Eosinophilic gastrointestinal diseases

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INTRODUCTION

Eosinophilic gastrointestinal diseases (EGIDs) are chronic, immune-mediated disorders characterized histologically by a pathologic increase in eosinophil-predominant tissue inflammation and clinically by gastrointestinal symptoms.

This topic will review the clinical manifestations, diagnosis, and management of non-eosinophilic esophagitis (EoE) EGIDs, including eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC). EoE is discussed in detail separately. (See "Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE)".)

NOMENCLATURE

Eosinophilic gastrointestinal disease (EGID) is an umbrella term that collectively refers to a group of conditions including eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC). The nomenclature for EGID has been revised by an international consensus as the term "eosinophilic gastroenteritis" was used by some as a catch-all phrase for all non-EoE EGIDs [1]. For the purpose of this topic, we will use the revised nomenclature: EGID will be used as an overall disease category. Eosinophils involving the esophagus will remain named EoE, and all other organ location involvement will be referred to as "non-EoE EGID." Within this category, individual locations of involvement will be further defined as: EoG (involvement of the stomach), EoN (involvement of just the small

intestine), and EoC (involvement of the colon). In cases of EoN, if a more specific location is known, it will be further defined to specify these locations (ie, eosinophilic duodenitis [EoD], eosinophilic jejunitis [EoJ] and eosinophilic ileitis [EoI]).

In some cases, patients may have concomitant inflammation of multiple segments of the gut including the esophagus. Nomenclature of multiple areas of the gut will include nomenclature of both areas of involvement. For instance, a patient with involvement of the stomach and duodenum will be referred to as having EoG and EoD. Multisegment disease involving the esophagus will include "with esophageal involvement" to the defined disease category to separate this from EoE, which is esophageal involvement alone. As more knowledge of multisegment disease is gained, this definition may be further defined.

EPIDEMIOLOGY

There are limited data on the prevalence of eosinophilic gastritis (EoG), enteritis (EoN), and colitis (EoC) due to the rarity of these diseases. The prevalence of eosinophilic gastroenteritis (EoGE) in the United States is estimated to be 22 to 28 per 100,000 persons based on prior survey data [2]. However, estimates from an insurance claims database suggest these diseases are much more rare [3]. Standardized estimated prevalence of EoG, EoGE, and EoC in this study was 6.3/100,000, 8.4/100,000, and 3.3/100,000, respectively. In this study, the prevalence of EoGE was highest in children <5 years, whereas EoG was more prevalent among older age groups. When present in adults, these diseases can occur at any age but typically present in the third through fifth decades, with a peak age of onset in the third decade [4-6]. Male-to-female ratio tends to be equal in these studies compared with eosinophilic esophagitis (EoE), which has a large male predominance [7].

PATHOGENESIS

The pathogenesis of eosinophilic gastrointestinal disease (EGID) has previously not been well understood. Multiple epidemiologic and clinical features suggest an allergic component, with 50 to 70 percent of patients having concomitant atopic conditions [4,7-9]. In addition, patients with non-eosinophilic esophagitis (EoE) EGIDs may have elevated serum immunoglobulin E (IgE) levels [9-12]. (See 'Clinical manifestations' below and 'Laboratory findings' below.)

Although the role of food allergy in non-EoE EGIDs has not been as clearly defined as with EoE, several reports have described an improvement in disease activity with an elemental or elimination diet [13-16]. Preliminary results from a pilot study suggest a food allergy-free diet in

adults improves histologic, endoscopic, symptomatic, and molecular features of eosinophilic gastritis/gastroenteritis (EoG/EoGE), suggesting a dominant role for food allergens in the pathogenesis [17].

In allergic EoG/EoGE patients, but not those with conventional anaphylactic food allergy, a population of interleukin-5 (IL-5) expressing food allergen-specific T helper 2 (Th2) cells has been identified [18]. This suggests that food exposure activates and drives the differentiation of IL-5+ Th2 cells in EoG/EoGE, leading to gut eosinophilia. The eotaxin family of chemokines appears to play a central role in the recruitment of eosinophils into the gut in response to antigen challenge [19]. Once eosinophils are recruited to the gastrointestinal tract, they are able to persist through the release of eosinophil-active cytokines, such as IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor [20]. Eosinophils can also cause local inflammation by release of eosinophil major basic protein, a cytotoxic cationic protein [21]. A study supporting the role of Th2 cytokines found that levels of Th2 cytokines (IL-4, IL-5, IL-13) and the eosinophil-related chemokine eotaxin-3 were upregulated [22]. They also demonstrated that EoG had a prominent and conserved transcriptome that had minimal overlap with that of EoE [22].

CLINICAL MANIFESTATIONS

The entire gastrointestinal tract from esophagus to colon can be affected in patients with eosinophilic gastrointestinal diseases (EGIDs) [4,23-25]. In patients with eosinophilic gastritis (EoG), inflammation is typically limited to the antrum and body of the stomach. While studies have suggested that eosinophilic gastroenteritis (EoGE) has a predilection for the distal antrum and proximal small bowel, this may reflect sampling bias because of the accessibility of these areas for biopsy and inflammation may be present distally [10]. It should be noted that involvement of the distal bowel can only be implicated if enteroscopy with biopsies of these regions is performed or if imaging studies implicate distal small bowel involvement.

Approximately 50 to 70 percent of patients with non-eosinophilic esophagitis (EoE) EGID have a history of an allergic disease including asthma, defined food sensitivities, eczema, or rhinitis [4,7-9]. The clinical features of EGIDs vary and are related to the location and extent of the organ involved as well as the layer(s) of bowel with eosinophilic infiltration [10].

Mucosal disease — Eosinophilic mucosal infiltration produces nonspecific symptoms that depend upon the area of the gastrointestinal tract that is involved. In a retrospective study of 40 patients with mucosal non-EoE EGID, the most common symptoms were abdominal pain, nausea, vomiting, early satiety, and diarrhea [4]. Only one-third of patients had a weight loss of

2.4 kg or more. Patients with diffuse small bowel disease/enteritis can develop malabsorption, protein-losing enteropathy, and failure to thrive [10,26].

Muscular layer disease — Eosinophilic infiltration of the muscle layer of the gastrointestinal tract results in wall thickening and impaired motility. Patients may present with symptoms of intestinal obstruction, including nausea, vomiting, gastric outlet obstruction, and abdominal distention [4,10,26]. Patients with pseudoachalasia or an esophageal stricture may present with dysphagia and regurgitation of undigested food. Eosinophilic infiltration may result in perforation or obstruction of the gastric outlet, small bowel, or rarely the colon [4,8-10,12,26-29]. (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Serosal disease — Patients with serosal EGID present with isolated ascites or ascites in combination with symptoms characteristic of mucosal or muscular gastritis, enteritis, or colitis [4]. An eosinophilic pleural effusion may also be present [26]. Typically, when the ascitic or pleural fluid is tested, high levels of eosinophils are found. (See "Pleural fluid eosinophilia".)

LABORATORY FINDINGS

Various laboratory tests may be abnormal in patients with non-eosinophilic esophagitis (EoE) eosinophilic gastrointestinal diseases (EGIDs).

- Peripheral eosinophil counts are usually elevated in patients but may be normal in approximately 20 percent of patients [4]. Peripheral eosinophil counts range from 5 to 35 percent, with an average absolute eosinophil count of 1000 cells/microL [30]. Mucosal and serosal EGID are characterized by higher eosinophil counts compared with disease that involves the muscular layer.

- Patients with malabsorption due to mucosal EGID may have an abnormal D-xylose test due to carbohydrate malabsorption and increased fecal fat excretion with prolonged prothrombin time [10,26]. Increased mucosal permeability may result in protein-losing enteropathy and resultant hypoalbuminemia. Anemia may result from impaired iron absorption and occult gastrointestinal bleeding [10,11,26]. (See "Protein-losing gastroenteropathy", section on 'Nonerosive gastrointestinal diseases' and "Approach to the adult patient with suspected malabsorption".)

- Non-EoE EGID is often associated with iron deficiency. The erythrocyte sedimentation rate is usually normal but can be modestly elevated in approximately 25 percent of patients [4,26].

- Serum IgE levels can be elevated, especially in children [4,9,10,12].

IMAGING FINDINGS

Imaging (eg, barium studies, abdominal computed tomography [CT] scan, or magnetic resonance imaging [MRI]) of the gastrointestinal tract may reveal thickening or nodularity in the antrum and thickened or "saw-tooth" mucosa in the small bowel [27]. Imaging in patients with muscular involvement may reveal irregular luminal narrowing, especially in the distal antrum and proximal small bowel. However, these findings are neither sensitive nor specific for eosinophilic gastritis/eosinophilic gastroenteritis.

EVALUATION

Eosinophilic gastritis or enteritis (EoG/EoN) should be suspected in a patient with abdominal pain, nausea, vomiting, early satiety, diarrhea, weight loss, or ascites associated with peripheral eosinophilia (eosinophil count >500 eosinophils/microL in the peripheral blood), and/or a history of food allergy or intolerance. Evaluation of a patient with suspected non-eosinophilic esophagitis (EoE) eosinophilic gastrointestinal disease (EGID) serves to exclude other causes of eosinophilia and establish the diagnosis.

Diagnosis — The diagnosis of non-EoE EGID is based on the presence of eosinophilic infiltration of the gastrointestinal tract on biopsy and/or eosinophilic ascitic fluid, lack of involvement of other organs, and absence of other causes of intestinal eosinophilia.

History and physical examination — Drug-induced peripheral eosinophilia should be excluded with a detailed review of past, current, and over-the-counter medications and dietary and herbal supplements. Dietary history should include the ingestion of raw or undercooked meat and history of residence in or recent travel to parasite-endemic areas.

The physical examination should focus on identifying lesions that suggest a possible cause of eosinophilia and determining the presence of extraintestinal organ involvement, which would suggest an alternative diagnosis. We specifically examine the skin, eyes, nose, lymph nodes, and abdomen in addition to performing cardiovascular, respiratory, and neurologic examinations. (See 'Differential diagnosis' below.)

Laboratory evaluation and other testing

- Laboratory evaluation should include a complete blood count with differential to determine the absolute eosinophil count. In addition, we also obtain serum electrolytes, albumin, serum iron, iron binding capacity, ferritin, and markers of inflammation, erythrocyte sedimentation rate or C-reactive protein. (See 'Laboratory findings' above.)

  As eosinophilia can be caused by a number of conditions other than EGID, initial tests that may be performed in patients with peripheral eosinophilia to exclude other etiologies include:

  - Review of the peripheral blood smear (for immature white blood cells, dysplastic features).
  - Serum chemistries for evidence of adrenal dysfunction (eg, hyponatremia, hyperkalemia).
  - Serum B12 level (elevated in myeloproliferative neoplasms).
  - Serum immunoglobulin subsets, as evidence of immune deficiency (IgE, immunoglobulin M [IgM], immunoglobulin G [IgG]).
  - Human immunodeficiency virus (HIV) serology.
  - Serum tryptase (elevated in systemic mastocytosis and some neoplastic hypereosinophilic syndromes).
  - Flow cytometry for lymphocyte subsets (may show clonality in lymphoid lymphoma or leukemia; reduced CD4 count in HIV/acquired immunodeficiency syndrome [AIDS]; selective deficiencies in immunodeficiency syndromes). (See "Approach to the patient with unexplained eosinophilia", section on 'Causes of eosinophilia'.)

- Stool studies and serologic studies should be performed to exclude a parasitic infection. This should include microscopy for ova and parasites and serologies for *Strongyloides* and *Toxocara* species. Additional testing for antibodies to fungi and parasites (eg, *Coccidioides*, *Echinococcus*, *Schistosoma*, *Trichinella spiralis*) may be indicated in patients with a history of travel to or residence in endemic areas. (See 'Differential diagnosis' below.)

- In patients with ascites, ascitic fluid analysis should include cell count with differential, Gram stain, culture, acid-fast bacillus stain, fungal and mycobacterial cultures, and cytology. Although there are no established criteria for ascitic fluid eosinophilia, studies have reported markedly elevated eosinophil counts (up to 88 percent) in patients with EGID [10].

- As the presence of other organ involvement excludes the diagnosis of EGID, we also perform the following testing:

  Renal function (serum chemistries, creatinine, urinalysis).

- Hepatic function (liver enzymes, total bilirubin).
- Cardiac function (troponin, electrocardiogram); those with elevated troponin should have an echocardiogram.
- Pulmonary function.

Endoscopy and biopsy — Endoscopic findings of mucosal disease are nonspecific and include nodular or polypoid gastric mucosa, thickened gastric folds, erythema, mucosal erosions, and, in severe cases, deep ulcerations (picture 1 and picture 2) [4,11,31,32]. An endoscopic reference system called the Eosinophilic Gastritis Reference System (EG-REFS) has been developed [33]. This scoring tool highlights common endoscopic features seen in EoG, including edema, gastric erosions/ulcerations, raised nodules, erythema, thickened folds, and pyloric stenosis. Because the stomach and duodenum are the most commonly affected sites, endoscopic evaluation is typically limited to the upper gastrointestinal tract. In patients with significant diarrhea, we also perform a colonoscopy with terminal ileum intubation to assess for eosinophilic colitis (EoC) or distal EoN. In patients where more distal intestinal involvement is suspected, imaging can be pursued as well as dedicated small bowel enteroscopy to obtain tissue diagnosis. As eosinophilic gastritis or gastroenteritis (EoG/EoGE) can be patchy in patients with mucosal disease, it is important that the following be performed:

- Biopsies should be taken from both normal- and abnormal-appearing mucosa, as normal-appearing mucosa can also demonstrate eosinophilic inflammation [32].

- Multiple biopsy samples (at least eight biopsies from the stomach and four from the duodenum) should be taken from both the stomach and small intestine, with additional biopsies of areas with visual abnormalities [11,34]. As gastrointestinal eosinophilia can be patchy, examination of multiple, nonoverlapping high-power fields (HPFs) in multiple biopsies is required for the diagnosis. In one study that included 88 subjects who met symptom criteria for EGID, of whom 72 met histologic criteria for EoG and eosinophilic duodenitis (EoD), an average of only 2.6 per 8 gastric biopsies and 2.2 per 4 duodenal biopsies per subject met thresholds for EoG/EoD [35].

Target biopsies should be taken from areas of endoscopic abnormalities, which are most common in the antrum and sometimes body. When obtaining biopsies of the duodenum, we recommend taking samples from both the duodenal bulb as well as the first and second portions of the duodenum. In cases where the mucosa is endoscopically normal, biopsies should be obtained in patients with a clinical suspicion of EGID. In patients with mucosal disease, upper endoscopy with biopsy of the stomach and small intestine is diagnostic in at least 80 percent of patients [4,11]. However, it is important to note that mucosal biopsies may be normal in patients with muscular or subserosal disease [4,32].

Full-thickness biopsy — As negative endoscopic mucosal biopsies do not definitively rule out muscular or subserosal EGID, laparoscopic full-thickness biopsy may be necessary to establish the diagnosis. In patients with bowel wall thickening and/or obstruction, this also serves to exclude an underlying malignancy. With newer biopsy techniques, large-capacity forceps or endoscopic mucosal resection of the suspected area can also be pursued to get deeper tissue acquisition in lieu of laparoscopic full-thickness biopsies. Imaging studies with tests like Upper GI Series/Small Bowel Follow-through, CT, or MR enterography may also give additional clues to a diagnosis of EGID in cases of muscular disease.

Histologic assessment — With the exception of the esophagus, eosinophils can be present in normal physiologic states throughout the rest of the gastrointestinal tract. The diagnosis of mucosal EGID is established by the presence of more than the expected number of eosinophils on microscopic examination of biopsies of the gastrointestinal tract (picture 1) [4,11,31,32]. Studies have shown there is still substantial variability in biopsy practice patterns among gastroenterologists who suspect an EGID [36]. As there is no established, defined cutoff for the number of eosinophils per HPF to diagnose EGID, the diagnosis should be confirmed by an experienced gastrointestinal pathologist to assess if the number of eosinophils is more than expected for a particular area. While there is movement to establish more formal diagnostic criteria in non-EoE EGID, the following cutoffs for the number of eosinophils per HPF have been suggested [37]:

- Stomach: ≥30 eosinophils per HPF in 5 HPF
- Duodenum: ≥52 eosinophils per HPF
- Ileum: >56 per HPF in the ileum
- Right colon: >100 per HPF
- Transverse and descending colon: >84 per HPF
- Rectosigmoid colon: >64 per HPF

DIFFERENTIAL DIAGNOSIS

Other diseases in which gastrointestinal symptoms are associated with peripheral eosinophilia can be distinguished from eosinophilic gastrointestinal diseases (EGIDs) based on the clinical presentation, laboratory tests, and/or biopsies of the gastrointestinal tract.

- **Intestinal infection** – Infection with *Ancylostoma*, *Anisakis*, *Ascaris*, *Strongyloides*, *Toxocara*, *Trichiura*, *Capillaria, Basidiobolomycosis,* and *Trichinella* can all cause gastrointestinal symptoms and peripheral eosinophilia. Infection with the dog hookworm *Ancylostoma caninum* can mimic EGID clinically and pathologically with eosinophilic infiltration of the

gut wall and ascites [38]. However, a parasitic infection can be excluded by examination of the stool for ova or parasites and/or serologic testing. In addition, stool examination in patients with a parasitic infection may reveal Charcot-Leyden crystals, which are the product of eosinophil granules. (See "Approach to the patient with unexplained eosinophilia" and "Eosinophil biology and causes of eosinophilia", section on 'Disorders with eosinophilic involvement of specific organs'.)

- **Malignancy** – Lymphoma, gastric cancer, and colon cancer can present with obstruction, peripheral eosinophilia, and a mass or bowel wall thickening on imaging. However, a malignancy can be differentiated from EGID by endoscopic or full-thickness biopsy. (See "Clinical features, diagnosis, and staging of gastric cancer" and "Clinical presentation and diagnosis of primary gastrointestinal lymphomas".)

- **Inflammatory bowel disease** – Rarely, inflammatory bowel diseases such as Crohn disease and ulcerative colitis may be associated with peripheral eosinophilia and/or an eosinophil-rich tissue infiltrate. These diseases can usually be differentiated from EGID by the presence of typical architectural distortion, focally enhanced neutrophilic exudates, and granulomas. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Diagnostic evaluation'.)

- **Hypereosinophilic syndrome** – Hypereosinophilic syndrome (HES) is an idiopathic condition associated with marked peripheral eosinophilia and may rarely present with predominant gastrointestinal symptoms. Many EGID patients may fulfill the diagnostic criterion for HES (absolute eosinophil count ≥1500 cells/mL present for over six months). However, in contrast with EGID, HES involves multiple organ systems (eg, heart, lungs, brain, and kidneys) [39]. If HES is suspected, referral to a hematologist and allergist should be pursued for further testing and evaluation. (See "Hypereosinophilic syndromes: Clinical manifestations, pathophysiology, and diagnosis", section on 'Clinical features'.)

- **Polyarteritis nodosa** – Polyarteritis nodosa (PAN) is associated with peripheral eosinophilia and abdominal pain. Nodular masses may also be visualized in the stomach but, in contrast with EGID, patients with PAN have systemic manifestations and a markedly elevated erythrocyte sedimentation rate, and on biopsy the eosinophilia is perivascular [26]. (See "Clinical manifestations and diagnosis of polyarteritis nodosa in adults", section on 'Clinical features'.)

- **Eosinophilic granulomatosis with polyangiitis** – An EGID, characterized by abdominal pain, diarrhea, gastrointestinal bleeding, and colitis, may precede or coincide with the vasculitic phase of eosinophilic granulomatosis with polyangiitis (Churg-Strauss

syndrome). Asthma is the cardinal feature of this disease (occurring in more than 95 percent of patients) and usually precedes the vasculitic phase by approximately 8 to 10 years. (See "Clinical features and diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss)", section on 'Clinical features'.)

- **Eosinophilic granuloma (Langerhans cell histiocytosis)** – Eosinophilic granuloma, like EGID, can present as a gastric antral mass. However, it can be differentiated from EGID by its typical granulomatous appearance on biopsy [40]. (See "Clinical manifestations, pathologic features, and diagnosis of Langerhans cell histiocytosis", section on 'Pathologic features'.)

DISEASE COURSE

The natural history and disease course of eosinophilic gastrointestinal disease (EGID) are not well defined as studies are limited to case reports and small series. While some untreated patients with EGID have been reported to rarely remit spontaneously, other patients may progress to severe malabsorption and malnutrition [10,32]. Other complications of untreated disease may include bowel obstruction or perforation in the setting of stricture formation and deep ulceration. In a small percentage of patients, EGID remits completely with treatment. The majority of patients, however, have chronic disease that will require long-term maintenance treatment. In one case series of patients with isolated gastric disease, 33 percent had multiple flares followed by full remission, and 67 percent had a continuous course of their disease. In patients with involvement of the proximal small bowel, 20 percent had a single flare without relapse, 60 percent had multiple flares followed by remission, and 20 percent had a continuous course of their disease. In another study surveying 786 Japanese patients, 61 percent had non-eosinophilic esophagitis (EoE) EGID, with 62 percent involving the small bowel and 49 percent involving the stomach. In this study, 66 percent of patients had continuous disease defined as persistent and severe [41].

Non-EoE EGIDs may have significant impact on patients' quality of life. Studies assessing common domains of health-related quality of life in adults with EoG/EoGE have shown impact in several domains, including psychosocial impact of diagnosis, impact on social relationships, financial impact, and impact on the body [42]. Survey studies collected in patients with EGID show a high disease burden with higher frequency of fatigue and isolation in patients with non-EoE EGID [43].

MANAGEMENT

Treatment of non-eosinophilic esophagitis (EoE) EGIDs is based on limited evidence and varies based upon the severity of symptoms and the presence of malabsorption/malnutrition (table 1). (See "Approach to the adult patient with suspected malabsorption" and "Overview of the treatment of malabsorption in adults".)

Initial therapy

Dietary therapy — In patients who are symptomatic or have evidence of malabsorption, we suggest an initial attempt at an empiric elimination diet, a six-food elimination diet, or an elemental diet. Based on studies in EoE, such diets should be undertaken for a minimum of four to six weeks [44].

Patients on an elemental diet are placed on an elemental formula, which eliminates all potential food allergens. The empiric elimination diet consists of avoidance of foods that most commonly cause immediate hypersensitivity in a population. The six-food elimination diet is the most commonly used empiric elimination diet. Specific foods that are avoided in the six-food elimination diet include soy, wheat, egg, milk, peanut/tree nuts, and fish/shellfish [45]. Elimination of fewer food allergens may also be tried in mild disease.

The main limitation of dietary therapy is patient compliance. Dietary therapy should be pursued in motivated patients and under the guidance of a dietitian trained in EGIDs. If a history of environmental allergens is identified, these should be treated in conjunction with the diet. The role of the dietitian includes patient education on the use of antigen-free foods, allergen avoidance, and food suggestions to ensure a nutritionally adequate diet. In addition, vitamin supplements may be necessary in patients who avoid foods containing calcium and vitamin D.

As in EoE, there can be a symptom/histologic disconnect, so investigation and biopsy of the mucosa is important in following disease activity [46]. We perform a repeat endoscopy with biopsy to follow response to treatment and/or degree of ongoing disease activity. If the dietary changes are successful at reducing symptoms and either peripheral eosinophilia or tissue eosinophilia, foods can be added back slowly in a systematic fashion from least allergenic to most allergenic. This approach is individualized and is not standardized across centers.

In patients with baseline peripheral eosinophilia, we check absolute eosinophil counts four to six weeks after instituting a dietary change. In patients with a peripheral eosinophilia, a reduction of >50 percent may be considered a response. However, the use of peripheral blood eosinophil count alone to monitor responses to therapeutic interventions has not been extensively studied and has limitations in patients lacking baseline peripheral eosinophilia. In addition, patients may have other allergic diseases (eg, atopic dermatitis, asthma) driving peripheral eosinophilia that do not respond to dietary therapy.

A small case series in adults with eosinophilic gastritis/gastroenteritis (EoG/EoGE) demonstrated clinical remission with a six-week course of dietary elimination. In this study, three of seven adults undergoing an empiric six-food elimination diet and all six adults undergoing an elemental diet had significant reduction in symptoms, complete histologic remission, endoscopic improvement, and normalization of peripheral eosinophilia within six weeks [15]. Preliminary results from a prospective dietary study that included 15 adults with EoG/EoGE demonstrated that after six weeks on elemental formula, histologic remission rates were 100 percent. This study also demonstrated improvement in symptoms, endoscopic features, and patient-reported outcome measures as well as the genetic transcriptome, which implicates a role for food allergens in the pathogenesis of non-EoE EGIDs [17].

Although food hypersensitivity plays an important role in EGID pathogenesis, no food allergy test (skin, patch, or allergen-specific IgE) has been shown to effectively identify specific culprit foods leading to clinical improvement of symptoms or tissue eosinophilia. Thus, similar to EoE, at present there is no evidence to support routine food allergy testing of EGID patients for use in clinical decision-making [47].

Glucocorticoids — If dietary measures do not result in improvement in symptoms, we suggest a trial of prednisone (typically 20 to 40 mg/day). However, evidence to support the use of glucocorticoids is limited to small series of patients [14,31]. Improvement in symptoms usually occurs within two weeks regardless of the layer of bowel involved [26,31]. Prednisone should then be tapered rapidly over the next two weeks. The goal of glucocorticoid therapy is to use the minimum dose needed to ameliorate severe EGID symptoms rather than use high doses to control tissue eosinophilia, as high doses of glucocorticoids are associated with systemic side effects. (See "Major side effects of systemic glucocorticoids", section on 'Organ-based toxicity of systemic glucocorticoids'.)

However, some patients require more prolonged therapy (up to several months) with a gradual oral glucocorticoid taper to produce complete resolution of symptoms [23,31]. Patients not responding to oral prednisone should be treated with equivalent intravenous glucocorticoids. Patients who fail to respond to intravenous glucocorticoids should undergo careful re-evaluation to rule out the presence of an underlying infection or alternate diagnoses including Crohn disease. (See 'Differential diagnosis' above.)

Recurrent symptoms — Patients who experience periodic flares months to years after the initial episode can be treated with another short course of oral prednisone, 20 to 40 mg/day, followed by a rapid taper [31].

In the majority of patients with EGID who experience recurrent symptoms during or immediately after the prednisone taper, long-term, low-dose maintenance therapy with prednisone (eg, 5 to 10 mg per day) is needed [10,26,31]. Alternatively, the controlled ileal release capsules may provide effective therapy in patients with distal disease. Successful transition from oral, conventional glucocorticoids to budesonide (nonenterically coated) has been reported in patients with EoG/EoGE involving the gastric antrum and small intestine [48-50]. It should be noted that the formulation of budesonide available for gastrointestinal use is in controlled ileal release capsules that do not release until the terminal ileum, largely bypassing the upper gastrointestinal tract. Case reports suggest that such budesonide formulations have been used off-label to target the upper gastrointestinal tract by dissolving the controlled release capsules in water or crushing the microspheres within the capsule for more proximal release [51,52].

Other therapies — Several other approaches have been described in case reports or small series to treat recurrent or refractory symptoms. However, none of these agents can be recommended for routine use based on limited available data.

- Lirentelimab is an anti-Siglec-8 antibody that depletes eosinophils and inhibits mast cells. In a randomized trial in which 65 adults with symptomatic EoG, eosinophilic duodenitis (EoD), or both were assigned to receive four monthly infusions of lirentelimab (low- or high-dose) or placebo, lirentelimab significantly reduced gastrointestinal eosinophils and total symptom score (mean difference 26 percentage points) [53]. Patients treated with lirentelimab had higher rates of mild to moderate infusion reactions compared with placebo (60 versus 23 percent). Further studies are needed to validate these results [53].

- Cromolyn (800 mg per day in four divided doses) has been effective for short- and long-term management of EoG/EoGE in some case reports, but conflicting results have also been reported [4,54,55]. Cromolyn works by preventing the release of mast cell mediators, including histamine, platelet-activating factor, and leukotrienes, and is also thought to reduce absorption of antigens by the small intestine.

- Ketotifen is an H1-antihistamine and mast cell stabilizer that has been associated with an improvement in clinical symptoms and tissue eosinophilia in small series of patients [56-58]. In adults, it is administered at a starting dose of 1 mg at night and increased to 2 to 4 mg per day for one to four months. Although ketotifen is available in some countries, it is not available in the United States.

- Leukotriene antagonist montelukast has been reported to be effective in some case reports but not in others [59-62].

- A clinical response to suplatast tosilate, which is a novel antiallergic drug that suppresses cytokine production, including interleukin (IL)-4 and IL-5 from T helper 2 cells, was described in a single patient [63].

- Humanized anti-IL-5 antibody treatment was associated with reduced peripheral and tissue eosinophil counts in a preliminary report of four patients but had no effect on symptoms [64]. In addition, rebound eosinophilia has been observed after treatment is discontinued [65].

- Omalizumab is an anti-IgE monoclonal antibody that has been associated with a significant improvement in symptoms and measures of IgE-mediated allergy in a case series that included nine patients [5]. Tissue eosinophilia was reduced, but the reduction was not statistically significant.

- Vedolizumab, which is an anti-alpha4/beta7 integrin antibody, has been studied in a retrospective case series of patients with EoGE to show improvement in three-fifths of adults with EoG/EoGE [66,67].

- Benralizumab is a monoclonal antibody against IL-5 receptor alpha, which is expressed on human eosinophils. In a small phase 2 study in PDGFR-negative hypereosinophilic syndrome (HES) patients who received benralizumab for 12 weeks, reduction in tissue eosinophilia was observed in seven patients with concomitant EGID [68].

Immunomodulators such as azathioprine have been used as steroid-sparing agents similar to an approach used in inflammatory bowel disease. One case report suggests improvement in a patient with combined EoE/EGID who was steroid dependent after starting on azathioprine [69]. Clinical trials investigating the use of benralizumab and dupilumab in patients with EoG are underway.

SUMMARY AND RECOMMENDATIONS

- Eosinophilic gastrointestinal diseases (EGIDs) are chronic inflammatory diseases characterized by eosinophilic infiltration of the gastrointestinal tract without other known causes of eosinophilia. Organs involved could be the esophagus, stomach, intestine, and colon. The most common of these diseases are eosinophilic gastritis (EoG) and eosinophilic enteritis (EoN), and new nomenclature has been developed based on the location of the organ involved. (See 'Nomenclature' above.)

- EGIDs are rare diseases that can affect patients of any age but typically present in the third through fifth decades. The pathogenesis of EGIDs is not well understood, but epidemiologic and clinical features suggest an allergic component. Approximately one-half of patients have a history of allergic disease, including asthma, defined food sensitivities, eczema, or rhinitis. (See 'Pathogenesis' above.)

- The signs and symptoms of EGID are related to the location, extent, and layer(s) of bowel involved with eosinophilic infiltration. The most common symptoms of eosinophilic mucosal infiltration are abdominal pain, nausea, early satiety, vomiting, diarrhea, and weight loss. Patients with eosinophilic infiltration of the muscle layer may have symptoms of intestinal obstruction with nausea, vomiting, and abdominal distention. Patients with subserosal EGID may present with isolated ascites or ascites in combination with symptoms characteristic of mucosal or muscular EGID. (See 'Clinical manifestations' above.)

- Non-eosinophilic esophagitis (EoE) EGID should be suspected in a patient with abdominal pain, nausea, vomiting, early satiety, diarrhea, weight loss, or ascites that are associated with peripheral eosinophilia and/or a history of food allergy or intolerance. The diagnosis of non-EoE EGID is based on the presence of eosinophilic infiltration of the gastrointestinal tract on biopsy and/or eosinophilic ascitic fluid, lack of involvement of other organs, and absence of other causes of intestinal eosinophilia by history, laboratory evaluation, and other testing. (See 'Evaluation' above and 'Differential diagnosis' above.)

- In motivated patients who are symptomatic or have evidence of malabsorption (table 1), we suggest dietary therapy with an empiric elimination diet (eg, a six-food elimination diet) or an elemental diet (**Grade 2C**). Dietary therapy should be pursued for a minimum of four to six weeks under the guidance of a dietitian trained in EGIDs.

  We perform a repeat endoscopy routinely to assess the response to treatment and/or degree of ongoing disease activity. If the dietary changes are successful at reducing symptoms and either the peripheral eosinophil count by >50 percent or tissue eosinophilia, then foods can be added back slowly in a systematic fashion from least allergenic to most allergenic. (See "Treatment of eosinophilic esophagitis (EoE)" and 'Dietary therapy' above.)

- In patients who decline a dietary approach or whose symptoms do not improve after dietary therapy for six weeks, we suggest a trial of prednisone (20 to 40 mg/day) (**Grade 2C**). Improvement usually occurs within two weeks regardless of the layer of bowel involved. Prednisone should then be tapered rapidly over the next two weeks. However,

some patients require prolonged therapy (up to several months) for resolution of symptoms. Patients who relapse immediately after steroid cessation may need long-term, low-dose maintenance therapy with prednisone or crushed budesonide. (See 'Glucocorticoids' above and 'Other therapies' above.)

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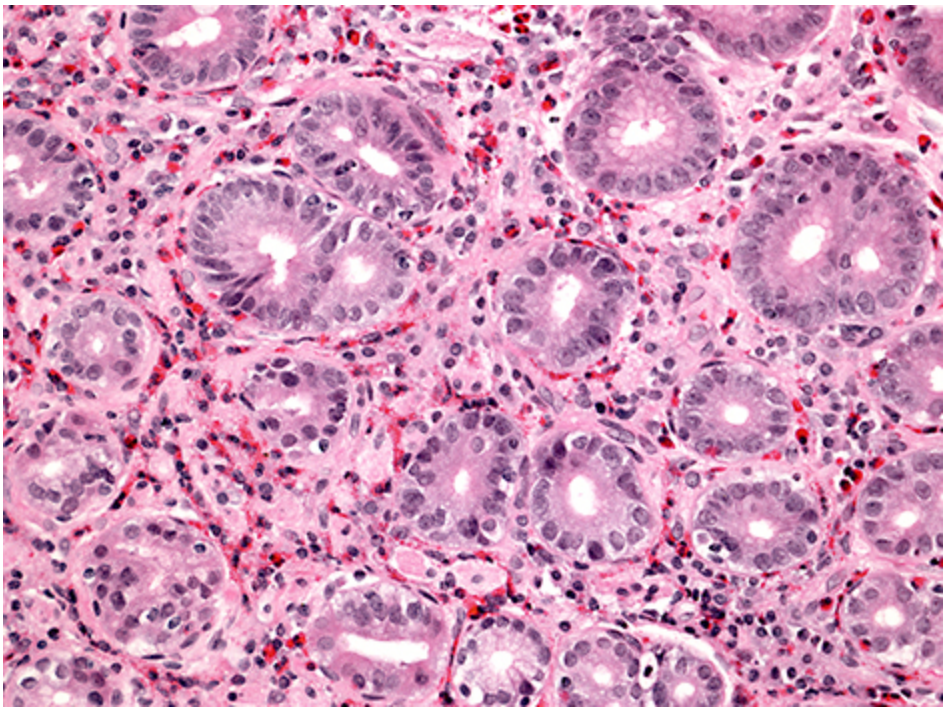
GRAPHICS

Eosinophilic gastroenteritis

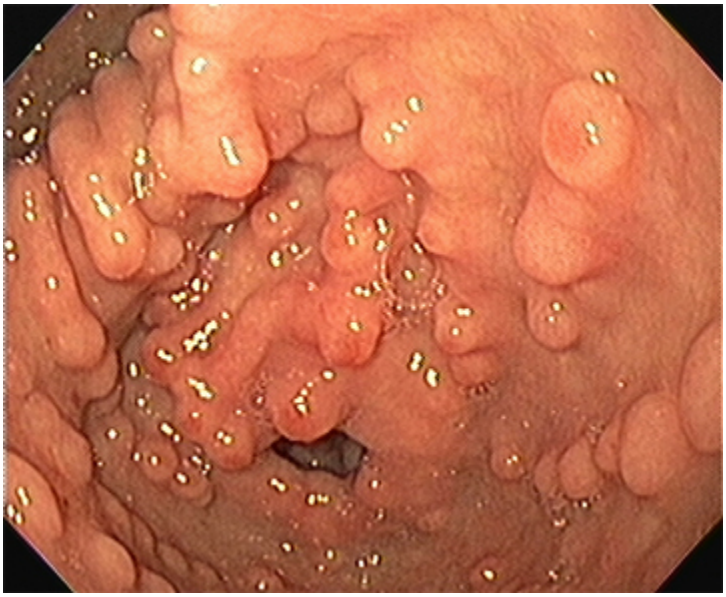


Medium power view of a gastric mucosal biopsy of a patient with eosinophilic gastroenteritis with chronic nausea, vomiting, and early satiety. Gastric biopsy reveals intense infiltration of pink eosinophils in the lamina propria characteristic of eosinophilic gastritis.

Courtesy of Calman Prussin, MD.

Graphic 50254 Version 1.0

Eosinophilic gastroenteritis



Endoscopic photo of a patient with eosinophilic gastroenteritis involving the mucosa showing nodularity and polypoid mucosa of the antrum.

Courtesy of Nirmala Gonsalves, MD.

Graphic 50409 Version 1.0

Signs and symptoms of intestinal malabsorption

Malabsorption of	Clinical features	Laboratory findings
Calories	Weight loss with normal appetite	
Fat	Pale and voluminous stool, diarrhea without flatulence, steatorrhea	Fractional fat excretion (% of dietary fat not absorbed) >7%
Protein	Edema, muscle atrophy, amenorrhea	Hypoalbuminemia, hypoproteinemia
Carbohydrates	Watery diarrhea, flatulence, acidic stool pH, milk intolerance, stool osmotic gap	Increased breath hydrogen
Vitamin B12	Anemia, subacute combined degeneration of the spinal cord (early symptoms are paresthesias and ataxia associated with loss of vibration and position sense)	Macrocytic anemia, vitamin B12 decreased, serum methylmalonic acid and homocysteine increased
Folate (Vitamin B9)	Anemia	Macrocytic anemia, serum and RBC folate decreased, serum homocysteine increased
Vitamin B, general	Cheilosis, painless glossitis, acrodermatitis, angular stomatitis	
Iron	Microcytic anemia, glossitis, pagophagia	Serum iron, ferritin and iron saturation decreased
Calcium and vitamin D	Paresthesia, tetany, pathologic fractures due to osteomalacia, positive Chvostek and Trousseau signs	Hypocalcemia, serum alkaline phosphatase increased, abnormal bone densitometry
Vitamin A	Follicular hyperkeratosis, night blindness	Serum retinol decreased
Vitamin K	Hematoma, bleeding disorders	Serum vitamin K, vitamin K-dependent coagulation factors decreased

RBC: red blood cell.

Graphic 76166 Version 10.0

Contributor Disclosures

Nirmala Gonsalves, MD Consultant/Advisory Boards: AbbVie [Eosinophilic gastrointestinal disorders]; Allakos [Eosinophilic gastrointestinal disorders]; AstraZeneca [Eosinophilic gastrointestinal disorders]; BMS [Eosinophilic gastrointestinal disorders]; Knopp [Eosinophilic gastrointestinal disorders]; Sanofi-Regeneron [Eosinophilic gastrointestinal disorders]. Speaker's Bureau: Sanofi-Regeneron [Eosinophilic gastrointestinal disorders]. All of the relevant financial relationships listed have been mitigated. **Lawrence S Friedman, MD** Other Financial Interest: Elsevier [Gastroenterology]; McGraw-Hill [Gastroenterology]; Wiley [Gastroenterology]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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