Eosinophilic colitis: an update on pathophysiology and treatment

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Background: Primary eosinophilic gastrointestinal disorders, a spectrum of inflammatory conditions, occurs when eosinophils selectively infiltrate the gut in the absence of known causes for such tissue eosinophilia. These may be classified into eosinophilic esophagitis, eosinophilic gastroenteritis and eosinophilic colitis (EC). This review focuses on EC: its pathogenesis, epidemiology, clinical presentation, diagnosis and current approach to treatment.

Sources of data: A literature review published in English was performed using Pubmed, Ovid, Google scholar search engines with the following keywords: eosinophilic gastrointestinal disorder, EC, eosinophils, colitis and gastrointestinal.

Areas of agreement: The basis for primary EC appears related to increased sensitivity to allergens, principally as a food allergy in infants and a T lymphocyte-mediated event in adults. Endoscopic changes are generally modest, featuring edema and patchy granularity.

Areas of controversy: Clear clinical and pathological diagnostic criteria of EC and its management strategy.

Growing points: Intestinal involvement of EC is primarily mucosal, presenting as a mild self-limited proctitis in infants and self-limited colitis in young adults. Therapeutic approaches based on case reports tend to use either elimination diets to avoid a presumed allergen; agents traditionally used in inflammatory disease or targeted drugs like anti-histamines or leukotriene receptor antagonists.

Areas timely for developing research: Prospective randomized controlled trials addressing the disease natural history, possible preventive methods and effective medical approach and long-term prognosis are required.

Keywords: eosinophilic gastrointestinal disorder/eosinophilic colitis/eosinophils/colitis/gastrointestinal
Eosinophils are bilobed granulocytes that stain brick red when stained with eosin. They are less commonly termed acidophils (i.e. ‘acid-loving’). These white blood cells arise from pluripotent stem cells in the bone marrow under the influence of cytokines like interleukin (IL)-5 along with IL-3 and the granulocyte-macrophage colony-stimulating factor (GM-CSF). IL-5 is the most specific to the eosinophil lineage; it causes selective expansion and bone marrow release of eosinophils. Eosinophils reside in the bone marrow and spend about 8 days while undergoing maturation.

They then relocate into the peripheral circulation where they constitute 1–3% of the granulocyte pool with an absolute eosinophil count of <350 per μl. Following a brief half-life of 8–12 h, eosinophils traffic to specific tissues, particularly the gastrointestinal tract, where they reside for at least a week. Here they are found in the submucosa throughout the gastrointestinal tract except for the esophagus that normally is devoid of eosinophils. Their location in the intestines allows ready access for these white blood cells to combat multicellular parasites, likely an evolutionary survival tool.

Translocation from blood to tissue entails adhesion and diapedesis. The chemokine (termed CC) family (eotaxin-1, -2 and -3) are highly specific, binding the CCR-3 receptor that is strongly expressed on eosinophils. Indeed, eotaxins are important in regulating eosinophil levels in the gut. Eosinophils harbor an array of cytotoxins whose release (by degranulation) and activation yield a host defense against helminthic infestations. They also produce tissue damage in inflammatory and allergic diseases. Their large specific granules, for example, contain cationic proteins: major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophilic derived neurotoxin (EDN) and eosinophilic peroxidase (EPO). The result is lysosomal, oxidative and cytotoxic damage: acting on extracellular targets like parasites and yielding inflammatory mediators. Eosinophils thus acutely produce cytokines, leukotrienes and lipid mediators of inflammation; they also trigger the release of histamine from basophils and mast cells. The result can be a hypersensitivity reaction. Furthermore, eosinophils may contribute to chronic inflammation and fibrosis. Thus, eosinophil function can be beneficial (killing parasites and viruses) or detrimental (causing chronic inflammation like asthma). IL-5 may be a particularly important mechanism by supporting the terminal differentiation and proliferation of eosinophil precursors while maintaining the viability of mature eosinophils. Its over production, at least in transgenic mouse models, results in profound eosinophilia, whereas IL-5 gene deletion markedly reduces
eosinophils infiltrating several organs including the gastrointestinal tract after allergen challenge.\textsuperscript{4–7}

Thus the pathogenesis of eosinophilic colitis (EC) appears based on genetic factors but is elicited by environmental exposure, acting through adaptive T-cell immunity that involves IL expression and the chemokine, eotaxin. Whether gut eosinophilic disorders are IgE or non-IgE mediated is unclear. Some reports suggest that IgE is responsible for mast cells accumulating in the colonic interstitium.\textsuperscript{8} Other studies point to a non-IgE-mediated process: a Th2-mediated intestinal allergic disorder involving CD4(+) Th2 lymphocytes.

### Classification of primary eosinophilic gastrointestinal disorders

Eosinophilia, often construed as an increase in circulating eosinophils, is a common accompaniment of hematological malignancies (e.g. leukemia), invasive parasites, medications, toxins, neoplasms, atopy (eczema, allergic rhinitis and asthma), other hypersensitivity disorders and eosinophilic syndromes. An excess of eosinophils in general can result from increased bone marrow production (eosinophilopoiesis) accompanied by their subsequent appearance in the peripheral circulation, and in certain instances, their accumulating in specific tissues. Blood eosinophilia (peripheral eosinophilia with an eosinophil count >600/\textmu l), however, is not necessarily associated with tissue eosinophilia. Eosinophilic infiltration of specific organs frequently is associated with inflammation: pulmonary, cutaneous, renal, cardiac, transplant rejection and gastrointestinal diseases. In eosinophilic gastrointestinal disorders (EGID), eosinophils infiltrate various sites along the gastrointestinal tract to a variable depth.

The clinical presentation of EGID depends upon the segment of the gastrointestinal tract affected, the depth to which the eosinophils infiltrate the wall and the local tissue response.\textsuperscript{9} This family of EGID may be categorized as eosinophilic esophagitis, eosinophilic gastroenteritis and EC. Some overlap exists particularly in the pediatric aged group, concerning the extent of gut involvement tract distal to the esophagus.\textsuperscript{10} Gut eosinophilia likely represents an even greater spectrum, extending from entities that are predominantly IgE-mediated (such as food anaphylaxis), through the primary EGID to those that are not IgE-mediated (like some inflammatory bowel diseases and celiac disease). Moreover, EGID frequently occurs independent of peripheral blood eosinophilia, the best examples being eosinophilic esophagitis and EC. This concept separates the pathobiology of EGID from
classical blood eosinophilic states like the hypereosinophilic syndrome (HES). In HES, the primary end-organs affected are the heart and skin, while the gut appears to be a rather innocent bystander, being merely infiltrated without exhibiting marked dysfunction.

Epidemiology of EGID

The esophagus normally lacks resident eosinophils but can attract these inflammatory cells, the best example being gastroesophageal reflux disease and sometimes as part of an allergic reaction often food-related. Primary eosinophilic esophagitis is likely not an IgE-mediated disease but rather represents a distinct condition that manifests as dysphagia often with food bolus impaction and retrosternal chest pain. Eosinophilic esophagitis now well-recognized entity occurs in ∼1% of the population. The markedly increase in its incidence is only partially due to heightened disease awareness as the disease prevalence has increased with time in geographically defined populations. Eosinophilic esophagitis is diagnosed by esophageal biopsies showing an increased number of eosinophils (>15/high powered field) although consensus guidelines are unclear as to the need to eliminate gastroesophageal reflux disease, the variability of esophageal biopsy numbers and sites, and the variability of histological interpretation. A history of atopy and food, drug and environmental allergies, plus a mild peripheral eosinophilia, all suggest eosinophilic esophagitis. Its cause also may have a genetic component because of a family history in some (10%) and evidence of food and aeroallergen hypersensitivity in many. Only a few have a history of true food anaphylaxis.

Eosinophilic gastroenteritis seems to be an inaccurate subclassification, as eosinophils can involve the whole gastrointestinal system including the biliary system in EGID. In eosinophilic gastroenteritis, extensive infiltration of the stomach occurs in 26–81% while the small intestine is involved in 28–100%. These broad ranges may reflect bias from the overall limited numbers of patients who have been reported. There also may be concurrent, though less prominent, involvement of the esophagus or colon/rectum. Here too, atopy and/or food hypersensitivities (delayed type) are evident in half of the patients, particularly in children who exhibit an elevated serum IgE.

EC is the rarest EGID entity with a paucity of cases being reported in the last three decades. Nonetheless, there has been an exponential rise in EC recognition, yielding 196 cases reported over the past decade (Fig. 1). EC can present primarily as a separate entity or can be a secondary manifestation of other disease affecting the gut. The diagnosis
Food allergy and etiology of EC

‘Atopy’, a genetic predisposition to any excessive IgE-mediated reaction, causes eczema, allergic rhinitis (hay fever) and/or asthma. Food allergy is part of this atopic syndrome and represents an adverse immune response towards certain food proteins.\(^\text{19}\) Food hypersensitivity disorders are best classified into three broad types: IgE-mediated, cell-mediated and mixed disorders. Each category has its unique spectrum of clinical features. IgE-mediated food allergies typically have a rapid onset following ingestion of specific foods and can affect multiple organ systems, yielding dermatological and respiratory reactions like urticaria, laryngospasm and an acute asthmatic attack. Such immediate hypersensitivity transpires when food-specific
IgE antibodies residing on mast cells and basophils come in contact with and bind to circulating food allergens. This then activates these inflammatory cells, releasing potent mediators and cytokines. In contrast, non-IgE-mediated food allergies present as more delayed hypersensitivity reactions, featuring more subacute or chronic symptoms that most commonly target the gastrointestinal tract. The precise etiology of primary EC is however unclear. Certainly, there is a genetic component: 16% with EGID have family members with a similar disorder. Further, an allergic component likely exists in EGID: 80% have a coexistent atopic disease while 62% experience specific food sensitivities.

**Eosinophilic proctocolitis of infancy**

Eosinophilic proctocolitis of infancy occurs in infants either being breast-fed or receiving a protein hydrolysate formula. Thus, the bloody diarrhea in infants with EC likely represents an allergic colitis, hence the term, ‘dietary protein-induced proctocolitis of infancy syndrome’. Evidence for mast cell accumulation and degranulation in colonic tissue supports a role for IgE. Some studies however suggest that circulating lymphocytes, sensitive to the food antigens, produce the clinical symptoms in infants with this food protein hypersensitivity. Although an allergen-free diet represents one therapeutic strategy for EGID, this is only occasionally successful. Adults with EC likely differ: food-related anaphylaxis is uncommon. Their disease more likely is non-IgE-mediated, but rather acts through a CD4 (+) Th2 lymphocyte-mediated mechanism.

**Clinical presentation and diagnosis of EC**

EC has a bimodal age distribution affecting infants and young adults, each with somewhat different clinical presentations. Its characteristic intense eosinophilic infiltration can involve specific segments of the colon or can be pan-colonic. There are no distinct clinical presentations that differentiate isolated colonic disease from more diffuse involvement that also affects the stomach and/or small intestine. Different clinical manifestations of EC depend mainly on the colonic layer(s) most affected by the eosinophilic infiltration. Mucosa predominant EC, the most common form, is associated with mucosal injury and presents with malabsorption, diarrhea and protein losing enteropathy. Transmural disease, reported to a lesser extent, presents more dramatically with colonic wall thickening and features of acute intestinal...
obstruction (intussusception or cecal volvulus) or even perforation.\textsuperscript{27} Serosal disease, an exceedingly rare form, presents with ascites in which eosinophils are the predominant cell type in up to 95\% of cases (Table 2).\textsuperscript{28,29}

Several conditions can prompt eosinophils to infiltrate the colon. Important secondary causes include parasitic helminthic infections (\textit{trichuris trichiura}, \textit{enterobius vermicularis} and \textit{strongyloides stercoralis})\textsuperscript{30–33} and drugs like clozapine,\textsuperscript{29} carbamazepine,\textsuperscript{27} rifampicin, gold,\textsuperscript{34,35} naproxen\textsuperscript{36,37} and calcineurin inhibitor (e.g. Tacrolimus) use in solid organ transplant recipients.\textsuperscript{38} Other secondary associations include autoimmune disease (e.g. scleroderma, Churg-Strauss syndrome), Tolosa-Hunt syndrome\textsuperscript{39} and as part of the HES (Table 3).

Allergic skin testing has its limitations in eosinophilic disorders as these lack sensitivity and specificity. A negative skin prick test (SPT) is quite useful for excluding an IgE-mediated food allergy; a negative SPT has value in conjunction with clinical presentations and laboratory findings for infants with eosinophilic proctocolitis in whom IgE is presumably important for disease activity. Conversely, a positive test response cannot ensure diagnosis but merely confirms some evidence for a food-induced allergy in the appropriate clinical setting with a clear history.

Endoscopic changes are rather modest and not characteristic, sometimes evident as patchy erythematous changes, loss of vascular pattern and superficial ulceration. In other cases the mucosa appears quite normal (Fig. 2). Essential is a biopsy diagnosis to demonstrate eosinophilic involvement of the colon. Biopsies will typically reveal sheets of eosinophils infiltrating the lamina propria, often with extension through the muscularis mucosa into the submucosa and occasionally into the muscularis propria. Crypt abscesses and lymphonodular hyperplasia also may be evident (Fig. 3).\textsuperscript{17,21,22,26,40} Diagnosis depends upon detecting a dense eosinophilic infiltration in one or more segments of the colon. Multiple biopsies are necessary. Not only is the distribution patchy in EC but also the eosinophil count normally has a broad range in different segments of the colon, exhibiting a proximal-to-distal

\begin{table}[h]
\centering
\caption{Possible clinical presentations of EC.}
\begin{tabular}{|l|}
\hline
Abdominal pain \\
Weight loss \\
Malabsorption \\
Bloody and non-bloody diarrhea \\
Peripheral eosinophilia \\
Eosinophilic ascites \\
Intestinal obstruction (volvulus, intussusceptions) \\
Protein losing enteropathy \\
Colonic thickening and perforation \\
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Eosinophilic proctocolitis (milk-protein proctocolitis)

Eosinophilic proctocolitis (milk-protein proctocolitis) is an entity that has been described classically in infants associated with ingestion of soy protein and cow’s milk.\textsuperscript{46,47} It too has a bimodal age distribution: an infantile form presenting at 2 months and an adolescent form mimicking ulcerative colitis.\textsuperscript{48} Infants typically have normal to soft stools with blood-streaks that arises during the first 2–3 months of age. The onset of bleeding is initially erratic over several days, and then wanes to occasional streaks of blood. In some, bloody diarrhea is pronounced and may lead to anemia. The infants otherwise are quite healthy and the colitis tends to be self-limiting. The abdominal examination is usually normal. Fecal smear may show an increased polymorphonuclear cell count. Sigmoidoscopy may reveal modest inflammatory changes with focal erythema and friability. Mucosal biopsies are definitive, revealing a dense eosinophilic infiltration of the lamina propria,

Table 3 Classification of EGID.

<table>
<thead>
<tr>
<th>Primary EGID</th>
<th>Secondary gut eosinophilia</th>
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<tbody>
<tr>
<td>Eosinophilic esophagitis</td>
<td>Reflux esophagitis</td>
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<tr>
<td>Primary eosinophilic gastroenteritis</td>
<td>Infections:</td>
</tr>
<tr>
<td></td>
<td>• Protozoal and other pathogens</td>
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<tr>
<td></td>
<td>Drugs: (e.g.: naproxen, clozapine, rifampicin, enalpril, carbamizpine, gold, interferons tacrolimus)</td>
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<tr>
<td>Primary EC</td>
<td>Systemic disease:</td>
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<tr>
<td></td>
<td>• HES</td>
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<td></td>
<td>• Connective tissue disease/vasculitis</td>
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<td></td>
<td>• Graft-versus-host disease</td>
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<td></td>
<td>• Gastroesophageal reflux disease</td>
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<td>• Helicobacter pylori gastritis</td>
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<td>• Celiac disease</td>
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<td></td>
<td>• Inflammatory bowel disease</td>
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<td>• Neoplasia</td>
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<td>• Transplantation</td>
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<td>Food hypersensitivity/allergy</td>
<td>Iatrogenic</td>
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<td></td>
<td>• IgE-mediated</td>
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<td>• non-IgE</td>
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<td>Food protein induced proctocolitis of infancy</td>
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distribution: cecum 35 eosinophils per high power field to the rectum 8–10 per high power field.\textsuperscript{15,41–45}
and/or even the muscularis; such rectosigmoid involvement can be diffuse or focal. Enlarged lymphoid nodules, associated with transmural eosinophilic infiltration of the colon is best visualized by cross sectional imaging.

**Treatment of EC**

Elimination, oligoantigenic and elemental (amino-acid based) diets can provide symptomatic relief in many patients with EC, particularly infants with proctitis.40,47 This strategy seeks to either eliminate certain food allergens that precipitate flares of EC or use a purely elemental diet containing simplified ingredients that are readily assimilated.
without further digestion (amino acids, hydrolyzed fats and carbohydrates). Such a diet can be effective in some instances but its poor palatability commonly diminishes compliance. Such a regimen is more effective in young children under 3 years as food hypersensitivity generally affect up to 6% of all infants. Fortunately, clinical tolerance develops in about 80% by 5 years of age. A major advantage of an elimination diet is its steroid-sparing use, preventing the potential adverse effect of growth retardation in these children. Diet elimination is less effective for adolescents and older adults as IgE-associated triggers are rarely identified. In more severe cases, medical therapy becomes clinically warranted.

Limited information is available concerning any benefit from medical therapies; EC is quite rare, precluding randomized clinical trials. Glucocorticoids therapy has been tried on the basis of case reports and medical experience. The presumed benefit of steroids is through inhibition of certain eosinophil growth factors such as IL-3, IL-5 and GM-CSF. Steroid regimens used in EC mimic those employed in inflammatory bowel disease with an induction dose of 40–60 mg/kg of prednisolone per day for 2 months followed by tapering over 6–8 weeks. Maintenance corticosteroids at lower doses have been used in more relapsing, chronic disease. Budesonide, a locally targeted steroid therapy, at 6 mg/day PO can induce and maintain remission for up to 2 years. The steroid agent with high first-pass hepatic clearance has a reduced influence on the hypothalamic–pituitary–adrenal axis and so produces fewer adverse side-effects and lesser bone density losses, compared with classical corticosteroids.

Immunomodulatory agents like azathioprine or 6-mercaptopurine down regulate or inhibit eosinophil growth factors, reducing...
Eosinophilic infiltration and improving symptoms. They are worth trying in severe, refractory or steroid-dependent EC. A combination of glucocorticosteroids and azathioprine decreases the tissue eosinophilia and improves the diarrhea, at least in eosinophilic gastroenteritis.

Montelukast (Singulair®) selectively blocks the action of leukotriene D4 (LTD4) on the cysteinyl leukotriene receptor (Cys-LT1), thus abrogating the recruitment and chemo-attraction of eosinophils to the gastrointestinal tract. Montelukast at 10–40 mg for several months can successfully maintain clinical remission in steroid-dependant patients with eosinophilic gastroenteritis, yielding a safe and effective steroid-sparing therapy. Its role has yet to be evaluated in EC, particularly in terms of any steroid-sparing benefit.

Ketotifen, a second-generation H1-antihistamine, works as a mast cell stabilizer and thereby prevents the release of histamine. It is a safe, effective alternative to traditional systemic steroids in eosinophilic gastritis (EG). Sodium cromoglycate, another mast cell stabilizer, alone or when combined with ketotifen, shows promise as induction and maintenance therapy for patients with EGID with no reports so far about its effectiveness in treating EC patients.

Novel approaches to EGID are focusing on biological agents like humanized monoclonal antibodies developed against targeted inflammatory mediators. Omalizumab, a recombinant, DNA-derived, humanized IgG1k monoclonal antibody, when given every 2 weeks for up to 8 weeks, reduces absolute eosinophil count after 3–4 months of therapy and provides symptomatic improvement in EGID. Mepolizumab, a humanized monoclonal antibody directed against IL-5 at 750 mg IV every 2 weeks for 16 weeks significantly reduces tissue eosinophils in eosinophilic esophagitis.

Prognosis for EC

The EC that develops in infancy carries a good prognosis. It tends to spontaneously resolve, often within days. After a few years these young children can even tolerate the implicated foods. In contrast, young adults with EC tend to have more chronic presentation with periods of modest activity and periods of apparent remission.

Summary

Primary EC, an emerging though uncommon disorder within the category of EGID, is becoming better defined over the past decade. Its pathophysiology, clinical features and natural history differ according
to the age of presentation: being rather mild, self-limited and more food-related in infants, but a modest chronic disease in young adults. The mode of presentation, especially in adults, depends on the colonic layer being predominantly infiltrated with eosinophils. Diagnosing primary EC is based on multiple colonic biopsies, a situation that is especially challenging in the absence of diagnostic criteria and requires careful elimination of secondary causes. Therapeutic approaches towards EC are based on case reports and small case series. Randomized controlled trials are needed to establish the best therapeutic approach. Prognosis is determined by the age of onset with a good prognosis in infancy and a somewhat more chronic relapsing and remitting course in adults.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

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