

Eosinophils in Gastrointestinal Disorders

Eosinophilic Gastrointestinal Diseases, Celiac Disease, Inflammatory Bowel Diseases, and Parasitic Infections



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KEYWORDS

- Eosinophil • Esophagitis • Eosinophilic esophagitis • Eosinophilic gastritis
- Eosinophilic gastroenteritis • Eosinophilic colitis • Parasitic infection

KEY POINTS

- Eosinophilic gastrointestinal diseases (EGIDs) describe a group of diseases occurring in children and adults and are characterized by symptoms related to gastrointestinal (GI) dysfunction and inflammation consistent with increased intestinal eosinophilia.
- Eosinophilic esophagitis, the most common EGID, presents in children with feeding problems, abdominal pain, and symptoms recalcitrant to acid inhibition, and in adults with food impaction and dysphagia.
- Eosinophilic gastritis, gastroenteritis, and colitis are uncommon and present with abdominal pain, vomiting, diarrhea, and bleeding.
- The association of celiac disease with eosinophils in the small intestinal and esophageal mucosa is increasingly recognized and requires individualized assessment and treatment.
- The association of inflammatory bowel diseases (IBDs) with mucosal eosinophilia and its secreted products is increasing, but the role of eosinophils in the pathogenesis of IBD remains uncertain.
- Intestinal helminth infection can produce a clinical picture indistinguishable from eosinophilic gastroenteritis.

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INTRODUCTION

The gastrointestinal (GI) tract possesses the greatest surface area of any organ in the body and contains the largest number of immune cells and products. Functionally, the gut must maintain critical functions of nutrition absorption and of oral tolerance. How this latter process occurs in such a fine-tuned and regulated fashion remains an area of active investigation.

Over the past few decades, the identification of eosinophils in the GI tract has begun to arouse suspicion that they play a role in GI health and/or disease.^{1,2} In contrast to the neutrophil, which is typically absent in the healthy GI tract, eosinophils reside in varying quantities in the mucosa. During disease states, eosinophils increase and have been implicated in the pathogenesis of ongoing inflammatory processes (Table 1). These observations are typically limited to enumerating eosinophils in the epithelium or mucosal surface; the exact depth, distribution, and state of activation in these circumstances are still undergoing definition.

This article focuses on 4 diseases in which mucosal eosinophils are clearly associated, eosinophilic gastrointestinal diseases (EGIDs), celiac disease, inflammatory bowel diseases (IBDs), and parasitic infections. Here we will provide an overview of their clinical features and summarize the association of eosinophils with each inflammatory state.

EOSINOPHILIC GASTROINTESTINAL DISEASES

Eosinophilic Esophagitis

Epidemiology

Eosinophilic esophagitis (EoE) has been reported in all continents, except Africa, and consistently has been shown to occur more commonly in male individuals with a 3:1 ratio.^{3–6} Because this is an emerging disease, the exact incidence is difficult to predict, but estimates range from 1 to 4 in 10,000 in North America. There does not appear to be a clear predilection toward one ethnicity.

Risk factors

Recent studies and clinical experiences provide some insights into potential risk factors but these are difficult to identify completely because the exact pathogenesis is uncertain. A recent twin study revealed that if a sibling has EoE, there exists a risk of 2.4% of subsequent children developing EoE.⁷ A variety of EoE genes provides clues to dysfunction of the epithelial barrier (filaggrin),⁸ immune system (thymic stromal lymphopoietin, eotaxin-3)^{9–11} and other yet to be identified areas (calpain-14).^{12,13}

Pathophysiology

Within the epithelia, the prominence of eosinophils, interleukin (IL)-5–expressing T cells, B cells, and increased mast cells suggests an immunologically mediated Th2-type inflammatory disease.¹⁴ In further support, clinical characterization of children and adults reveals many highly atopic patients possess a Th2-type inflammatory profile. Basic studies in experimental models of EoE reveal that T-cell-deficient mice, but not B-cell-deficient mice, were protected from esophageal inflammation and esophageal inflammation induced by aero-allergens and food allergens, IL-13, and IL-5.^{15–20} Together, these clinical and basic studies provide strong support for allergy as a pathogenic etiology for EoE. In contrast, some patients do not exhibit the same degree of atopy and thus may indicate alternative mechanisms and EoE phenotypes.²¹

Pathologic remodeling represents the likely underlying mechanism of problematic EoE complications, such as esophageal stricture and food impaction.^{22–25} A number of basic and translational studies suggest a wide variety of mechanisms related to

Table 1
Gastrointestinal diseases associated with eosinophilia

Disease	Clinical Presentation	Laboratory Findings (Possible Findings)	Radiographic Findings (Possible Findings)	Histological Findings	Therapy
Eosinophilic esophagitis (EoE)	Poor growth, feeding difficulties, dysphagia, food impaction	Peripheral eosinophilia	Esophageal mucosal irregularity, narrowing or stricture, Schatzki rings	Mucosal eosinophilia >15 eos/HPF, lamina propria fibrosis	Dietary avoidance of allergens and/or topical steroid
Eosinophilic gastritis (EG)	Abdominal pain, vomiting, hematemesis	Peripheral eosinophilia, anemia	Thickened gastric mucosal folds, ulceration, partial obstruction	Mucosal eosinophilia >30 eos/HPF or twice normal value	Dietary avoidance of allergens, corticosteroids, immunosuppressive agents
Eosinophilic gastroenteritis (EGE)	Abdominal pain, diarrhea, protein-losing enteropathy	Peripheral eosinophilia, anemia, hypoalbuminemia	Small bowel mucosal thickening	Dense mucosal eosinophilia	Dietary avoidance of allergens, corticosteroids, immunosuppressive agents
Eosinophilic colitis	Abdominal pain, diarrhea, hematochezia, tenesmus	Peripheral eosinophilia, anemia, hypoalbuminemia	Colonic mucosal thickening	Mucosal eosinophilia >65 eos/HPF or twice normal value	Dietary avoidance of allergens, corticosteroids, immunosuppressive agents
Celiac disease	Abdominal pain, diarrhea, weight loss, bloating, extraintestinal manifestations	Peripheral eosinophilia	Small bowel mucosal thickening	Duodenal villous blunting, intraepithelial lymphocytes; esophageal eosinophilic infiltrate	Gluten-free diet; if esophageal eosinophilia, consider gluten-free diet plus PPI therapy; if esophageal eosinophilia persists despite treatment, consider treatment for EoE
Inflammatory bowel disease	Abdominal pain, diarrhea, weight loss, bloody stools	Peripheral eosinophilia, anemia, elevated inflammatory markers	Bowel wall thickening, abscesses, stricture formation	Mucosal eosinophilia may be present	Corticosteroids, antibiotics, aminosalicylates, immunomodulators surgery

Abbreviations: eos/HPF, eosinophils per high-power field; PPI, proton pump inhibitor.

altered permeability, fibrosis, epithelial mesenchymal transition, and dysmotility. Phospholamban, transforming growth factor- β , and other inflammatory mediators are involved, but their exact role in the pathogenesis of esophageal dysfunction, dysmotility, and fibrosis is uncertain.^{26–30}

Clinical features

The clinical presentation of EoE varies depending on the patient's abilities to report symptoms associated with esophageal dysfunction.^{4,31–35} For instance, young children often present with nonspecific symptoms, such as vomiting, abdominal pain, and feeding problems; whereas adolescents and adults report dysphagia, heartburn, retrosternal pain, or recurrent food impactions. Symptoms that are unresponsive to medical or surgical treatments for gastroesophageal reflux disease (GERD) should raise consideration for EoE. Alternatively, patients may develop coping strategies surrounding eating difficulties and it may be necessary to ask additional questions, such as, "Do you avoid foods like meats or breads? Do you need to use liquids, ketchup, or gravy to help your food go down? Are you the last one to leave the table? Do you chew your food for a long time?"³⁶

EoE in adolescents and adults presents with symptoms that can be intermittent or regular, severe or subtle. For instance, swallowing disturbances may be only noticeable when food's consistency is dry or textured, a large food bolus is ingested, or when patients eat too quickly. Alternatively, patients may note only rare and isolated instances of food impactions. EoE remains one of the most common causes of food impaction presenting to emergency rooms.^{37–41} Retrosternal pain can often be exacerbated by the ingestion of alcohol.³⁵

Physical examinations are usually normal except for manifestations of other atopic diseases that can occur in up to 75% of patients. Peripheral eosinophilia may or may not be present. Approximately 70% of patients have elevated total immunoglobulin (Ig) E levels. Esophagrams can be very helpful in examining luminal circumference, as esophageal narrowing may not be detected at the time of endoscopy.⁴² Contrast radiography can detect isolated or long-segment esophageal strictures or Schatzki rings. Histopathology is not pathognomonic and other causes of mucosal eosinophilia, such as GERD, should be ruled out before assigning the diagnosis of EoE.⁴³ The epithelial surface appears highly proliferative, as evidenced by basal cell hyperplasia, and contains not only eosinophils but also other leukocytes, including lymphocytes, mast cells, and basophils.

Association with eosinophilia

EoE is associated with eosinophilia in 2 circumstances. First, some patients may manifest peripheral eosinophilia, but this finding is nonspecific and may be related to associated atopic diseases. Second, the healthy esophageal mucosa, unlike the rest of the GI tract, is completely devoid of eosinophils. In the proper clinical context, the presence of eosinophils in the esophageal mucosa is highly suggestive of the diagnosis of EoE. Other causes of this inflammation need to be ruled out. Enumeration of eosinophils is problematic because of the limited sample size assessed with mucosal biopsies (2–3 mm per biopsy) that leads to uncertainty as to the extent of eosinophilia, state of eosinophil activation, and its impact on associated resident and recruited cells.⁴³ Future studies defining functional readouts, clinically meaningful outcome metrics, and histologic parameters that focus on histologic features other than eosinophil numbers are needed.

Acute and chronic management

Overview Although research studies continue to focus on both symptoms and histologic responses to treatments, debate still rages among clinicians who wonder

whether the focus of EoE treatment should be directed toward only a symptomatic response or if symptomatic and histologic response is necessary. It is the opinion of the authors that there are at least 3 good reasons to treat patients to clinical and histologic remission. First, treatment may enhance the quality of life because dysphagia, with its ongoing risk of food impaction, can have a marked negative and limiting impact on the patient's daily life.^{44–46} Second, treatment reduces the risk of severe esophageal injury by preventing long-lasting food impactions, an incident occurring at the time of esophageal contractions or secondary to stricture formation.⁴⁷ Third, treatment prevents esophageal damage caused by tissue remodeling due to unbridled eosinophilic inflammation.⁴⁸ Clinical experience, as well as a growing body of literature, supports the premise that treatment can impact the natural history, but future long-term studies will provide critical information to answer these treatment questions.

Acute Acute treatment relates to treatment of esophageal foreign body impaction. When this occurs, patients need to have emergent removal of the foreign body, most often a food product. Patients are taken to the operating room and provided airway protection for safe removal of the esophageal foreign body. Following removal, evaluations need to ensue to determine the reason for the impaction, such as ongoing inflammation or isolated or long-segment esophageal narrowing.

Chronic EoE is a chronic disease, so treatment needs to be not only initiated, but also continued. The 3 D's of treatment, drugs, diet, and dilation, have been used with remarkable outcomes.⁴⁹

Drugs

Systemic and topical corticosteroids Although effective in reducing symptoms and resolving mucosal eosinophilia, the chronic use of prednisone is not desired, leading to a number of studies in adults and children using topical swallowed steroids delivered by a metered dose inhaler (MDI).^{21,50–55} Steroids administered in this way provide less of a systemic burden, are deposited directly on the esophageal mucosa, and are highly effective in resolving symptoms and mucosal eosinophilia with response rates ranging from 50% to 90%. One prospective pediatric trial comparing swallowed topical fluticasone with oral prednisone, showed similarity in responses and that relapse occurred at same rate when either of these medications was discontinued.⁵⁶ The inability of some children to be able to correctly use MDIs to take the steroids led to the development of a viscous product. This product consists of mixing liquid budesonide respules with sucralose, thus creating a mixture termed oral viscous budesonide.^{57,58} Because EoE is a chronic disease, it is important to remember that if treatment is stopped, symptoms and inflammation will likely recur; thus, it is the practice of the authors to continue topical steroid treatment with the minimal amount of steroid necessary. Long-term studies are still necessary to identify the best maintenance strategy.

Proton pump inhibitors Proton pump inhibitors (PPIs) play at least 3 potential roles in the care of patients with EoE.^{59,60} PPIs are potent drugs in stopping acid production from parietal cells and therefore are useful in ruling out GERD as a cause for esophageal eosinophilia. Second, patients with EoE may have comorbid GERD and need intermittent treatment with PPIs or other acid suppression. Finally, emerging data suggest that PPIs can downregulate epithelial expression of proinflammatory cytokines, such as IL-8 and eotaxin-3, molecules that are known to be critical for leukocyte infiltration.^{61,62} These latter findings support a potential role for PPIs in the treatment of EoE.

Biologic agents Humanized anti-IL-5 antibody has been shown to significantly reduce esophageal eosinophilia in adult and pediatric subjects.^{63–65} Significant improvement in symptoms has not been consistently shown, and placebo-treated subjects respond in a similar positive fashion. Anti-IL-13 was effective in reducing mucosal eosinophilia in an adult study.⁶⁶

Diet Dietary management of EoE seeks to eliminate the offending food allergen in patients with EoE and takes 1 of 3 forms.⁶⁷ Elemental, targeted elimination and 6 food group elimination diets have all been useful in removing allergenic stimuli from contacting the esophageal mucosa and reducing symptoms. Each has significant positive and negative aspects that will be highlighted in the following sections.

Elemental diet Amino acid–based formulas are highly effective (often >96% response) in treating children and adults with EoE, as shown in a limited number of studies.^{68,69} Because patients with EoE may have multiple food sensitizations and highly accurate predictive testing for EoE food triggers awaits discovery, an elemental diet can be very useful in inducing a remission. Problematic features of this treatment are adherence to a formula-based diet, cost, and convenience.

Targeted diet A targeted elimination diet based on skin and specific serum IgE (ImmunoCAP) testing for allergenic foods is effective in 53% to 72% of patients.^{70–72} Targeted testing is based on the diet history and can be highly beneficial because it is not as restrictive as the elemental diet. Convenience and determining the clinically relevant allergens are potential problems with this approach.

Six food group elimination diet Elimination of the most common allergenic food groups, termed the 6-food elimination diet, is another successful approach to treating EoE, with approximately 74% undergoing remission.^{73–78} This is based on empirical removal of the most common food allergen groups (dairy, soy, wheat, egg, nuts, fish). A potential drawback of the 6-food elimination diet is the elimination of a food that may not serve as an offending allergen. There are other potential elimination diets that have shown some efficacy, including the 4-food elimination diet (dairy, wheat, egg, legumes) as well as milk-only elimination.^{74,79,80}

Dilation Dilation of isolated or long segments of the narrowed esophagus is often necessary to allow safe passage of food. A number of recent studies have shown the long-lasting benefits of this approach as well as the low incidence of complications, including pain and perforations.^{81–88} Dilation does not address the underlying pathophysiology of EoE, as it has no anti-inflammatory effect.

Other considerations The inclusion of subspecialists' expertise in treating patients with EoE can provide significant benefit. A gastroenterologist can provide experience with identifying comorbid GI diseases, such as GERD, and perform endoscopies to assess for mucosal healing and dilations. An allergist can be a vital participant to help identify EoE-related food allergens as well as comorbid allergic diseases such as IgE-mediated food allergies, asthma, atopic dermatitis, rhinitis, and conjunctivitis.^{89,90} A dietician can be a key participant in developing a practical plan to eliminate foods and ensure adherence.^{91,92} Feeding specialists may be needed to teach new feeding skills or interrupt acquired habits to maximize eating.^{36,93,94} Psychosocial expertise may be necessary to help severely affected patients cope with this chronic disease.^{45,95}

Differential diagnosis The differential diagnosis for young children with refluxlike symptoms, abdominal pain, or feeding dysfunction includes anatomic malformations

and peptic disease. Mucosal eosinophilia can be confused most commonly with GERD. In adults, dysphagia and food impaction can be presentations of esophageal cancer, peptic stricture, achalasia, motility disorders, and GERD.

Prognosis EoE is a chronic disease that requires ongoing treatment, or symptoms and inflammation will return.⁴⁸ Complications associated with EoE include esophageal stricture, food impactions, and feeding dysfunction, leading to malnutrition. To date, EoE has not been associated with cancers and does not lead to shortened life span.

Eosinophilic gastritis, gastroenteritis, and colitis

Eosinophilic gastritis (EG), gastroenteritis (EGE), and colitis (EC) are rare diseases characterized by GI symptoms that occur in association with dense mucosal eosinophilia. Other diseases that can be associated with these findings need to be ruled out before the diagnosis of EG, EGE, or EC can be made. These diseases occur in both children and adults, and because they are uncommon, epidemiologic features, risk factors, and pathophysiological mechanisms are not certain.

Clinical features Patients with EG can present with nonspecific symptoms, including vomiting, abdominal pain, or even hematemesis.^{96–98} Laboratory analyses can reveal peripheral eosinophilia and anemia but rarely show signs of peripheral inflammation, such as elevated sedimentation rate or C-reactive protein. Radiographic imaging may reveal thickened mucosal folds, ulceration, or partial obstruction.

EGE presents with symptoms consistent with small intestinal dysfunction, such as abdominal pain, diarrhea, and peripheral edema secondary to protein and blood loss.⁹⁹ Some patients may develop protein-losing enteropathy or profound anemia requiring albumin or blood transfusions. Upper GI with small bowel follow-through can reveal mucosal thickening, and direct luminal imaging with endoscopy or capsule studies can reveal ulcers, polyps, or normal mucosa.

A wide severity of symptoms has been associated with EC.^{100–105} Some reports note diarrhea and lower abdominal pain, whereas others describe hematochezia, tenesmus, and severe rectal pain with a presentation quite similar to that of IBD. Laboratory testing can reveal anemia and hypoalbuminemia but does not always show signs of peripheral inflammation such as elevated sedimentation rate or C-reactive protein.

Association with eosinophilia

The normal numbers of eosinophils vary along the gastrointestinal tract. Except for the esophagus, which has no eosinophils, normal values for eosinophil counts in the rest of the GI tract are less certain. At least 2 studies identified an increasing gradient of eosinophils from the proximal small intestine to the colon.^{106,107}

EG, EGE, and EC are associated with dense mucosal eosinophilia. Initial studies classified these EGIDs as mucosal, muscular, and serosal diseases related to not only the site of eosinophilia but also to their clinical presentations.^{108,109} For example, muscular disease presented with symptoms of GI obstruction and serosal disease with ascites. With the advent of GI endoscopy, increasing attention has been paid to the mucosal variety.

Presently, histologic features of EGIDs focus strictly the number of mucosal eosinophils. Because eosinophils are normal constituents of the intestinal mucosa, clear definitions of an absolute diagnostic threshold number of eosinophil for EG, EGE, and EC remain under investigation. Thresholds for EG or EC continue to undergo definition; review of the literature and clinical experience suggest that a reasonable

threshold value for EG is greater than 25 to 30 eosinophils per high-power field (eos/HPF) and for EC is greater than 65 eos/HPF.^{106,107} As with EoE, additional features related to eosinophils, such as location and level of degranulation, as well as features associated with other resident cells (epithelia, fibroblasts, neurons, and others) and infiltrating cells will be critical to increasing understanding disease pathogenesis and providing diagnostic clarity.

Acute and chronic management

Treatment options for EG, EGE, and EC remain quite limited and have focused on the use of corticosteroids, immunosuppressive agents, and diet restriction.^{96,103,110,111} No prospective controlled trials have been completed, and recommendations have been based on case series and clinical experiences. Systemic steroid use is often necessary for acute management, and topical steroid use with budesonide (Entocort) or aminosalicylates has been used for chronic management.¹⁰⁰ Clinical experiences suggest that eosinophilia past the esophagus is less likely to respond to removal of dietary allergens. Using the minimal amount of steroids for treatment and monitoring for side effects, such as bone demineralization and adrenal suppression, are important considerations.

Differential diagnosis

EG and EGE should be differentiated from peptic disease, Menetrier disease, vasculitis, and allergic enteropathy. In addition to vasculitis and allergy, EC must be differentiated from IBD.

Natural history

Tertiary centers report the world’s largest clinical experiences and descriptions of the natural history of adults with EGIDs.^{108,109,112} Over the course of the past 50 years, they found an increase from 1 patient per year from 1950 to 1987 to 3 per year between 1987 and 2007. No significant complications were reported. Clinical experiences suggest that patients with EG and EC may have a waxing and waning course, but no long-term studies are available.

CELIAC DISEASE

Key points for celiac disease are shown in **Box 1**.

Epidemiology

Celiac disease occurs primarily in Non-Hispanic white individuals, with a prevalence of 1 in 133 in the United States and Europe.^{113–115} Celiac disease affects both children and adults with female individuals being affected twice as often as male individuals. With better serologic testing, the number of “asymptomatic” patients, either with risk factors listed in the next section who were identified at screening or with an

Box 1
Key points for celiac disease

- Celiac disease is an immune-mediated disease in which gluten-containing foods stimulate a reproducible clinical and histologic response.
- Removal of gluten from the diet remains the primary treatment.
- The association with eosinophils in the small intestinal and esophageal mucosa is increasingly recognized and requires individualized assessment and treatment.

abnormal duodenal biopsy done at the time of an endoscopy performed for alternative reasons, is increasing.

Risk Factors

Celiac disease is both associated with environmental factors and carries a strong genetic disposition, especially in those patients with human leukocyte antigen (HLA)-DQ2 and HLA-DQ8.¹¹⁶ In fact, a recent large multicenter prospective cohort study showed that children homozygous for HLA DR3-DQ2 were at particularly high risk for developing celiac disease.¹¹⁷ At-risk groups also include first-degree and second-degree relatives of those with celiac disease and patients with autoimmune thyroid disease, Down syndrome, Type 1 diabetes, Williams and Turner syndromes, and IgA deficiency; these patients may have a higher prevalence than the general population. A recent study showed that early introduction of wheat is not a risk factor for developing celiac disease.¹¹⁸

Pathophysiology

A multiple-hit model has been proposed as underlying celiac disease. Although 40% of the Western world is susceptible based on HLA typing, only 1% develops disease. Once the disease has been initiated, enzymatically digested gluten fragments bind to predisposing HLA molecules and trigger a T-cell response and mucosal damage. Tissue transglutaminase is released and modifies gluten peptides, allowing the peptides to bind to HLA molecules with higher affinity, further perpetuating inflammation.¹¹⁹ Inflammation is characterized by findings ranging from lymphocytic inflammation of the lamina propria with increased intraepithelial lymphocytes to total villous blunting.

Clinical Features

Clinically, celiac disease can present at any age but is most often recognized in young children soon after the introduction of wheat-containing foods into their diet. Symptoms, including diarrhea, steatorrhea, weight loss, and bloating, are related to villous damage with resultant malabsorption. Laboratory findings include anemia, hypoalbuminemia, and elevated transaminases.¹²⁰ Other patients may have non-GI-related symptoms, such as short stature, neurologic symptoms (ataxia, epilepsy, depression, and neuropathy), dermatitis herpetiformis, and dental enamel defects.

In patients with suspected celiac disease, celiac disease-specific antibodies should be measured. Most commonly, IgA class antitissue transglutaminase type 2 (TG2) antibodies are initially obtained in conjunction with total serum IgA level. If screening testing is positive, diagnosis should be confirmed with the procurement of a mucosal biopsy.¹¹⁶ A gluten-free diet should not be initiated until the diagnostic process is complete. Clinical experience suggests a mucosal biopsy may not be necessary to establish a diagnosis, but this has not become the standard of care in the United States yet.

Association with Eosinophilia

An eosinophilic infiltrate also has been described in the duodenal mucosa of patients with active celiac disease.¹²¹ In a case series of 150 newly diagnosed patients, biopsy specimens showed anywhere between 3 and 50 eos/HPF. Mucosal eosinophilia was associated with advanced histologic staging of the disease, suggesting that eosinophils may play a role in mucosal damage.¹²²

Recently, a link between esophageal eosinophilia and celiac disease has been noted. Although celiac disease and EoE are separate gastrointestinal disorders, several studies have postulated a coexistence of esophageal eosinophilia in patients

with celiac disease. In a study of 1000 randomly selected adults from the general population, there was no increased risk of celiac disease in persons with esophageal eosinophilia.¹²³ In a second study, the prevalence of esophageal eosinophilia was measured in a retrospective analysis of 120 children with celiac disease compared with healthy controls. This study found no differences in the incidence of esophageal eosinophilia between the two.¹²⁴ These results imply that esophageal eosinophilia in patients with celiac disease may be incidental rather than causal. Reports of improvement of esophageal eosinophilia on a gluten-free diet have been mixed, with some studies showing resolution and others show no improvement.^{125–128} Based on these limited data, we suggest that patients with celiac disease and esophageal eosinophilia first undergo treatment with a PPI and a gluten-free diet. Depending on clinical symptoms and response to treatment, additional dietary elimination or topical corticosteroids for treatment of EoE can be considered. Thus, esophageal eosinophilia may be a representation of immunologic dysregulation underlying celiac disease or may occur independently as a manifestation of EoE. Future studies determining the fate of eosinophilic inflammation after celiac treatment will begin to tease out mechanisms of this finding.

Acute and Chronic Management

Treatment for celiac disease is based on complete elimination of gluten from the diet.¹²⁹ To guide care, a recent National Institutes of Health panel suggested the mnemonic, *CELIAC* representing, Consultation with a skilled dietitian, Education about the disease, Lifelong adherence to a gluten-free diet, Identification and treatment of nutritional deficiencies, Access to an advocacy group, Continuous long-term follow-up by a multidisciplinary team (<http://celiac.nih.gov/materials.aspx>). Dietitians are central to the management of patients with celiac disease to ensure that the diet is gluten-free and nutritionally replete.

INFLAMMATORY BOWEL DISEASES

Key points for IBDs are shown in **Box 2**.

Epidemiology

IBD often presents in the second or third decade; however, childhood presentation can occur. Ulcerative colitis (UC) incidence is 2 to 19 per 100,000, and Crohn disease (CrD) incidence is 3 to 20 per 100,000. UC tends to occur more commonly in male individuals; whereas, CrD occurs more often in female individuals. A first-degree relative with IBD is found in 10% to 25% of patients.

Box 2

Key points for inflammatory bowel diseases

- Inflammatory bowel diseases (IBD) consist of at least 2 immune-mediated chronic inflammatory diseases of the gastrointestinal tract: Crohn disease and ulcerative colitis.
- Treatments for IBDs include corticosteroids for acute exacerbations, and 5-aminosalicylates, immunosuppressives and biologics directed against tumor necrosis factor- α for maintenance management.
- The association of IBDs with mucosal eosinophilia and its secreted products is increasing, but the role of eosinophils in the pathogenesis of IBD remains uncertain.

Risk Factors

A number of factors seem to pose increased risk for developing IBD, but these vary between UC and CrD.¹³⁰ For instance, smoking is associated with an increased risk of CrD but may be protective in UC. Dietary factors may contribute to the development of IBD with processed, fried, and sugary foods being associated with the development of IBDs, whereas long-term intake of dietary fiber is protective.

Pathophysiology

The intestinal tract is composed of a complex and ingenious architecture that blends together soluble elements, extracellular matrices, and a wide array of cells to create an effective barrier separating luminal contents from the rest of the body. Functional elements, such as secretion of trefoil peptides and cryptdins and rhythmic peristalsis, aid in protecting the epithelial barrier from penetration and binding of noxious particles and microbes. In addition, the innate and adaptive immune system arm the underlying mucosa with nonspecific and acquired elements to process antigenic materials that are encountered. When any of these elements is ineffective, the potential for inflammation ensues.

In the case of IBD, the etiology remains unknown, but it is thought that environmental factors as well as genetic predisposition lead to gastrointestinal immune dysregulation.^{131–133} To date, more than 160 genetic loci are associated with human IBDs.¹³⁴ When grouping these loci and gene products, a pattern of expression related to mucosal homeostasis, inflammation, and healing can help to visualize the potential underlying defects observed in these diseases. For instance, dysregulation of homeostasis can take the form of altered intestinal permeability, increased antigen uptake, and change in patterns of tolerance. Although inflammation is necessary to limit the exposure of the immunomicromilieu to exogenous antigens, when uncontrolled, clinical manifestations of IBD may arise. For instance, a large body of research is investigating not only the specific microbiome associated with the mucosa affected by IBD, but also how these microbial patterns are sensed.¹³⁵ Healing defects may not allow for proper resolution of mucosal injury and inflammation and perpetuate IBD. The role of exogenous factors, such as diet, is an active area of investigation as mentioned earlier, with certain nutritional components being protective, such as vitamin D and high fiber, and others, in excess, being permissive, such as total or polyunsaturated fats and sugary foods.

Clinical Features

Most patients with CrD have abdominal pain, diarrhea, and weight loss.¹³⁶ Although grossly bloody stool can be seen with colonic disease, it is unusual with isolated small bowel disease. Other features of CrD, including growth retardation, nausea and vomiting, perirectal disease, or extraintestinal manifestations, occur in up to 25% of patients.¹³⁷ UC presents with diarrhea, rectal bleeding, and abdominal pain.¹³² Diagnosis is confirmed by histologic characteristics of chronic inflammatory changes, including cryptitis in UC and transmural infiltration of lymphocytes and granuloma formation in CrD.

Association with Eosinophilia

Eosinophils have been implicated in the pathogenesis of IBD; however, their relationship to these diseases remains unclear.^{2,138,139} At least 2 different postulates have been developed. The most commonly held belief, based on clinical observations and mouse models, is that eosinophils accumulate in the mucosa where they

synthesize and release inflammatory mediators that lead to tissue damage.^{139–151} A less common thought is that eosinophils may serve an innate protective role that heals or prevents inflammation. This is based on the clinical finding that mucosal eosinophilia precedes the onset of IBD and mouse data supporting a role for eosinophils in healing epithelial barrier function.¹⁵² Future studies determining the underlying role of eosinophils in the pathogenesis of IBD will permit clinical studies examining the utility of measuring eosinophils as biomarkers.

Mucosal eosinophilia

Early studies describing mucosal biopsies of patients with IBD revealed mucosal eosinophilia compared with healthy controls. Unlike the esophagus, eosinophils are resident cells of the small and large intestines; the normal number of eosinophils is not well-defined, making interpretation of pathologic intestinal eosinophilia difficult.² Clinical implications of mucosal eosinophils in IBD are unknown, especially because mucosal eosinophilia is increased in IBD compared with irritable bowel syndrome. One study found that the severity of eosinophilic inflammation in patients with UC was the most significant predictor of lack of response to therapy.¹⁵³

Eosinophil products and inflammatory bowel disease

Eosinophils secrete eosinophil granule proteins (EGP), such as ECP, EPO, EDN, and MBP, and increased EGP levels of these products in tissues and stool effluent provide circumstantial support for a role in IBD. Early electron microscopic studies of colonic resection specimens from patients with CrD identified numerous eosinophils, extracellular eosinophil MBP granule deposition, and cytotoxic tissue changes.^{154,155} At least one study revealed not only increased mucosal eosinophilia, but also IL-5, in resected colon of patients with CrD, a finding that was associated with endoscopic recurrence.¹⁵⁶ A number of studies have analyzed the concentrations of EGPs in stool and correlated increased EGP concentrations with severity of disease. Granule proteins may indicate relapse as suggested in a study demonstrating that ECP and EPX fecal levels increased when intestinal inflammation increased.¹⁵⁷ Finally, declining stool EGP levels may indicate disease remission. For instance, fecal EPX levels in patients with UC decreased after corticosteroid treatment.¹⁵⁸

These last studies raise the possibility that eosinophils may be beneficial in IBD. To address this, we induced colitis in wild-type and eosinophil-deficient PHIL mice.¹⁵² When colitis was induced in PHIL mice, they developed more severe colitis than their eosinophil-competent controls. These mice also had greater numbers of neutrophils and increased levels of chemokines that attract neutrophils. Further dissection of the mechanism revealed that PHIL mice were lacking in the barrier protective molecule, protectin D1. Rescue of PHIL with protectin reduced the severity of colitis. In contrast to these findings, at least 2 other studies have shown a deleterious role for eosinophils in mouse colitis.^{159,160}

Acute and Chronic Management

The acute management of the severely ill patient with IBD consists of bowel rest, intravenous fluids, and nutrition, and immunosuppression with corticosteroids, but after the diagnosis, most patients can be cared for as outpatients.¹⁶¹ Medications are focused on reducing inflammation and maintaining remission.¹⁵¹ Immunosuppressives used include 6-mercaptopurine, azathioprine, and biologics including anti-tumor necrosis factor (TNF) antibodies.¹⁶² Additional medications include 5-aminosalicylates that can be administered as topical agents, swallowed or in enema form, depending on the site of the inflammation. In some circumstances, antibiotics may be helpful,

and recent works have begun to investigate the role of the microbiome in IBD therapeutics.¹⁶³ Care must be taken to ensure adequate nutrition to supply calories, proteins, and micronutrients, especially to the growing child.¹⁶⁴ Surgery may be indicated in some patients with recalcitrant disease, obstruction, or uncontrollable hemorrhage.

Differential Diagnosis

The differential diagnosis for patients with abdominal pain, bloody diarrhea, and anemia includes infections, immunodeficiency, eosinophilic colitis, and vasculitis. The diagnosis of IBD is based on exclusion of these entities and the findings of chronic inflammation on mucosal biopsies and, in the case of CrD, granulomas.

Prognosis

Patients with IBD experience a course of exacerbations and remissions. If a patient with CrD is in remission for 1 year, there is an 80% chance of remaining in remission for subsequent years. Patients with CrD may have an increased risk of cancer, and those taking a combination of anti-TNF medications and azathioprine may be at increased risk of hepatosplenic T-cell lymphoma.¹⁶⁵ Two-thirds of patients with UC will have 1 relapse in the 10 years after diagnosis. Up to one-third of patients will require surgery or colectomy for complications. There is an increased risk of cancer that begins 10 years after the onset of symptoms.

PARASITIC INFECTIONS

Key points for parasitic infections are shown in **Box 3**.

Introduction

Blood eosinophilia is a common finding in tropical developing countries and is strongly associated with the presence of parasitic disease, particularly intestinal helminth infection.¹⁶⁴ In travelers returning from the tropics, there is a significant chance of helminth infection in the setting of eosinophilia.¹⁶⁵ Even in patients who are asymptomatic, eosinophilia can be associated with intestinal parasitic infections.¹⁶⁶ Despite the association of eosinophilia with parasitic infection, patients may have eosinophilia in the absence of infection and vice versa.^{164,165} In fact, in a large study looking at 14,298 returning travelers, fewer than 50% of patients with helminth infections had blood eosinophilia.¹⁶⁵ Sustained peripheral eosinophilia is usually associated with parasites that invade tissues, as this leads to contact with immune effector cells. Conversely, infections that are entirely intraluminal, such as tapeworm infection, are unlikely to cause peripheral eosinophilia.¹⁶⁷

Although intestinal parasites are relatively common in some developing countries, they are an uncommon cause of GI disease in developed countries. In a large

Box 3

Key points for parasitic infections

- Intestinal parasites are an uncommon cause of gastrointestinal disease in developed countries.
- Patients may have eosinophilia in the absence of parasitic infections and vice versa.
- Intestinal helminth infection can produce a clinical picture indistinguishable from eosinophilic gastroenteritis.

systematic review and meta-analysis assessing GI pathogens in developed and developing countries, parasites were the least common cause of GI illness after viral and bacterial causes, respectively, and of the parasitic causes of GI disease, *Giardia intestinalis*, and *Cryptosporidium* species (neither of which are associated with eosinophilia) were the most common.¹⁶⁶ Nevertheless, it is important to consider helminth infection in the differential diagnosis of a patient presenting with blood or tissue eosinophilia and gastrointestinal symptoms, because therapy is typically curative and differs substantially from that for other causes of GI disorders. *Strongyloides stercoralis* is of particular importance because administration of corticosteroids, which may be used to treat EGID, can lead to the development of potentially fatal hyperinfection syndrome.

Although some parasitic infections, such as trichinosis, can cause acute GI symptoms associated with eosinophilia, these symptoms are transient and associated with other clinical manifestations. Consequently, patients rarely present to gastroenterologists. In contrast, patients with chronic intestinal parasitic infection, such as that caused by hookworm or *Strongyloides*, may present with nonspecific GI complaints with or without peripheral eosinophilia. Moreover, as in EGID, endoscopic biopsies may reveal tissue eosinophilia (Table 2). Although a comprehensive discussion of parasitic causes of EGIDs is beyond the scope of this article (and is reviewed by O'Connell and Nutman, elsewhere in this issue), hookworm infection and strongyloidiasis provide 2 illustrative examples.

Hookworm Infection

Ancylostoma duodenale and *Necator americanus*, commonly referred to as "hookworms," are estimated to infect up to 740 million people worldwide.¹⁶⁷ Although newer studies are lacking, prevalence in the United States was estimated to be 19.6% in 1982, particularly in the southern United States, including Appalachia.¹⁷² Hookworms are found in soil and generally penetrate human skin and migrate to the lungs. Hookworm larvae are then swallowed with bronchial secretions and eventually mature worms attach to the wall of the small intestine. A pruritic skin rash is sometimes noticeable at site of penetration into skin. Chronic infections are generally asymptomatic unless there is a large intestinal worm burden. Although this can cause a gastroenteritislike syndrome, most concerning are an associated anemia from production of an anticoagulant substance and protein-losing enteropathy.¹⁷³ Laboratory evaluation can reveal eosinophilia and a moderate increase in IgE levels.^{174,175} Diagnosis is made by microscopic visualization of hookworm eggs or larvae in feces. First-line treatment is albendazole.

Strongyloidiasis

Strongyloides stercoralis is endemic worldwide, including the United States and Europe, with an estimated global prevalence of up to 100 million people. Outbreaks of strongyloidiasis have been reported in the southeastern part of the United States, particularly Kentucky, Tennessee, and Florida.^{172–175} Transmission occurs when larvae from infected soil penetrate the skin. Because of its unique autoinfective life cycle, the parasite can persist for decades in an infected host,¹⁷⁶ whereas some individuals with strongyloidiasis complain of abdominal pain, diarrhea, urticaria, or rash, many are asymptomatic.¹⁷³ Immunosuppression (typically with corticosteroids) causes potentially fatal acceleration of the autoinfective cycle (hyperinfection syndrome) and/or dissemination of infection. Peripheral and small bowel eosinophilia are commonly seen and can mimic EGID.¹⁷⁷ Diagnosis can be difficult in immunocompetent hosts because larvae are excreted only intermittently and in small numbers,

Table 2
Selected parasitic diseases associated with gastrointestinal manifestations and eosinophilia

Parasite	Clinical Presentation	Peripheral Blood Eosinophil Count	Tissue Eosinophilia	Diagnosis	Treatment
Hookworm (<i>Ancylostoma duodenale</i> and <i>Necator americanus</i>)	Skin rash on inoculation, asymptomatic to mild GI disease, anemia and protein-losing enteropathy with large burden	Elevated	GI	Direct visualization of eggs or larvae on microscopy	Albendazole
<i>Trichinella spiralis</i>	Diarrhea may be seen early in infection before the development of myalgia and other symptoms	Elevated	Muscle	Serology, muscle biopsy	Albendazole, steroids
<i>Strongyloides stercoralis</i>	Abdominal pain, diarrhea, rash, or asymptomatic in chronic infection	Elevated	GI	Multiple modalities, including stool and serology	Ivermectin, albendazole
<i>Cystispora belli</i>	Diarrhea	Elevated	GI ¹⁶⁸	Stool examination for cysts	Trimethoprim sulfamethoxazole
<i>Anisakis</i>	Abdominal pain, allergic gastroenteritis	Elevated	GI ^{169–171}	Endoscopic visualization of worm	Removal of worm

Abbreviation: GI, gastrointestinal.

and commercial serologic tests vary in sensitivity and specificity and do not distinguish active from past infection.¹⁷⁸ Recommended treatment is with ivermectin (200 µg/kg daily for 1–2 days) or albendazole (400 mg daily for 3 days and followup at 2 weeks to confirm cure).

Diagnostic Approach

In patients with unknown eosinophilia, parasitic infection should be considered. The approach to these patients will depend on their travel history, other medical conditions, and clinical signs and symptoms. Eosinophilia should first be confirmed by obtaining an absolute eosinophil count. If history and physical examination do not elucidate a cause of eosinophilia and parasitic infection is still considered a potential etiology, 3 separate stool samples and appropriate serology should be obtained.¹⁶⁹

FUTURE CONSIDERATIONS AND SUMMARY

The diversity of circumstances in which mucosal eosinophils are found in the gut provides a wealth of scientific intrigue and clinical confusion. An increasing body of research focuses on mucosal eosinophilia that is captured by biopsy forceps at the time of endoscopy, but this limited sampling may lead to underestimating the impact of eosinophils that are dispersed throughout the mucosa as well as deeper in the muscular layers. Although there are clinical circumstances when it is highly likely that eosinophils participate in the pathogenesis of a disease, such as EoE, other situations are less certain. The finding of eosinophils in association with other diseases, such as celiac and IBD, raises questions as to whether their role is one of harm or healing. Future studies that help characterize eosinophils in the GI tract, understand its functional role, and determine its viability as a therapeutic target and biomarker will provide much insight into GI health and disease.

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