin patch) might be more useful in adolescent and adults, although show similar limitations as RAST and AST.\(^\text{42}\) Faecal calprotectin is a reliable non-invasive tool to assess intestinal inflammation,\(^\text{37}\) but has shown no help in diagnosing EC since its value is usually within the normal limit range.\(^\text{38}\) This might be related specifically to the inflammatory infiltrate type, poor in neutrophils, whose cytosol contains calprotectin.\(^\text{39, 40}\)

Radiology and imaging studies might be helpful, although findings are usually not specific both in children and adults. EC radiological findings are nodularity of the wall, colonic wall thickening (usually circumferential and located from ascending to the descending colon), “halo sign” (due to layering of the bowel wall) and “araneid-limb-like”. This latter sign is usually located in ascending and transverse colon and it is due to contrast enhancement of mucosal sinuses in the longitudinal section of the bowel on computed tomography (CT) scans, enlarged from mucosal thickening.\(^\text{32, 43}\)
Endoscopic appearance of EC is variable and, in most cases, similarly to microscopic colitis shows normal mucosa; several non-specific endoscopic findings might be present, such as erythematous patchy mucosa, ulcers, polyps and pseudo-polyps. Histology is considered the gold-standard, but the clear cut-off for normal eosinophilic counts are not yet defined as well as for other EGIDs such as eosinophilic esophagitis. Because eosinophils are normally present in colonic mucosa of both children and adults and their number depends of several factors, such as age, region, climate, alimentary diet, drugs use and so on. Several studies have tried to address valid cut-offs, and the latest evidence shows that reasonable cut-off might be >50/high-power field (HPF) in right colon, >35/HPF in the transverse colon and > 25/HPF in the left colon. EC is diagnosed with sheets or clusters of eosinophils located in the lamina propria with minimal acute and chronic inflammation. These clusters may show cryptitis degranulation and/or crypt abscesses and might be found also in muscularis mucosa, submucosa or both. Since the patchy distribution nature of the disease, multiple endoscopic biopsies are required but, unfortunately, there are no formal guidelines for histological diagnosis. Some authors suggest to take at least 5-6 biopsies from both abnormal and normal endoscopic mucosa in terminal ileum and in each colonic segment. Surgical biopsies should be considered the best option, since they provide a full thickness sample, in order to fully discriminates between the three types of EC, but this is a more invasive procedure, limited to selected cases.

Once colonic eosinophilic infiltration has been confirmed, it is important to rule out secondary conditions that lead to hypereosinophilia in order to establish a correct diagnosis. The differential diagnosis is wide and includes conditions like parasitic infections (i.e. Strongyloides stercoralis, Schistosoma spp, Trichuris trichiura, Angiostrongylus costaricensis, Gnathostoma spp, Ascaris lumbricoides, Ancylostoma caninum, Ascaris suum, Enterobius vermicularis and Dientamoeba fragilis), drugs (i.e. non-steroidal anti-inflammatory drugs, antiplatelet agents, carbamazepine, clozapine, rifampicin, tacrolimus, enalapril, gemfibrozil, therapeutic gold compound and
estroprogestinic agents), vasculitis (i.e. Churg-Strauss syndrome, polyarteritis nodosa), connective
tissue diseases (i.e. scleroderma, dermatomyositis, and polymyositis), IBD, celiac disease,
myeloproliferative disorders (i.e. hypereosinophilic syndrome) and malignancies (chronic
eosinophilic leukaemia, systemic mastocytosis, malignant lymphoma; GI adenocarcinomas might
occasionally show a brisk eosinophilic response and EC might be associated with graft-vs-host
disease in bone marrow transplanted patients). 41
A resume of the diagnostic workflow is represented in figure 1.

Treatment
Since EC is a rare disease, actually there are no strong evidence on available treatments. In fact,
most of the evidence are drawn from small uncontrolled case series and case reports. 4 In general,
EC tends to be more aggressive in adolescent and adults, while in infants is rather more benign and
usually resolves within days after removing the food-allergen implicated. 1
Food-eliminating diet (i.e. removal of milk, wheat, soy, eggs, nuts, and shellfish) is considered the
first-line non-pharmacological therapy in EGIDs, 32 but its role seems to be really effective only in
children with EC, 44 whereas there is no clear evidence in adults. 26 Furthermore, the usefulness of
diet is limited by the poor compliance in older children and adults. 4
The use of corticosteroids is considered the first-line pharmacological therapy if dietary approach is
impractical or failed to achieve a valid response. 32 Their beneficial effects are related to their ability
to inhibit eosinophil growth factors (i.e. IL-3, IL-5 and Granulocyte-macrophage colony-stimulating
factor - GM-CSF). 33 There are no randomized controlled trials to date on the efficacy of steroids in
EC. Oral prednisone (20–40 mg per day) for 2 weeks has been shown to induce clinical remission in
most patients, 45 however some reports suggested even the need of higher doses (0.5–1 mg/kg). 32
Maintenance treatment might be required in patients in whom EC relapses during/after drug
tapering and low dose systemic corticosteroids are often used (5-10 mg prednisone per day, or the
minimum dose effective in maintaining clinical response), although possible undesirable long-term side-effects are always to be considered. Budesonide might be a reasonable alternative, thanks to its low biodisponibility (3-9 mg per day).

Steroid-spare agents are also a good choice in patients who requires maintenance therapy or fails to respond to corticosteroids. Mesalazine has been used in some cases. Immunomodulatory agents such as azathioprine/6-mercaptopurine or anti-TNF agents (i.e. infliximab, adalimumab) have been tried in severe, steroid-refractory or steroid-dependent EC with good results. Other options might include mast-cell stabilisers (i.e. sodium cromoglycate and ketotifen), and the leukotriene receptor antagonist (montelukast), although their role in EC has yet to be evaluated.

A novel antibody directed against C-C chemokine receptor type 3 (CCR3), an eotaxin receptor expressed by eosinophils that facilitates their recruitment to sites of inflammation, has been shown to decrease eosinophilic inflammation and diarrhea in a mouse model of eosinophilic gastroenteritis. Since human body harbors between 10 trillion and 100 trillion microbial cells (called microbiota), which is approximately equal to 10 times the total number of body cells, and considering that the major part is located in GI tract, it is logical to try to cure colonic diseases acting on microbiota and to hypothesize its potential role in several extraintestinal diseases mediated by an impaired permeability. Faecal microbiota transplantation has proven efficacy in the treatment of inflammatory diseases of the gut. It has been reported that this treatment, in addition to oral corticosteroids, successfully cured a patient with severe refractory eosinophilic enterocolitis. However, it is unclear whether faecal microbiota transplantation could cure definitively EC and maintain the long-term clinical remission without the use of corticosteroids.

Surgery, performed as segmental colonic resection (without clear evidence if prefer primary anastomosis rather than diversion) should be limited to patients with complications of intestinal inflammation, such as strictures, bowel obstruction or perforation. Nevertheless, even in the
setting of an acute abdomen, symptoms might respond to conservative management with immunosuppression.\textsuperscript{32, 50}

**Conclusions**

EC is a rare disease, which still lacks the correct understanding of its pathophysiology and structured guidelines for diagnosis (especially clear cut-off values) and treatment. Unfortunately, there are very few studies which address these needs up to now. Therefore, several larger case-control and cohort studies are required to meet this necessity.

**References**


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Figure 1. Diagnostic flow chart for the diagnosis of eosinophilic colitis.