

Evaluation of the Patient with Suspected Eosinophilic Gastrointestinal Disease

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KEYWORDS

- Eosinophilic gastrointestinal disease
- Eosinophilic gastrointestinal disorders
- Eosinophilic gastritis • Eosinophilic gastroenteritis
- Eosinophilic enteritis • Eosinophilic colitis

Over the past decade, eosinophilic esophagitis (EoE) morphed from a rarely recognized entity into a frequently entertained diagnostic consideration in patients of all ages presenting with any of a variety of gastrointestinal complaints.¹ This miniepidemic has spawned interest in the appropriate evaluation and management of eosinophilic gastrointestinal diseases (EGIDs), of which EoE is the most common. Diagnostic consideration of EGIDs is prompted by identification of abnormal eosinophilic infiltration on morphologic evaluation of gastrointestinal tissues obtained by biopsy or resection from patients with gastrointestinal complaints. To solidify the diagnosis, other potential causes of gastrointestinal eosinophilia must be excluded. EGIDs have been classified in regard to the site involved (esophageal, gastric, small intestinal, colonic, or multiple) and tissue localization of the eosinophil accumulation (mucosal, muscular, serosal, diffuse, or transmural).^{1–3}

In categorizing the larger group of all disorders associated with gastrointestinal eosinophilia, EGIDs are referred to as primary eosinophil-associated disorders to

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distinguish them from secondary eosinophil-associated disorders, where eosinophil accumulation is attributed to an identified cause. Thus, EGIDs, or primary eosinophil-associated gastrointestinal disorders, include EoE, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis or proctitis.⁴ Demonstration of atopy in approximately 75% of these patients and recognition of familial involvement in more than 10% has prompted further categorization of EGIDs into atopic, nonatopic, and familial varieties.¹ Secondary eosinophil-associated gastrointestinal disorders include those disorders where eosinophil accumulation can be attributed to a distinct cause. These disorders are further categorized as (1) those due to eosinophilic disorders, usually hypereosinophilic syndrome; and (2) those due to noneosinophilic disorders, such as inflammatory bowel diseases, infectious diseases, connective tissue disorders, vasculitides, neoplasia, and iatrogenic causes. As EoE is covered elsewhere in this issue, this article focuses upon the approach to the evaluation and management of the remaining EGIDs.

HISTORY

As with any medical condition, the initial step in diagnosing EGID is a thorough history accurately delineating all symptoms, the timing of their onset, duration, progression, aggravating or alleviating factors, and response or lack thereof to previous treatment. Some EGIDs are age-limited, as exemplified by allergic proctocolitis of infancy, whereas others, such as eosinophilic gastroenteritis, occur at any age, although the peak incidence is between ages 20 to 50 years.^{2,5,6} Curiously, serosal disease is much more common in women over 40 years of age (accounting for over 75% of these patients), whereas males outnumber females in other EGIDs.⁷ Although the majority of reported cases involve Caucasians, isolated case reports from various locations throughout the world suggest no ethnic group is immune.⁸

Signs and symptoms vary depending upon the location and layer of gastrointestinal tissue involved. Classification of EGIDs by layer of gastrointestinal involvement was first proposed by Klein² in 1970. Mucosal involvement is by far the most common and is accompanied by one or more of the following symptoms: decreased appetite, early satiety, nausea, vomiting, gastric dysmotility, abdominal pain, malabsorption, diarrhea, anemia, failure to thrive, occult blood in the stool, and protein-losing enteropathy. Involvement of the muscular layer usually presents with colicky abdominal pain and symptoms of gastric outlet or intestinal obstruction. Serosal involvement, the least common, is accompanied by abdominal distention and eosinophilic ascites. Combinations of these symptoms occur with involvement of more than one tissue layer.

A personal history of allergic disease, such as eczema, asthma, allergic rhinitis, or animal dander sensitivity, heightens suspicion because the majority of patients with EGIDs are atopic, although the absence of other allergic disease does not preclude the diagnosis. Suspected foods and symptoms attributed to the ingestion of these foods should be listed, as questioning often reveals evidence of food allergy. Although comorbid food-induced anaphylaxis is relatively uncommon in these patients, it should not be overlooked. A dietary history is required to document regularly ingested foods, checking for the ingestion of those that increase the risk of parasite exposure, and to evaluate the nutritional adequacy of the diet.

Medication or environmental exposures predisposing to conditions associated with gastrointestinal eosinophilia should be identified and investigated. Where a person lives is an important variable as geographic location exerts a significant influence, with 35-fold higher numbers of colonic eosinophils associated with warmer climates,

presumably because of differences in exposure to microbes and aeroallergens and because of regional differences in dietary allergen exposures.⁹ Note that seasonal variations in symptoms may correlate with exposures to pollens or other allergens to which the patient is sensitized.¹⁰ Make a complete record of medication history, including allergen immunotherapy and the use of over-the-counter medications, such as nonsteroidal anti-inflammatory drugs, vitamin supplements, and herbal remedies. Environmental exposures, including occupational and recreational exposures, should be elicited. Such exposures could include those related to foreign travel, camping, ingestion of well or stream water, farm work, and contact with animals.

Questioning about the presence of similar gastrointestinal symptoms in other family members is worthwhile because of the recognized familial tendency of these disorders. Allergic disease is often present in immediate family members. The presence of malignancy, immunodeficiency, inflammatory bowel disease, collagen vascular diseases, or other eosinophilic disorders in other family members should be ascertained.

An often-overlooked aspect of the history is questioning to determine the emotional well-being of the patient and other family members. Feeding difficulties and failure to thrive are often associated with EGIDs in infants and young children, and the frequent delay in obtaining an accurate diagnosis is often stressful for parents and patients alike. Detection of developmental delays in young children stemming from malnutrition or other causes is vital. Coping with elimination diets and chronic illness can be emotionally draining. By recognizing illness-related anxiety or depression and intervening early, and by providing education and psychologic support, the clinician can significantly improve the patient's quality of life.

PHYSICAL EXAMINATION

Although there are no physical findings diagnostic of EGID, a thorough physical examination is indicated to assess nutritional status and to identify physical findings suggestive of other diseases that might explain gastrointestinal symptoms. Longitudinal tracking of weight and other growth parameters, particularly in children, is necessary to monitor the impact of disease and dietary aberrations. Checking for physical findings of allergic rhinoconjunctivitis, asthma, or eczema is encouraged and, if present, noting whether these conditions are flared or well controlled provides useful information as total IgE levels and peripheral eosinophil counts often rise in patients with poorly controlled allergic disease. A careful examination of the abdomen to identify areas and degrees of tenderness, the presence of abdominal distention, organomegaly, ascites, or increased stool is an important aspect of the evaluation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of EGIDs includes a host of conditions, referred to as secondary eosinophil-associated gastrointestinal disorders, that cause abdominal symptoms in combination with gastrointestinal eosinophilia.¹ Entities to be considered include systemic eosinophilic disorders with gastrointestinal involvement, such as hypereosinophilic syndromes, and other causes, including infections, inflammatory bowel diseases, celiac disease, food allergies, connective tissue disorders, vasculitis, neoplasia, responses to immunologic injury, and iatrogenic causes, such as reactions to medications. Parasitic infestations involving helminths, hookworms, pinworms, and a variety of other parasites have been associated with gastrointestinal tissue eosinophilia.^{11–13} Clearing of gastric eosinophilia upon eradication of *Helicobacter pylori* has been reported, but further documentation of this association is warranted.¹⁴ Increased numbers of activated eosinophils as evidenced by degranulation are noted in the

inflamed gastrointestinal tissues of patients with Crohn's disease and ulcerative colitis where eosinophils are not the predominant cell type.¹⁵ Interestingly, higher numbers of eosinophils in the mucosa of patients with ulcerative colitis have been reported as a favorable prognostic finding.¹⁶ The hypercellular gastrointestinal lamina propria encountered in celiac disease contains increased eosinophil numbers, along with elevated numbers of lymphocytes, plasma cells, mast cells, and basophils.⁴ The identification and removal of offending foods from the diet of food-allergic patients can lead to resolution of gastrointestinal eosinophilia, as is often seen in infants with allergic proctocolitis.⁵ Varying levels of gastrointestinal eosinophilia have been observed in scleroderma, systemic lupus erythematosus, and dermatomyositis, in addition to vasculitides, such as Churg-Straus syndrome and periarteritis nodosa.¹⁷ Graft-versus-host disease in bone marrow transplant patients is often associated with increased eosinophil numbers in the colon and rectum.⁴ The use of oral tacrolimus for suppression of rejection in patients with solid organ transplants is associated with gastrointestinal eosinophilia accompanying food allergies in approximately 10% of the recipients.^{18,19} A host of other medications have been implicated as causing gastrointestinal eosinophilia that usually resolves with discontinuation of the drug. Examples include nonsteroidal anti-inflammatory drugs, interferon, enalapril, carbamazepine, and co-trimoxazole.²⁰

Hypereosinophilic syndromes must also be considered in patients presenting with gastrointestinal tissue eosinophilia and elevated peripheral eosinophil counts. The hypereosinophilic syndromes are recognized by the presence of more than 1500 circulating eosinophils per cubic millimeter for longer than 6 months without any identified cause, in association with organ damage not attributable to a cause other than eosinophilic infiltration. The presence of multiple organ involvement in these patients and the association of endomyocardial disease with prolonged eosinophilia prompt continued surveillance for extragastrointestinal involvement in patients presenting with EGIDs. These syndromes have been the topic of recent reviews and a previous issue of the *Immunology and Allergy Clinics*.²¹ The diagnostic evaluation for hypereosinophilic syndromes is briefly detailed in **Box 1**.

DIAGNOSIS OF EOSINOPHILIC GASTROINTESTINAL DISEASE

Diagnosis of EGID requires a high index of suspicion, as the symptoms and presentations are nonspecific, often sharing features with more commonly encountered gastrointestinal disorders, such as infection, inflammatory bowel diseases, and iatrogenic and functional gastrointestinal disorders.⁷ There are no confirmatory laboratory tests, and the morphologic evaluation of biopsies or surgical specimens is required to confirm the diagnosis. Because of the patchy nature of these disorders and, with the exception of EoE, the lack of uniformly accepted diagnostic criteria, the diagnosis can be overlooked or remain in question if multiple biopsies are not taken. When biopsy specimens are evaluated and eosinophilic infiltration is identified, other causes of eosinophil infiltration must be excluded before the diagnosis is confirmed. As a result, it is all too common for patients with these disorders to be symptomatic for extended periods before an accurate diagnosis is made.^{22,23}

Laboratory Evaluation

Unfortunately, no laboratory tests are diagnostic of EGIDs. Laboratory tests that may be useful in distinguishing EGIDs from other diseases associated with tissue eosinophilia are listed in **Box 1**. Peripheral blood eosinophilia is noted in about two thirds of patients with eosinophilic gastroenteritis²⁴ and may be found in patients with

Box 1**Diagnostic evaluation of EGID***General*

- Histologic evaluation of multiple biopsy specimens
- Immunohistological analysis of biopsy specimens for eosinophil or mast cell granule proteins: eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, and major basic protein for eosinophils; tryptase for mast cells
- Serum, urinary, and fecal markers: eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil protein X
- Complete blood count with differential
- Immunophenotyping of eosinophils and T cells: IL-5 receptor alpha-chain and chemokine receptor-3 for eosinophils; CD3 for T cells
- Total IgE and food-specific IgE (by ImmunoCAP, Phadia) levels
- Skin-prick testing and atopy patch testing
- Erythrocyte sedimentation rate/c-reactive protein
- Infection evaluation: *Helicobacter pylori*; helminths, hookworms, pinworms, and other parasites
- Autoantibody evaluation: tissue transglutaminase for celiac disease, antineutrophil cytoplasmic antibodies for vasculitides and inflammatory bowel disease; *Saccharomyces cerevisiae* IgG and IgA antibodies for inflammatory bowel disease

Additional testing in the presence of hypereosinophilia

- Bone marrow examination with cytogenetics and special staining
- ECG and echocardiogram
- Pulmonary function testing
- CT of chest, abdomen, and pelvis
- Tissue biopsies as indicated by other involved sites
- Measurement of serum vitamin B12 and tryptase
- Evaluation for *FIPL1-PDGFR*A mutation
- T and B cell receptor rearrangement studies

eosinophilic colitis. Higher levels of fecal eosinophilic cationic protein and serum eosinophilic cationic protein, eosinophil-derived neurotoxin, and eosinophil protein X have been found in patients with eosinophilic gastroenteritis, compared with those having ulcerative colitis or Crohn's disease.²⁵ Higher levels of urinary eosinophil-derived neurotoxin, serum eosinophil-derived neurotoxin, and eosinophilic cationic protein have been measured in patients with eosinophilic colitis.²⁶ Clinical studies have also shown that there is increased secretion of IL-4 and IL-5 by peripheral blood T cells in patients with eosinophilic gastroenteritis.²⁷ In patients with the mucosal form of eosinophilic gastroenteritis, who have malabsorption or protein-losing enteropathy, there may be increased fecal fat excretion, prolonged prothrombin time, reduced serum iron concentration, hypoalbuminemia, and hypogammaglobulinemia. Patients who have the serosal form of eosinophilic gastroenteritis usually have marked eosinophilia in the ascitic fluid.²

Evaluation of Allergic Disease

The majority of patients with eosinophilic gastroenteritis have increased total IgE levels and a history of other atopic diseases, including asthma, eczema, or allergic rhinitis. Most also have positive food-specific IgE levels and positive skin tests to food allergens.¹ The use of the atopy patch test in the food allergy workup of EGIDs has been shown to be beneficial in some studies as well.^{28,29} However, the role of food allergy as an inciting agent in other forms of EGIDs besides EoE has not been as clearly defined. In contrast to EoE and eosinophilic gastroenteritis, eosinophilic colitis is more commonly a non-IgE-associated EGID, and thus skin tests to foods and food-specific IgE levels are more often negative.³⁰ Nonetheless, a thorough allergy history and food sensitization evaluations are warranted regardless of the type of EGID. Although it has primarily been reported in EoE, certain patients may also have seasonal variation of EGIDs due to exposure to seasonal environmental allergens, such as pollens,^{31,32} so environmental allergen testing is recommended as well.

Radiological Evaluation

Radiological examinations generally do not provide much assistance in the diagnosis of EGIDs because they lack significant sensitivity or specificity. However, barium studies may suggest the diagnosis by revealing gastric antral stenosis with mucosal irregularity, gastric pseudopolypoid, or thickening in the small bowel due to edema.³³ Ultrasonography may show diffuse, nonspecific bowel wall infiltration with persistence of a multilayer echo pattern, and it can be useful in detecting ascites in the serosal form of eosinophilic gastroenteritis.^{34,35} CT findings of EGID depend on the layer of involved tissue, but generally consist of nodular and irregular fold thickening in the stomach, bowel wall thickening, and luminal narrowing without obstruction. CT findings may also be useful for the evaluation of the degree and extent of eosinophilic infiltration and help guide transmural biopsy by endoscopy.^{36,37}

Endoscopic Evaluation

While the esophageal tissue should not contain any eosinophils under normal conditions, eosinophils can be present at baseline throughout the remainder of the intestine. However, no standards for the normal number of baseline eosinophils have been established beyond the esophagus. Thus, there are no standards for the numbers of eosinophils diagnostic for EGIDs other than EoE. Nonetheless, there are certain endoscopic and pathologic findings that help support the diagnosis.

Endoscopic findings may be nonspecific and include erythema, friability, ulcerations, erosions, nodules, and loss of vascularity. Patients with eosinophilic gastritis may have micronodules or polyposis consisting of aggregates of lymphocytes and eosinophils.¹ Gross endoscopic findings may be normal as well because normal-appearing mucosa can harbor eosinophilic infiltration. Therefore, multiple biopsies should be taken from both normal- and abnormal-appearing tissue given the patchy involvement of EGIDs.

Pathologic Evaluation

On pathologic examination, the presence of infiltrating eosinophils within the intestinal crypts and gastric glands is supportive of eosinophilic gastroenteritis.³⁰ Histologic analysis of the tissue often reveals extracellular deposition of eosinophil remnants, including major basic protein and eosinophilic cationic protein.¹ Mast cells have also been detected in intestinal biopsies of eosinophilic gastroenteritis patients in numbers higher than those for normal control patients.³⁸ The diagnosis of the muscular form of

eosinophilic gastroenteritis may require laparoscopic full-thickness biopsies because the lack of mucosal involvement often makes endoscopic biopsies nondiagnostic. In colonic biopsy specimens of patients with eosinophilic colitis, there may be diffuse eosinophilic infiltration in the lamina propria or focal aggregates of eosinophils in the lamina propria, crypt epithelium, and muscularis mucosa with preservation of the underlying mucosal architecture. Extracellular deposition of major basic protein and eosinophilic cationic protein, accumulation of mast cells, and, occasionally, submucosal multinucleated giant cells have also been noted in colonic tissue biopsies.^{39,40}

TREATMENT

EGIDs other than EoE are relatively uncommon, so data on the treatment are limited to case reports and retrospective case series rather than prospective, randomized therapeutic clinical studies. For eosinophilic gastritis and eosinophilic gastroenteritis, referral to an allergist for skin testing to foods and environmental allergens, serum food-specific IgE testing by ImmunoCAP, and atopy patch testing is warranted. However, the role of food allergy in these EGIDs is not as well defined as it is in EoE. Nevertheless, if specific food sensitivities can be identified, patients have responded to targeted elimination diets.^{38,41} If elimination diets are used, patients should be educated about the complexity of strict avoidance and should be evaluated by a nutritionist to ensure that no gaps in essential nutrients occur. Complete resolution of symptoms and disease has also been documented with the use of amino acid-based elemental formulas, although it is difficult for most patients to maintain such a strict diet.⁴² If no food sensitization is discovered, or if a targeted elimination diet is not feasible or has failed to alleviate symptoms, then treatment with systemic corticosteroids, such as prednisone or methylprednisolone, or with topical corticosteroids, such as enteric coated budesonide, or with both systemic and topical corticosteroids is reasonable.^{43–46} Various other treatment approaches have been used with varying degrees of success, including mast cell stabilizers (oral cromoglycate),^{47,48} leukotriene antagonists (montelukast),^{49–52} antihistamines (ketotifen),^{53–55} suplatast tosilate,⁵⁶ humanized anti-IL-5 antibody,^{57,58} and anti-IgE antibody (omalizumab).⁵⁹ If environmental allergens are identified, they should also be treated with antihistamines and intranasal corticosteroids.

For eosinophilic colitis, the treatment varies and depends on the clinical subtype. In eosinophilic colitis of infancy, it may be as simple as eliminating cow's milk or soy proteins, as these are the most frequent cause of this disease, which usually resolves by ages 1 to 3 years.³⁹ In milk-induced allergic proctocolitis, elimination of cow's milk protein results in resolution of bloody diarrhea with subsequent tolerance to milk, usually by age 1 year. However, treatment of eosinophilic colitis in older individuals is more problematic because IgE-mediated triggers are rarely identified. This means elimination diets are rarely effective. Therefore, treatment of eosinophilic colitis has primarily involved attempts at medical management with various drugs, including mast cell stabilizers (cromoglycate), leukotriene antagonists (montelukast), and antihistamines, although these are rarely efficacious. Anti-inflammatory drugs, such as topical or systemic corticosteroids and aminosalicylates, are more commonly used and appear to be more effective, although controlled clinical trials have not been performed.¹

NATURAL HISTORY

Little is known about the natural history of eosinophilic gastritis, gastroenteritis, enteritis, and colitis as it has not yet been evaluated in longitudinal clinical studies, likely as

a result of the difficulty in establishing a robust cohort of patients with these disorders for long-term follow-up. However, from currently available data and recent experience with EoE, it is likely that these diseases have similar courses, with complete resolution in some patients and recurrent or persistent disease in others.⁶⁰ When these diseases present in infancy and specific sensitization to foods can be identified, the prognosis appears favorable with possible remission in later childhood.¹ It is possible for different segments of the gastrointestinal tract to be affected over time and, because these diseases can be predecessors to other disease processes, such as hypereosinophilic syndromes, routine endoscopic and cardiopulmonary evaluations are recommended.

SUMMARY

EGIDs can affect any segment of the gastrointestinal tract, singly or in combination, and are named accordingly: EoE, gastritis, gastroenteritis, enteritis, and colitis. The diagnosis of EGID is primarily dependent on the clinical history and histopathology of multiple biopsy specimens after ruling out other causes of intestinal eosinophilia. The diagnosis of EGID other than EoE is complicated by the lack of uniformly accepted diagnostic criteria. Treatment involves evaluation for food sensitivity, elimination diets, and the use of antiallergy and anti-inflammatory medications with varying degrees of success. Little is known about the natural history of EGIDs, underscoring the need for long-term follow-up studies of patients with these disorders.

REFERENCES

1. Rothenberg ME. Eosinophilic gastrointestinal disorders. *J Allergy Clin Immunol* 2004;113:11–28.
2. Klein NC, Hargrove RL, Sleisenger MH, et al. Eosinophilic gastroenteritis. *Medicine* 1970;49(4):299–319.
3. Mueller S. Classification of eosinophilic gastrointestinal diseases. *Best Pract Res Clin Gastroenterol* 2008;22:425–40.
4. Zuo L, Rothenberg ME. Gastrointestinal eosinophilia. *Immunol Allergy Clin North Am* 2007;27:443–55.
5. Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr* 2000;30:S58–60.
6. Kahn S, Orenstein SR. Eosinophilic gastroenteritis: epidemiology, diagnosis and management. *Paediatr Drugs* 2002;4:563–70.
7. Straumann A. Idiopathic eosinophilic gastrointestinal diseases in adults. *Best Pract Res Clin Gastroenterol* 2008;22:481–96.
8. Kahn S, Orenstein SR. Eosinophilic gastroenteritis. *Gastroenterol Clin North Am* 2008;37:333–48.
9. Pascal RR, Gramlich KM, Gansler TS. Geographic variations in eosinophil concentration in normal colonic mucosa. *Mod Pathol* 1997;10:363–5.
10. Polydorides AD, Banner BF, Jannaway PJ, et al. Evaluation of site-specific and seasonal variation in colonic mucosal eosinophils. *Hum Pathol* 2008;39:832–6.
11. Chira O, Badea R, Dumitrascu D, et al. Eosinophilic ascites in a patient with toxocara canis infection. A case report. *Rom J Gastroenterol* 2005;14:397–400.
12. Tsiouris P, Galeas T, Moussia M, et al. Two cases of eosinophilic gastroenteritis and malabsorption due to *Enterobius vermicularis*. *Dig Dis Sci* 2005;50:2389–92.
13. Kocabay G, Gul E, Catatay A, et al. Is eosinophilic gastroenteritis a primary disease or a secondary developing entity due to parasitosis? *South Med J* 2006;99:901.

14. Papadopoulos AA, Tzathas C, Polymeros D, et al. Symptomatic eosinophilic gastritis cured with *Helicobacter pylori* eradication. *Gut* 2005;54:1822.
15. Carvalho AT, Elia CC, de Souza HS, et al. Immunohistochemical study of intestinal eosinophils in inflammatory bowel disease. *J Clin Gastroenterol* 2003;36:120–5.
16. Heatley RV, James PD. Eosinophils in the rectal mucosa. A simple method of predicting the outcome of ulcerative proctocolitis? *Gut* 1979;20:787–91.
17. Barbie DA, Mangi AA, Lauwers GY. Eosinophilic gastroenteritis associated with systemic lupus erythematosus. *J Clin Gastroenterol* 2004;38:883–6.
18. Lykavieris P, Frauger E, Habes D, et al. Angioedema in pediatric liver transplant recipients under tacrolimus immunosuppression. *Transplantation* 2003;75:152–65.
19. Atkins FM. Systemic FK506 and post transplant food allergy in children. *J Pediatr Gastroenterol Nutr* 2003;37(4):525–6.
20. Talley NJ. Gut eosinophilia in food allergy and systemic and autoimmune diseases. *Gastroenterol Clin North Am* 2006;37:307–32.
21. Klion AD, Alam R. Hypereosinophilic syndromes. *Immunol Allergy Clin N Am* 2007;27(3):333–570.
22. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109–16.
23. Straumann A, Spictin HP, Bernoulli R, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. *Schweiz Med Wochenschr* 1994;124:1419–29.
24. Straumann A, Simon HU. The physiological and pathophysiological roles of eosinophils in the gastrointestinal tract. *Allergy* 2004;59:15–25.
25. Bischoff SC, Mayer J, Nguyen QT, et al. Immunohistological assessment of intestinal eosinophilic activation in patients with eosinophilic gastroenteritis and inflammatory bowel disease. *Am J Gastroenterol* 1999;94:3521–9.
26. Inamura H, Tomita M, Okano A, et al. Serial blood and urine levels of EDN and ECP in eosinophilic colitis. *Allergy* 2003;58:959–60.
27. Jaffe JS, James SP, Mullins GE, et al. Evidence for an abnormal profile of interleukin-4 (IL-4), IL-5, and gamma-interferon (gamma-IFN) in peripheral blood T cells from patients with allergic eosinophilic gastroenteritis. *J Clin Immunol* 1994;14:299–309.
28. Spergel JM, Brown-Whitehorn T, Beausoleil JL, et al. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:509–11.
29. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;95:336–43.
30. Conus S, Simon HU. General laboratory diagnostics of eosinophilic GI diseases. *Best Pract Res Clin Gastroenterol* 2008;22:441–53.
31. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003;112:796–7.
32. Spergel JM. Eosinophilic esophagitis and pollen. *Clin Exp Allergy* 2005;35:1421–2.
33. MacCarty RL, Talley NJ. Barium studies in diffuse eosinophilic gastroenteritis. *Gastrointest Radiol* 1990;15:183–7.
34. Stevof C, Rao S, Parsons W, et al. EUS and histopathologic correlates in eosinophilic esophagitis. *Gastrointest Endosc* 2001;54:373–7.
35. Maroy B. Nonmucosal eosinophilic gastroenteritis: sonographic appearance at presentation and during follow-up of response to prednisone therapy. *J Clin Ultrasound* 1998;26:483–6.

36. Horton KM, Corl FM, Fishman EK. CT of non-neoplastic diseases of the small bowel: spectrum of disease. *J Comput Assist Tomogr* 1999;23:417–28.
37. Zheng X, Cheng J, Pan K, et al. Eosinophilic enteritis: CT features. *Abdom Imaging* 2008;33:191–5.
38. Chehade M, Magid MS, Mofidi S, et al. Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up. *J Pediatr Gastroenterol Nutr* 2006;42:516–21.
39. Guajardo JR, Rothenberg ME. Eosinophilic esophagitis, gastroenteritis, gastroenterocolitis, and colitis. In: Metcalfe DD, Sampson HA, Simon RA, editors. *Food allergy: adverse reactions to foods and additives*. 3rd edition. Malden (MA): Blackwell Publishing; 2003. p. 217–26.
40. Ohtsuka Y, Shimizu T, Shoji H, et al. Neonatal transient eosinophilic colitis causes lower gastrointestinal bleeding in early infancy. *J Pediatr Gastroenterol Nutr* 2007;44:501–5.
41. Chen MJ, Chu CH, Lin SC, et al. Eosinophilic gastroenteritis: clinical experience with 15 patients. *World J Gastroenterol* 2003;9:2813–6.
42. Justinich C, Katz A, Gurbindo C, et al. Elemental diet improves steroid-dependent eosinophilic gastroenteritis and reverses growth failure. *J Pediatr Gastroenterol Nutr* 1996;23:81–5.
43. Tan AC, Kruimal JW, Naber TH. Eosinophilic gastroenteritis treated with non-enteric-coated budesonide tablets. *Eur J Gastroenterol Hepatol* 2001;13:425–7.
44. Siewert E, Lammert F, Koppitz P, et al. Eosinophilic gastroenteritis with severe protein-losing enteropathy: successful treatment with budesonide. *Dig Liver Dis* 2006;38:55–9.
45. Elsing C, Placke J, Gross-Weege W. Budesonide for the treatment of obstructive eosinophilic jejunitis. *Z Gastroenterol* 2007;45:187–9.
46. Lombardi C, Salmi A, Savio A, et al. Localized eosinophilic ileitis with mastocytosis successfully treated with oral budesonide. *Allergy* 2007;62:1343–5.
47. Van Dellen RG, Lewis JC. Oral administration of cromolyn in a patient with protein-losing enteropathy, food allergy, and eosinophilic gastroenteritis. *Mayo Clin Proc* 1994;69:441–4.
48. Perez-Millan A, Martin-Lorente JL, Lopez-Morante A, et al. Subserosal eosinophilic gastroenteritis treated efficaciously with sodium cromoglycate. *Dig Dis Sci* 1997;42:342–4.
49. Neustrom MR, Friesen C. Treatment of eosinophilic gastroenteritis with montelukast. *J Allergy Clin Immunol* 1999;104:506.
50. Schwartz DA, Pardi DS, Murray JA. Use of montelukast as steroid-sparing agent for recurrent eosinophilic gastroenteritis. *Dig Dis Sci* 2001;46:1787–90.
51. Quack I, Sellin L, Buchner NJ, et al. Eosinophilic gastroenteritis in a young girl—long term remission under montelukast. *BMC Gastroenterol* 2005;5:24.
52. Urek MC, Kujundzic M, Banic M, et al. Leukotriene receptor antagonists as potential steroid sparing agents in a patient with serosal eosinophilic gastroenteritis. *Gut* 2006;55:1363–4.
53. Melamed I, Feanny SJ, Sherman PM, et al. Benefit of ketotifen in patients with eosinophilic gastroenteritis. *Am J Med* 1991;90:310–4.
54. Katsinelos P, Pilpilidis I, Xiarchos P, et al. Oral administration of ketotifen in a patient with eosinophilic colitis and severe osteoporosis. *Am J Gastroenterol* 2002;97:1072.
55. Bolukbas FF, Bolukbas C, Uzunkoy A, et al. A dramatic response to ketotifen in a case of eosinophilic gastroenteritis mimicking abdominal emergency. *Dig Dis Sci* 2004;49:1782–5.

56. Shirai T, Hashimoto D, Suzuki K, et al. Successful treatment of eosinophilic gastroenteritis with suplatast tosilate. *J Allergy Clin Immunol* 2001;107:924–5.
57. Prussin C, James SP, Huber MM, et al. Pilot study of anti-IL-5 in eosinophilic gastroenteritis [Abstract]. *J Allergy Clin Immunol* 2003;111:S275.
58. Kim YJ, Prussin C, Martin B, et al. Rebound eosinophilia after treatment of hyper-eosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700. *J Allergy Clin Immunol* 2004;114:1449–55.
59. Foroughi S, Foster B, Kim NY, et al. Anti-IgE treatment of eosinophilic-associated gastrointestinal disorders. *J Allergy Clin Immunol* 2007;120:594–601.
60. Lee CM, Changchien CS, Chen PC, et al. Eosinophilic gastroenteritis: 10 years experience. *Am J Gastroenterol* 1993;88:70–4.