HHS Public Access

Author manuscript

Immunol Allergy Clin North Am. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Immunol Allergy Clin North Am. 2015 August ; 35(3): 413–437. doi:10.1016/j.iac.2015.04.003.

Eosinophils in Gastrointestinal disorders- eosinophilic gastrointestinal diseases, celiac disease, inflammatory bowel diseases and parasitic infections

Pooja Mehta and **Glenn T. Furuta, MD**

Digestive Health Institute, Children's Hospital Colorado, Gastrointestinal Eosinophilic Diseases Program, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

Synopsis

The gastrointestinal tract provides an intriguing organ for considering the eosinophil's role in health and disease. The normal gastrointestinal (GI) tract, except for the esophagus, is populated by eosinophils that are present throughout the mucosa in varying numbers. This latter fact raises the possibility that eosinophils participate in innate mechanisms of defense. In contrast, a number of clinical studies provide a wealth of data that associates increased numbers of eosinophils with inflammatory GI diseases; these findings prompt concerns that eosinophils may have a deleterious effect on the gut. In this article we present clinical features of 4 disease processes that have been associated with eosinophilia and suggest areas requiring investigation as to their clinical significance and scientific relevance.

Keywords

eosinophil; esophagitis; eosinophilic esophagitis; eosinophilic oesophagitis; eosinophilic gastritis; eosinophilic gastroenteritis; eosinophilic colitis; parasitic infection

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.

Corresponding author: Glenn T. Furuta, Professor of Pediatrics, University of Colorado School of Medicine, Denver, Colorado; Digestive Health Institute, Children's Hospital Colorado, Aurora, Colorado, Phone-720-777-7457, glenn.furuta@childrenscolorado.org.

Pooja Mehta has nothing to disclose.

Over the last 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. [12] 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 four diseases in which mucosal eosinophils are clearly associated, eosinophilic gastrointestinal diseases, celiac disease, inflammatory bowel diseases, 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—EoE has been reported in all continents, except Africa, and consistently has been shown to occur more commonly in males with a 3:1 ratio. [345,6] Since this is an emerging disease, the exact incidence is difficult to exactly predict but estimates range from 1–4 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 since 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 provide clues to dysfunction of the epithelial barrier (filaggrin), [8] immune system (thymic stromal lymphopoietin, eotaxin-3) [9,10 11] and other yet to be identified areas (calpain-14). [12,13]

Pathophysiology—Within the epithelia, the prominence of eosinophils, 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 posses 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- and food- allergens, IL-13, and IL-5. [1516–1920] 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]

Pathological 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 altered permeability, fibrosis, epithelial mesenchymal transition and dysmotility. Phosopholamban, TGF-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 non-specific 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 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 only note 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 IgE 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 gastroesophageal reflux disease, 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 two circumstances. First, some patients may manifest peripheral eosinophilia, but this finding is non-specific 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 histological parameters that focus on histological features other than eosinophil numbers are needed.

Acute and Chronic Management

Overview: While research studies continue to focus on both symptoms and histological responses to treatments, debate still rages amongst clinicians who wonder whether the focus of EoE treatment should be directed towards only a symptomatic response or if symptomatic and histological response is necessary. It is the opinion of the authors that there are at least three good reasons to treat patients to clinical and histological 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, ttreatment 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 three D's of treatment, drugs, diet and dilation have been used with remarkable outcomes. [49]

Drugs

Systemic and Topical Corticosteroids: While 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 50–90%. One prospective pediatric trial comparing swallowed topical fluticasone to 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 utilize 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] Since 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 (PPIs): 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 gastroesophageal reflux (GERD) as a cause for esophageal eosinophilia. Second, patients with EoE may have co-morbid GERD and need intermittent treatment with PPIs or other acid suppression. Finally, emerging data suggests that PPIs can downregulate epithelial expression of pro-inflammatory 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 placeb- 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 one of three forms. [67] Elemental, targeted elimination and six 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 below.

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] Since EoE patients 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 53–72% of patients. [70–72] Targeted testing is based on the diet history and can be highly beneficial since 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 six-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 SFED 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 four 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 sub-specialists' expertise in treating EoE patients can provide significant benefit. A gastroenterologist can provide experience with identifying co-morbid 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 co-morbid 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 assure 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 reflux like symptoms, abdominal pain or feeding dysfunction is large and 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 lifespan.

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 non-specific 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. [100–103104,105] 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 inflammatory bowel disease. 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 two 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 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. Since 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 EG continue to undergo definition; review of the literature and clinical experience suggest that a reasonable threshold value for EG is greater than 25–30 eos / HPF and for EC is greater than 65 eos / HPF.[106,107] As with EoE, additional features related to eosinophils, such as location, 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—Treatments options for EG, EGE and EC remain quite limited and have focused on the use of corticosteroids, immunosuppressive agents and diet restriction. [96, 110103, 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 aminiosalicylates 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's 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 last 50 years, they found an increase from 1 patient per year from 1950–1987 to 3 per year

between 1987 and 2007. No significant complications were reported. Clinical experiences suggest that patients with eosinophilic gastroenteritis and colitis 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 Caucasians, with a prevalence of 1 in 133 in the United States and Europe. [113–115] Celiac disease affects both children and adults with females being affected twice as often as males. With better serological testing, the number of "asymptomatic" patients, either with risk factors listed below who were identified at screening or with an 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 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, neurological 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 anti-tissue 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 has also 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 to 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 to normal 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 while others show no improvement.[125–128] Based on this limited data, we suggest that patients with celiac disease and esophageal eosinophilia first undergo treatment with a proton pump inhibitor 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 immunological dysregulation underlying celiac disease or occur independently as a manifestation of EoE. Future studies determining the fate of eosinophilic inflammation following 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 NIH panel suggested the mnemonic, ***CELIAC*** representing, ***C***onsultation with a skilled dietitian, ***E***ducation about the disease, ***L***ifelong adherence to a gluten-free diet, ***I***dentification and treatment of nutritional deficiencies, ***A***ccess to an advocacy group, ***C***ontinuous long-term follow-up by a multidisciplinary team. (http://celiac.nih.gov/materials.aspx) Dieticians are central to the management of patients with celiac disease to insure that the diet is gluten-free and nutritionally replete.

Inflammatory Bowel Diseases

Key points for inflammatory bowel diseases (IBD) are shown in Box 2.

Epidemiology

Inflammatory bowel disease often presents in the 2nd or 3rd decade; however, childhood presentation can occur. UC incidence is 2–19 per 100,000, and CrD incidence is 3–20 per 100,000. UC tends to occur more commonly in males; whereas, CrD occurs more often in females. A first degree relative with IBD is found in 10–25% of patients.

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 non-specific 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.[131132133] To date, over 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. While 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

The majority of patients with CrD have abdominal pain, diarrhea, and weight loss. [136] Though 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 IBD patients' mucosal biopsies revealed mucosal eosinophilia compared to healthy controls. Unlike the esophagus, eosinophils are resident cells of the small and large intestine; the normal number of eosinophils is not well-defined making interpretation of pathological intestinal eosinophilia difficult. [2] Clinical implications of mucosal eosinophils in IBD are unknown, especially since mucosal eosinophilia is increased in IBD compared to irritable bowel syndrome. One study found that the severity of eosinophilic inflammation in UC patients was the most significant predictor of lack of response to therapy .[153]

Eosinophil products and IBD—It is well known that 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 CrD patients 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 CrD patients, 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 UC patients 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 a 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 IBD patient consists of bowel rest, intravenous fluids and nutrition and immunosuppression with corticosteroids, but following 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-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 insure 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—IBD patients experience a course of exacerbations and remissions. If a CrD patient is in remission for one 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 UC patients will have one relapse in the 10 years following 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 returning travelers 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, less 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]

Though intestinal parasites are relatively common in some developing countries, they are an uncommon cause of gastrointestinal disease in developed countries. In a large systematic review and meta-analysis assessing gastrointestinal pathogens in developed and developing countries, parasites were the least common cause of gastrointestinal illness after viral and bacterial causes, respectively, and of the parasitic causes of gastrointestinal 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, since therapy is typically curative and differs substantially from that for other causes of gastrointestinal disorders. *Strongyloides stercoralis* is of particular importance since 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 gastrointestinal 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 non-specific gastrointestinal 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 eosinophilic gastrointestinal diseases is beyond the scope of this chapter (and is reviewed by O'Connell and Nutman in this volume), hookworm infection and strongyloidiasis provide two 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]. Though 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 [169]. 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 several. 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. Though this can cause a gastroenteritis-like syndrome, most concerning are an associated anemia from production of an anticoagulant substance and protein–losing enteropathy [168]. Laboratory evaluation can reveal eosinophilia

and a moderate increase in IgE levels[170,171]. 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. [168–171]Transmission occurs when larvae from infected soil penetrate the skin. Due to its unique autoinfective life cycle, the parasite can persist for decades in an infected host [172], whereas some individuals with strongyloidiasis complain of abdominal pain, diarrhea, urticaria, or rash, many are asymptomatic [168]. 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 [173]. The spectrum of GI strongyloidiasis: an endoscopic-pathologic study). Diagnosis can be difficult in immunocompetent hosts since larvae are excreted only intermittently and in small numbers and commercial serologic tests vary in sensitivity and specificity and do not distinguish active from past infection [174]. Recommended treatment is with ivermectin (200 mcg/kg daily for 1–2 days) or albendazole (400 mg given as two doses one week apart).

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, as well as clinical signs and symptoms. First, eosinophilia should first be confirmed by obtaining an absolute eosinophil count. If history and physical exam 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 [176].

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. While there are clinical circumstances when it is highly likely that eosinophils participate in the pathogenesis of a disease, such as EoE, others 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.

Acknowledgments

Glenn T. Furuta is Co-Founder of EnteroTrack and recipient of NIH grant 1K24DK100303 and Consortium for Eosinophilic Gastrointestinal Diseases Research (CEGIR) (U54 AI117804) is part of the Rare Diseases Clinical

Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS..

References

1. Furuta GT, Atkins FD, Lee NA, Lee JJ. Changing roles of eosinophils in health and disease. Annals of allergy, asthma & immunology. 2014 Jul; 113(1):3–8.
2. Yantiss RK. Eosinophils in the GI tract: How many is too many and what do they mean? Modern pathology. 2015 Jan; 28(Suppl 1):S7–S21. [PubMed: 25560601]
3. Attwood S, Smyrk T, Demeester T, Jones J. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Digestive diseases and sciences. 1993; 38:109–116. [PubMed: 8420741]
4. Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vogtlin J. [Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings]. Schweiz Med Wochenschr. 1994 Aug 20; 124(33):1419–1429. [PubMed: 7939509]
5. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). The American journal of gastroenterology. 2013 May; 108(5):679–692. quiz 693. [PubMed: 23567357]
6. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. The Journal of allergy and clinical immunology. 2011 Jul; 128(1):3–20. e26; quiz 21–22. [PubMed: 21477849]
7. Alexander ES, Martin LJ, Collins MH, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2014 Nov; 134(5):1084–1092. e1081. [PubMed: 25258143]
8. Matoso A, Mukkada VA, Lu S, et al. Expression microarray analysis identifies novel epithelial-derived protein markers in eosinophilic esophagitis. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2013 May; 26(5):665–676.
9. Rothenberg ME, Spergel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. Nature genetics. 2010 Apr; 42(4):289–291. [PubMed: 20208534]
10. Sherrill JD, Gao PS, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2010 Jul; 126(1):160–165. e163. [PubMed: 20620568]
11. Blanchard C, Durual S, Estienne M, Emami S, Vasseur S, Cuber JC. Eotaxin-3/CCL26 gene expression in intestinal epithelial cells is up-regulated by interleukin-4 and interleukin-13 via the signal transducer and activator of transcription 6. Int J Biochem Cell Biol. 2005 Dec; 37(12): 2559–2573. [PubMed: 16084752]
12. Kottyan LC, Davis BP, Sherrill JD, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. Nature genetics. 2014 Aug; 46(8):895–900. [PubMed: 25017104]
13. Sleiman PM, Wang ML, Cianferoni A, et al. GWAS identifies four novel eosinophilic esophagitis loci. Nature communications. 2014; 5:5593.
14. Sherrill JD, Rothenberg ME. Genetic and epigenetic underpinnings of eosinophilic esophagitis. Gastroenterology clinics of North America. 2014 Jun; 43(2):269–280. [PubMed: 24813515]
15. Mishra A, Schlotman J, Wang M, Rothenberg ME. Critical role for adaptive T cell immunity in experimental eosinophilic esophagitis in mice. J Leukoc Biol. 2007 Apr; 81(4):916–924. [PubMed: 17194734]
16. Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. Gastroenterology. 2003 Nov; 125(5):1419–1427. [PubMed: 14598258]
17. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. Journal of immunology. 2002 Mar 1; 168(5):2464–2469.

18. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. J Clin Invest. 2001 Jan; 107(1):83–90. [PubMed: 11134183]
19. Mishra A, Hogan SP, Lee JJ, Foster PS, Rothenberg ME. Fundamental signals that regulate eosinophil homing to the gastrointestinal tract. J Clin Invest. 1999 Jun; 103(12):1719–1727. [PubMed: 10377178]
20. Cho JY, Doshi A, Rosenthal P, et al. Smad3 Deficient Mice Have Reduced Esophageal Fibrosis and Angiogenesis in a Mouse Model of Egg Induced Eosinophilic Esophagitis. Journal of pediatric gastroenterology and nutrition. 2014 Feb 28.
21. Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. Gastroenterology. 2014 Aug; 147(2):324–333. e325. [PubMed: 24768678]
22. Lucendo AJ. Cellular and molecular immunological mechanisms in eosinophilic esophagitis: an updated overview of their clinical implications. Expert review of gastroenterology & hepatology. 2014 Aug; 8(6):669–685. [PubMed: 24742298]
23. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. Gastroenterology clinics of North America. 2014 Jun; 43(2):297–316. [PubMed: 24813517]
24. Aceves SS. Remodeling and fibrosis in chronic eosinophil inflammation. Digestive diseases. 2014; 32(1–2):15–21. [PubMed: 24603375]
25. Cheng E, Souza RF, Spechler SJ. Tissue remodeling in eosinophilic esophagitis. American journal of physiology. Gastrointestinal and liver physiology. 2012 Dec 1; 303(11):G1175–G1187. [PubMed: 23019192]
26. Cho JY, Rosenthal P, Miller M, et al. Targeting AMCase reduces esophageal eosinophilic inflammation and remodeling in a mouse model of egg induced eosinophilic esophagitis. International immunopharmacology. 2014 Jan; 18(1):35–42. [PubMed: 24239745]
27. Beppu LY, Anilkumar AA, Newbury RO, Dohil R, Broide DH, Aceves SS. TGF-beta1-induced phospholamban expression alters esophageal smooth muscle cell contraction in patients with eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2014 Nov; 134(5): 1100–1107. e1104. [PubMed: 24835503]
28. Abdulnour-Nakhoul SM, Al-Tawil Y, Gyftopoulos AA, et al. Alterations in junctional proteins, inflammatory mediators and extracellular matrix molecules in eosinophilic esophagitis. Clin Immunol. 2013 Aug; 148(2):265–278. [PubMed: 23792687]
29. Kagalwalla AF, Akhtar N, Woodruff SA, et al. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. The Journal of allergy and clinical immunology. 2012 May; 129(5):1387–1396. e1387. [PubMed: 22465212]
30. Mishra A, Wang M, Pemmaraju VR, et al. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. Gastroenterology. 2008 Jan; 134(1):204–214. [PubMed: 18166354]
31. Fox VL, Nurko S, Furuta GT. Eosinophilic esophagitis: it's not just kid's stuff. Gastrointestinal endoscopy. 2002 Aug; 56(2):260–270. [PubMed: 12145607]
32. Liacouras CA. Eosinophilic esophagitis in children and adults. Journal of pediatric gastroenterology and nutrition. 2003 Nov-Dec;37(Suppl 1):S23–S28. [PubMed: 14685074]
33. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clinical gastroenterology and hepatology. 2005 Dec; 3(12):1198–1206. [PubMed: 16361045]
34. Putnam PE. Eosinophilic esophagitis in children: clinical manifestations. Gastroenterology clinics of North America. 2008 Jun; 37(2):369–381. [PubMed: 18499025]
35. Straumann A, Aceves SS, Blanchard C, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. Allergy. 2012 Apr; 67(4):477–490. [PubMed: 22313241]
36. Mukkada VA, Haas A, Maune NC, et al. Feeding Dysfunction in Children With Eosinophilic Gastrointestinal Diseases. Pediatrics. 2010 Aug 9; 126(3):e672–e677. Sep. [PubMed: 20696733]

37. Desai TK, Stecevic V, Chang CH, Goldstein NS, Badizadegan K, Furuta GT. Association of eosinophilic inflammation with esophageal food impaction in adults. Gastrointestinal endoscopy. 2005 Jun; 61(7):795–801. [PubMed: 15933677]
38. Nonevski IT, Downs-Kelly E, Falk GW. Eosinophilic esophagitis: an increasingly recognized cause of dysphagia, food impaction, and refractory heartburn. Cleve Clin J Med. 2008 Sep; 75(9): 623–626. 629–633. [PubMed: 18788223]
39. Straumann A, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer A. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. Clinical gastroenterology and hepatology. 2008 May; 6(5):598–600. [PubMed: 18407800]
40. Hurtado CW, Furuta GT, Kramer RE. Etiology of esophageal food impactions in children. Journal of pediatric gastroenterology and nutrition. 2011 Jan; 52(1):43–46. [PubMed: 20975581]
41. El-Matary W, El-Hakim H, Popel J. Eosinophilic esophagitis in children needing emergency endoscopy for foreign body and food bolus impaction. Pediatric emergency care. 2012 Jul; 28(7): 611–613. [PubMed: 22743755]
42. Gentile N, Katzka D, Ravi K, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. Alimentary pharmacology & therapeutics. 2014 Dec; 40(11–12):1333–1340. [PubMed: 25287184]
43. Collins MH. Histopathology of eosinophilic esophagitis. Digestive diseases. 2014; 32(1–2):68–73. [PubMed: 24603383]
44. Franciosi JP, Hommel KA, DeBrosse CW, et al. Quality of life in paediatric eosinophilic oesophagitis: what is important to patients? Child: care, health and development. 2012 Jul; 38(4): 477–483.
45. Klinnert MD, Silveira L, Harris R, et al. Health-related quality of life over time in children with eosinophilic esophagitis and their families. Journal of pediatric gastroenterology and nutrition. 2014 Sep; 59(3):308–316. [PubMed: 24897164]
46. Lucendo AJ, Sanchez-Cazalilla M, Molina-Infante J, et al. Transcultural adaptation and validation of the "Adult Eosinophilic Esophagitis Quality of Life Questionnaire" into Spanish. Revista espanola de enfermedades digestivas. 2014 Jun; 106(6):386–394. [PubMed: 25361449]
47. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in Diagnosis of Eosinophilic Esophagitis Increases Risk for Stricture Formation, in a Time-Dependent Manner. Gastroenterology. 2013 Aug 13.
48. Menard-Katcher P, Marks KL, Liacouras CA, Spergel JM, Yang YX, Falk GW. The natural history of eosinophilic oesophagitis in the transition from childhood to adulthood. Alimentary pharmacology & therapeutics. 2013 Jan; 37(1):114–121. [PubMed: 23121227]
49. Straumann A. Treatment of eosinophilic esophagitis: diet, drugs, or dilation? Gastroenterology. 2012 Jun; 142(7):1409–1411. [PubMed: 22542829]
50. Schroeder S, Fleischer DM, Masterson JC, Gelfand E, Furuta GT, Atkins D. Successful treatment of eosinophilic esophagitis with ciclesonide. The Journal of allergy and clinical immunology. 2012 May; 129(5):1419–1421. [PubMed: 22480537]
51. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010 Nov; 139(5):1526–1537. 1537 e1521. [PubMed: 20682320]
52. Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. Mayo Clin Proc. 2003 Jul; 78(7):830–835. [PubMed: 12839078]
53. Teitelbaum J, Fox V, Twarog F, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. Gastroenterology. 2002; 122:1216–1225. [PubMed: 11984507]
54. Faubion WA Jr. Perrault J, Burgart LJ, Zein NN, Clawson M, Freese DK. Treatment of eosinophilic esophagitis with inhaled corticosteroids. Journal of pediatric gastroenterology and nutrition. 1998 Jul; 27(1):90–93. [PubMed: 9669733]
55. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology. 2006 Nov; 131(5): 1381–1391. [PubMed: 17101314]

56. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clinical gastroenterology and hepatology. 2008 Feb; 6(2):165–173. [PubMed: 18237866]
57. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology. 2010 Aug; 139(2):418–429. [PubMed: 20457157]
58. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral Viscous Budesonide: A Potential New Therapy for Eosinophilic Esophagitis in Children. The American journal of gastroenterology. 2007 Jun 20.
59. Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Digestive diseases and sciences. 2009 Nov; 54(11):2312–2317. [PubMed: 19714466]
60. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. The American journal of gastroenterology. 2007 Jun; 102(6):1301–1306. [PubMed: 17531015]
61. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut. 2013 Jun; 62(6): 824–832. [PubMed: 22580413]
62. Zhang X, Cheng E, Huo X, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. PloS one. 2012; 7(11):e50037. [PubMed: 23185525]
63. Otani IM, Anilkumar AA, Newbury RO, et al. Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2013 Jun; 131(6):1576–1582. [PubMed: 23623266]
64. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. The Journal of allergy and clinical immunology. 2012 Feb; 129(2):456–463. 463 e451–453. [PubMed: 22206777]
65. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology. 2011 Nov; 141(5):1593–1604. [PubMed: 21835135]
66. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2014 Sep 13.
67. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of Dietary Interventions for Inducing Histologic Remission in Patients With Eosinophilic Esophagitis: A Systematic Review and Meta-analysis. Gastroenterology. 2014 Jun; 146(7):1639–1648. [PubMed: 24534634]
68. Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. The American journal of gastroenterology. 2013 May; 108(5):759–766. [PubMed: 23381017]
69. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995 Nov; 109(5):1503–1512. [PubMed: 7557132]
70. Greenhawt M, Rubenstein JH. A tailored vs empiric diet--which is best for eosinophilic esophagitis? Gastroenterology. 2013 Jun; 144(7):1560–1561. [PubMed: 23623872]
71. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. The Journal of allergy and clinical immunology. 2012 Aug; 130(2):461–467. e465. [PubMed: 22743304]
72. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2012 Jun; 129(6):1570–1578. [PubMed: 22541246]
73. Rodriguez-Sanchez J, Gomez Torrijos E, Lopez Viedma B, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. Allergy. 2014 Jul; 69(7): 936–942. [PubMed: 24816218]

74. Molina-Infante J, Arias A, Barrio J, Rodriguez-Sanchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol. 2014 Nov; 134(5):1093–1099. e1091. [PubMed: 25174868]

75. Gonsalves N, Kagalwalla AF. Dietary treatment of eosinophilic esophagitis. Gastroenterology clinics of North America. 2014 Jun; 43(2):375–383. [PubMed: 24813522]

76. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. The Journal of allergy and clinical immunology. 2013 Mar; 131(3):797–804. [PubMed: 23375693]

77. Lucendo AJ, Arias A, Gonzalez-Cervera J, Mota-Huertas T, Yague-Compadre JL. Tolerance of a cow's milk-based hydrolyzed formula in patients with eosinophilic esophagitis triggered by milk. Allergy. 2013 Aug; 68(8):1065–1072. [PubMed: 23906026]

78. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clinical gastroenterology and hepatology. 2006 Sep; 4(9):1097–1102. [PubMed: 16860614]

79. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. Journal of pediatric gastroenterology and nutrition. 2012 Dec; 55(6): 711–716. [PubMed: 22820121]

80. Kruszewski PG, Russo JM, Franciosi JP, Varni JW, Platts-Mills TA, Erwin EA. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Diseases of the esophagus. 2015 Feb 26.

81. Ukleja A, Shiroky J, Agarwal A, Allende D. Esophageal dilations in eosinophilic esophagitis: a single center experience. World journal of gastroenterology. 2014 Jul 28; 20(28):9549–9555. [PubMed: 25071351]

82. Schoepfer A. Treatment of eosinophilic esophagitis by dilation. Digestive diseases. 2014; 32(1–2): 130–133. [PubMed: 24603396]

83. Lipka S, Keshishian J, Boyce HW, Estores D, Richter JE. The natural history of steroid-naive eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years. Gastrointestinal endoscopy. 2014 Oct; 80(4): 592–598. [PubMed: 24703087]

84. Ally MR, Dias J, Veerappan GR, Maydonovitch CL, Wong RK, Moawad FJ. Safety of dilation in adults with eosinophilic esophagitis. Diseases of the esophagus. 2013 Apr; 26(3):241–245. [PubMed: 22676406]

85. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. The American journal of gastroenterology. 2010 May; 105(5):1062–1070. [PubMed: 19935783]

86. Hirano I. Dilation in eosinophilic esophagitis: to do or not to do? Gastrointestinal endoscopy. 2010 Apr; 71(4):713–714. [PubMed: 20363413]

87. Dellon ES, Gibbs WB, Rubinas TC, et al. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. Gastrointestinal endoscopy. 2010 Apr; 71(4):706–712. [PubMed: 20170913]

88. Bohm M, Richter JE, Kelsen S, Thomas R. Esophageal dilation: simple and effective treatment for adults with eosinophilic esophagitis and esophageal rings and narrowing. Diseases of the esophagus. 2010 Jul; 23(5):377–385. [PubMed: 20353444]

89. Chehade M, Aceves SS, Furuta GT, Fleischer DM. Food allergy and eosinophilic esophagitis: what do we do? The journal of allergy and clinical immunology. In practice. 2015 Jan-Feb;3(1):25–32. [PubMed: 25577614]

90. Aceves SS. Food allergy testing in eosinophilic esophagitis: what the gastroenterologist needs to know. Clinical gastroenterology and hepatology. 2014 Aug; 12(8):1216–1223. [PubMed: 24035776]

91. Papadopoulou A, Koletzko S, Heuschkel R, et al. Management guidelines of eosinophilic esophagitis in childhood. Journal of pediatric gastroenterology and nutrition. 2014 Jan; 58(1):107–118. [PubMed: 24378521]

92. Henry ML, Atkins D, Fleischer D, Pan Z, Ruybal J, Furuta GT. Factors contributing to adherence to dietary treatment of eosinophilic gastrointestinal diseases. Journal of pediatric gastroenterology and nutrition. 2012 Mar; 54(3):430–432. [PubMed: 22094899]

93. Menard-Katcher C, Henry M, Furuta GT, Atkins D, Maune NC, Haas AM. Significance of feeding dysfunction in eosinophilic esophagitis. World journal of gastroenterology. 2014 Aug 21; 20(31): 11019–11022. [PubMed: 25152606]

94. Pentiuk SP, Miller CK, Kaul A. Eosinophilic Esophagitis in Infants and Toddlers. Dysphagia. 2007 Jan; 22(1):44–48. [PubMed: 17024545]

95. Klinnert MD. Psychological impact of eosinophilic esophagitis on children and families. Immunology and allergy clinics of North America. 2009 Feb; 29(1):99–107. x. [PubMed: 19141345]

96. Ko HM, Morotti RA, Yershov O, Chehade M. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. The American journal of gastroenterology. 2014 Aug; 109(8):1277–1285. [PubMed: 24957155]

97. Caldwell JM, Collins MH, Stucke EM, et al. Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. The Journal of allergy and clinical immunology. 2014 Nov; 134(5):1114–1124. [PubMed: 25234644]

98. Lwin T, Melton SD, Genta RM. Eosinophilic gastritis: histopathological characterization and quantification of the normal gastric eosinophil content. Modern pathology. 2011 Apr; 24(4):556–563. [PubMed: 21169993]

99. Prussin C. Eosinophilic gastroenteritis and related eosinophilic disorders. Gastroenterology clinics of North America. 2014 Jun; 43(2):317–327. [PubMed: 24813518]

100. Alfadda AA, Shaffer EA, Urbanski SJ, Storr MA. Eosinophilic colitis is a sporadic self-limited disease of middle-aged people: a population-based study. Colorectal disease. 2014 Feb; 16(2): 123–129. [PubMed: 24138295]

101. Fernandez Salazar LI, Borrego Pintado H, Velayos Jimenez B, Gonzalez Hernandez JM. Differential diagnosis and management of histologic eosinophilic colitis. Journal of Crohn's & colitis. 2013 Feb; 7(1):e20–e21.

102. Brandon JL, Schroeder S, Furuta GT, Capocelli K, Masterson JC, Fenton LZ. CT imaging features of eosinophilic colitis in children. Pediatric radiology. 2013 Jun; 43(6):697–702. [PubMed: 23361493]

103. Alfadda AA, Storr MA, Shaffer EA. Eosinophilic colitis: epidemiology, clinical features, and current management. Therapeutic advances in gastroenterology. 2011 Sep; 4(5):301–309. [PubMed: 21922029]

104. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterology clinics of North America. 2014 Jun; 43(2):257–268. [PubMed: 24813514]

105. Gaertner WB, Macdonald JE, Kwaan MR, et al. Eosinophilic colitis: university of Minnesota experience and literature review. Gastroenterology research and practice. 2011; 2011:857508. [PubMed: 21837236]

106. DeBrosse CW, Case JW, Putnam PE, Collins MH, Rothenberg ME. Quantity and distribution of eosinophils in the gastrointestinal tract of children. Pediatric and developmental pathology. 2006 May-Jun;9(3):210–218. [PubMed: 16944979]

107. Lowichik A, Weinberg A. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. Modern pathology. 1996; 110–114:9.

108. Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut. 1990 Jan; 31(1):54–58. [PubMed: 2318432]

109. Cello JP. Eosinophilic gastroenteritis-a complex disease entity. The American journal of medicine. 1979; 67:1097–1104. [PubMed: 517550]

110. Fleischer DM, Atkins D. Evaluation of the patient with suspected eosinophilic gastrointestinal disease. Immunology and allergy clinics of North America. 2009 Feb; 29(1):53–63. ix. [PubMed: 19141341]

111. Yan BM, Shaffer EA. Primary eosinophilic disorders of the gastrointestinal tract. Gut. 2009 May; 58(5):721–732. [PubMed: 19052023]
112. Chang JY, Choung RS, Lee RM, et al. A shift in the clinical spectrum of eosinophilic gastroenteritis toward the mucosal disease type. Clinical gastroenterology and hepatology. 2010 Aug; 8(8):669–675. quiz e688. [PubMed: 20451664]
113. Liu E, Lee HS, Agardh D. Risk of celiac disease according to HLA haplotype and country. The New England journal of medicine. 2014 Sep 11.371(11):1074. [PubMed: 25207776]
114. Soon IS, Butzner JD, Kaplan GG, Debruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. Journal of pediatric gastroenterology and nutrition. 2013 Jul; 57(1):72–80. [PubMed: 23539047]
115. Catassi C, Kryszak D, Bhatti B, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Annals of medicine. 2010 Oct; 42(7):530–538. [PubMed: 20868314]
116. Husby S, Koletzko S, Korponay-Szabo IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. Journal of pediatric gastroenterology and nutrition. 2012 Jan; 54(1):136–160. [PubMed: 22197856]
117. Liu E, Lee HS, Aronsson CA, et al. Risk of pediatric celiac disease according to HLA haplotype and country. The New England journal of medicine. 2014 Jul 3; 371(1):42–49. [PubMed: 24988556]
118. Aronsson CA, Lee HS, Liu E, et al. Age at gluten introduction and risk of celiac disease. Pediatrics. 2015 Feb; 135(2):239–245. [PubMed: 25601977]
119. Koning F. Pathophysiology of celiac disease. Journal of pediatric gastroenterology and nutrition. 2014 Jul; 59(Suppl 1):S1–S4.
120. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA, American College of G. ACG clinical guidelines: diagnosis and management of celiac disease. The American journal of gastroenterology. 2013 May; 108(5):656–676. quiz 677. [PubMed: 23609613]
121. Colombel JF, Torpier G, Janin A, Klein O, Cortot A, Capron M. Activated eosinophils in adult coeliac disease: evidence for a local release of major basic protein. Gut. 1992 Sep; 33(9):1190–1194. [PubMed: 1427370]
122. Brown IS, Smith J, Rosty C. Gastrointestinal pathology in celiac disease: a case series of 150 consecutive newly diagnosed patients. American journal of clinical pathology. 2012 Jul; 138(1): 42–49. [PubMed: 22706856]
123. Ludvigsson JF, Aro P, Walker MM, et al. Celiac disease, eosinophilic esophagitis and gastroesophageal reflux disease, an adult population-based study. Scandinavian journal of gastroenterology. 2013 Jul; 48(7):808–814. [PubMed: 23672638]
124. Ahmed OI, Qasem SA, Abdulsattar JA, Snow AN, Hill ID. Esophageal Eosinophilia in Pediatric Patients with Celiac Disease; Is it a Causal or an Incidental Association? Journal of pediatric gastroenterology and nutrition. 2014 Nov 25.
125. Verzegnassi F, Bua J, De Angelis P, Dall'oglio L, Di Leo G, Ventura A. Eosinophilic oesophagitis and coeliac disease: is it just a casual association? Gut. 2007 Jul; 56(7):1029–1030. [PubMed: 17566042]
126. Quaglietta L, Coccorullo P, Miele E, Pascarella F, Troncone R, Staiano A. Eosinophilic oesophagitis and coeliac disease: is there an association? Alimentary pharmacology & therapeutics. 2007 Aug; 26(3):487–493. [PubMed: 17635383]
127. Leslie C, Mews C, Charles A, Ravikumara M. Celiac disease and eosinophilic esophagitis: a true association. Journal of pediatric gastroenterology and nutrition. 2010 Apr; 50(4):397–399. [PubMed: 19841598]
128. Ooi CY, Day AS, Jackson R, Bohane TD, Tobias V, Lemberg DA. Eosinophilic esophagitis in children with celiac disease. Journal of gastroenterology and hepatology. 2008 Jul; 23(7 Pt 1): 1144–1148. [PubMed: 18070017]
129. Fasano A, Catassi C. Clinical practice. Celiac disease. The New England journal of medicine. 2012 Dec 20; 367(25):2419–2426. [PubMed: 23252527]
130. Burisch J, Munkholm P. Inflammatory bowel disease epidemiology. Current opinion in gastroenterology. 2013 Jul; 29(4):357–362. [PubMed: 23695429]

131. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004 May; 126(6):1504–1517. [PubMed: 15168363]

132. Danese S, Fiocchi C. Ulcerative colitis. The New England journal of medicine. 2011 Nov 3; 365(18):1713–1725. [PubMed: 22047562]

133. Graham DB, Xavier RJ. From genetics of inflammatory bowel disease towards mechanistic insights. Trends in immunology. 2013 Aug; 34(8):371–378. [PubMed: 23639549]

134. Ellinghaus D, Bethune J, Petersen BS, Franke A. The genetics of Crohn's disease and ulcerative colitis--status quo and beyond. Scandinavian journal of gastroenterology. 2015 Jan; 50(1):13–23. [PubMed: 25523552]

135. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. Gastroenterology. 2014 May; 146(6):1489–1499. [PubMed: 24560869]

136. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. 2007 May 12; 369(9573):1641–1657. [PubMed: 17499606]

137. Isene R, Bernklev T, Hoie O, et al. Extraintestinal manifestations in Crohn's disease and ulcerative colitis: results from a prospective, population-based European inception cohort. Scandinavian journal of gastroenterology. 2015 Mar; 50(3):300–305. [PubMed: 25535653]

138. Katsanos KH, Zinovieva E, Lambri E, Tsianos EV. Eosinophilic-Crohn overlap colitis and review of the literature. Journal of Crohn's & colitis. 2011 Jun; 5(3):256–261.

139. Woodruff SA, Masterson JC, Fillon S, Robinson ZD, Furuta GT. Role of eosinophils in inflammatory bowel and gastrointestinal diseases. Journal of pediatric gastroenterology and nutrition. 2011 Jun; 52(6):650–661. [PubMed: 21593640]

140. Choy MY, Walker-Smith JA, Williams CB, MacDonald TT. Activated eosinophils in chronic inflammatory bowel disease. Lancet. 1990 Jul 14; 336(8707):126–127. [PubMed: 1975316]

141. Bischoff SC, Wedemeyer J, Herrmann A, et al. Quantitative assessment of intestinal eosinophils and mast cells in inflammatory bowel disease. Histopathology. 1996 Jan; 28(1):1–13. [PubMed: 8838115]

142. Bischoff SC, Grabowsky J, Manns MP. Quantification of inflammatory mediators in stool samples of patients with inflammatory bowel disorders and controls. Digestive diseases and sciences. 1997 Feb; 42(2):394–403. [PubMed: 9052525]

143. Troncone R, Caputo N, Esposito V, et al. Increased concentrations of eosinophilic cationic protein in whole-gut lavage fluid from children with inflammatory bowel disease. Journal of pediatric gastroenterology and nutrition. 1999 Feb; 28(2):164–168. [PubMed: 9932849]

144. Stevceva L, Pavli P, Husband A, Matthaei KI, Young IG, Doe WF. Eosinophilia is attenuated in experimental colitis induced in IL-5 deficient mice. Genes and immunity. 2000 Feb; 1(3):213–218. [PubMed: 11196714]

145. Chen W, Paulus B, Shu D, Wilson, Chadwick V. Increased serum levels of eotaxin in patients with inflammatory bowel disease. Scandinavian journal of gastroenterology. 2001 May; 36(5): 515–520. [PubMed: 11346206]

146. Carvalho AT, Elia CC, de Souza HS, et al. Immunohistochemical study of intestinal eosinophils in inflammatory bowel disease. Journal of clinical gastroenterology. 2003 Feb; 36(2):120–125. [PubMed: 12544193]

147. Furuta GT, Nieuwenhuis EE, Karhausen J, et al. Eosinophils alter colonic epithelial barrier function: role for major basic protein. American journal of physiology. Gastrointestinal and liver physiology. 2005 Nov; 289(5):G890–G897. [PubMed: 16227527]

148. Uzunismail H, Hatemi I, Dogusoy G, Akin O. Dense eosinophilic infiltration of the mucosa preceding ulcerative colitis and mimicking eosinophilic colitis: report of two cases. The Turkish journal of gastroenterology. 2006 Mar; 17(1):53–57. [PubMed: 16830279]

149. Wedemeyer J, Vosskuhl K. Role of gastrointestinal eosinophils in inflammatory bowel disease and intestinal tumours. Best practice & research. Clinical gastroenterology. 2008; 22(3):537–549. [PubMed: 18492570]

150. Masterson JC, McNamee EN, Jedlicka P, et al. CCR3 Blockade Attenuates Eosinophilic Ileitis and Associated Remodeling. The American journal of pathology. 2011 Nov; 179(5):2302–2314. [PubMed: 21945903]

151. Wedrychowicz A, Tomasik P, Pieczarkowski S, Kowalska-Duplaga K, Grzenda-Adamek Z, Fyderek K. Clinical value of serum eosinophilic cationic protein assessment in children with inflammatory bowel disease. Archives of medical science : AMS. 2014 Dec 22; 10(6):1142–1146. [PubMed: 25624851]

152. Masterson JC, McNamee EN, Fillon SA, et al. Eosinophil-mediated signalling attenuates inflammatory responses in experimental colitis. Gut. 2014 Sep 10.

153. Zezos P, Patsiaoura K, Nakos A, et al. Severe eosinophilic infiltration in colonic biopsies predicts patients with ulcerative colitis not responding to medical therapy. Colorectal disease. 2014 Dec; 16(12):O420–O430. [PubMed: 25040651]

154. Dvorak AM, Osage JE, Monahan RA, Dickersin GR. Crohn's disease: transmission electron microscopic studies. III. Target tissues. Proliferation of and injury to smooth muscle and the autonomic nervous system. Hum Pathol. 1980 Nov; 11(6):620–634. [PubMed: 6161074]

155. Dvorak AM. Ultrastructural evidence for release of major basic protein-containing crystalline cores of eosinophil granules in vivo: cytotoxic potential in Crohn's disease. J Immunol. 1980 Jul; 125(1):460–462. [PubMed: 6155407]

156. Dubucquoi S, Janin A, Klein O, et al. Activated eosinophils and interleukin 5 expression in early recurrence of Crohn's disease. Gut. 1995 Aug; 37(2):242–246. [PubMed: 7557575]

157. Saitoh O, Kojima K, Sugi K, et al. Fecal eosinophil granule-derived proteins reflect disease activity in inflammatory bowel disease. The American journal of gastroenterology. 1999 Dec; 94(12):3513–3520. [PubMed: 10606313]

158. Peterson CG, Sangfelt P, Wagner M, Hansson T, Lettesjo H, Carlson M. Fecal levels of leukocyte markers reflect disease activity in patients with ulcerative colitis. Scand J Clin Lab Invest. 2007; 67(8):810–820. [PubMed: 18034391]

159. Maltby S, Wohlfarth C, Gold M, Zbytnuik L, Hughes MR, McNagny KM. CD34 is required for infiltration of eosinophils into the colon and pathology associated with DSS-induced ulcerative colitis. The American journal of pathology. 2010 Sep; 177(3):1244–1254. [PubMed: 20696776]

160. Ahrens R, Waddell A, Seidu L, et al. Intestinal macrophage/epithelial cell-derived CCL11/eotaxin-1 mediates eosinophil recruitment and function in pediatric ulcerative colitis. Journal of immunology. 2008 Nov 15; 181(10):7390–7399.

161. Leiman DA, Lichtenstein GR. Therapy of inflammatory bowel disease: what to expect in the next decade. Current opinion in gastroenterology. 2014 Jul; 30(4):385–390. [PubMed: 24902037]

162. Rutgeerts P, Vermeire S, Van Assche G. Biological therapies for inflammatory bowel diseases. Gastroenterology. 2009 Apr; 136(4):1182–1197. [PubMed: 19249397]

163. Hansen JJ, Sartor RB. Therapeutic Manipulation of the Microbiome in IBD: Current Results and Future Approaches. Current treatment options in gastroenterology. 2015 Jan 18.

164. Lee D, Albenberg L, Compher C, et al. Diet in the Pathogenesis and Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2015 Jan 15.

165. Lichtenstein GR, Rutgeerts P, Sandborn WJ, et al. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. The American journal of gastroenterology. 2012 Jul; 107(7):1051–1063. [PubMed: 22613901]

166. Fletcher S, Van Hal S, Andresen D, et al. Gastrointestinal pathogen distribution in symptomatic children in Sydney, Australia. Journal of epidemiology and global health. 2013 Mar; 3(1):11–21. [PubMed: 23856534]

167. McCarty TR, Turkeltaub JA, Hotez PJ. Global progress towards eliminating gastrointestinal helminth infections. Current opinion in gastroenterology. 2014 Jan; 30(1):18–24. [PubMed: 24241244]

168. Berk SL, Verghese A, Alvarez S, Hall K, Smith B. Clinical and epidemiologic features of strongyloidiasis. A prospective study in rural Tennessee. Archives of internal medicine. 1987 Jul; 147(7):1257–1261. [PubMed: 3606282]

169. Centers for Disease C, Prevention. Notes from the field: strongyloides infection among patients at a long-term care facility--Florida, 2010–2012. MMWR. Morbidity and mortality weekly report. 2013 Oct 25.62(42):844. [PubMed: 24153317]

170. Centers for Disease C, Prevention. Notes from the field: Strongyloidiasis in a rural setting--Southeastern Kentucky, 2013. MMWR. Morbidity and mortality weekly report. 2013 Oct 25.62(42):843. [PubMed: 24153316]

171. Russell ES, Gray EB, Marshall RE, et al. Prevalence of Strongyloides stercoralis antibodies among a rural Appalachian population--Kentucky, 2013. The American journal of tropical medicine and hygiene. 2014 Nov; 91(5):1000–1001. [PubMed: 25157122]

172. Pelletier LL Jr. Baker CB, Gam AA, Nutman TB, Neva FA. Diagnosis and evaluation of treatment of chronic strongyloidiasis in ex-prisoners of war. The Journal of infectious diseases. 1988 Mar; 157(3):573–576. [PubMed: 3343527]

173. Thompson BF, Fry LC, Wells CD, et al. The spectrum of GI strongyloidiasis: an endoscopic-pathologic study. Gastrointestinal endoscopy. 2004 Jun; 59(7):906–910. [PubMed: 15173813]

174. Requena-Mendez A, Chiodini P, Bisoffi Z, Buonfrate D, Gotuzzo E, Munoz J. The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. PLoS neglected tropical diseases. 2013; 7(1):e2002. [PubMed: 23350004]

175. Kim MJ, Kim WH, Jung HC, Chai JW, Chai JY. Isospora belli Infection with Chronic Diarrhea in an Alcoholic Patient. The Korean journal of parasitology. 2013 Apr; 51(2):207–212. [PubMed: 23710089]

176. Esteve C, Resano A, Diaz-Tejeiro P, Fernandez-Benitez M. Eosinophilic gastritis due to Anisakis: a case report. Allergologia et immunopathologia. 2000 Jan-Feb;28(1):21–23. [PubMed: 10757855]

177. Kim SG, Jo YJ, Park YS, et al. Four cases of gastric submucosal mass suspected as anisakiasis. The Korean journal of parasitology. 2006 Mar; 44(1):81–86. [PubMed: 16514287]

178. Montalto M, Miele L, Marcheggiano A, et al. Anisakis infestation: a case of acute abdomen mimicking Crohn's disease and eosinophilic gastroenteritis. Digestive and liver disease. 2005 Jan; 37(1):62–64. [PubMed: 15702862]

Box 1

Key Points for Celiac Disease

- Celiac disease is an immune-mediated disease in which gluten-containing foods stimulate a reproducible clinical and histological 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.

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's disease (CrD) and ulcerative colitis (UC).
- Treatments for IBDs include corticosteroids for acute exacerbations, and 5-aminosalicylates, immunosuppressives and biologics directed against TNF-α for maintenance management.
- The association of IBDs with mucosal eosinophilia and its secreted products is increasing, but eosinophils' role in the pathogenesis of IBD remains uncertain.

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

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 (IBD) with mucosal eosinophilia and its secreted products is increasing, but eosinophils' role in the pathogenesis of IBD remains uncertain.
- Intestinal helminth infection can produce a clinical picture indistinguishable from eosinophilic gastroenteritis

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, immunosup-pressive agents
Celiac Disease	Abdominal pain, diarrhea, weight loss, bloating, extra-intestinal 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

Table 2

Selected parasitic diseases associated with gastrointestinal manifestations and eosinophilia

PARASITE	CLINICAL PRESENTATION	PERIPHERAL BLOOD EOSINOPHIL COUNT	TISSUE EOSINO-PHILIA	DIAGNOSIS	TREATMENT
Hookworm (Ancylostoma duodenale and Necator americanus)	Skin rash on inoculation, asymptomatic to mild gastrointestinal disease, anemia and protein-losing enteropathy with large burden	Elevated	GI	Direct visualization of eggs or larvae on microscopy	Albendazole
Trichinella spiralis	Diarrhea may be seen early in infection prior to the development of myalgia and other symptoms	Elevated	Muscle	Serology, muscle biopsy	Albendazole, steroids
Strongyloides stercoralis	Abdominal pain, diarrhea, rash, or asymptomatic in chronic infection	Elevated	GI	Multiple modalities including stool and serology	Ivermectin, albendazole
Cystisospora belli	Diarrhea	Elevated	GI175	Stool examination for cysts	Trimethoprim sulfamethoxazole
Anisakiasis	Abdominal pain; allergic gastroenteritis	Elevated	GI176-178	Endoscopic visualization of worm	Removal of worm