

Eosinophilic Gastroenteritis and Citrus-Induced Urticaria

**Arvind Kumar¹, Suzanne S. Teuber¹, Stanley Naguwa¹,
Thomas Prindiville², and M. Eric Gershwin^{1,*}**

¹*Division of Rheumatology, Allergy, and Clinical Immunology, Department of Internal Medicine, School of Medicine, University of California, Davis, Davis, CA,* ²*Division of Gastroenterology, Department of Internal Medicine, School of Medicine, University of California, Davis, Davis, CA*

Abstract

The immunological basis of eosinophilic gastroenteritis (EGE) is an interesting contrast between the enigma of urticaria and the increasing usage of molecular technology in clinical allergy. Little is known about the natural history of EGE. It has been known to spontaneously remit, but the typical course, especially in adults, is one of chronic and intermittent disease. Given the often chronic nature of this disease, it is important to use relatively benign treatments initially and limit the use of systemic corticosteroids. Also, given the fact that eosinophilic infiltration of the gastrointestinal tract may also be a manifestation of other potentially dangerous disease processes, such as malignancy or hypereosinophilic syndrome, which may be initially diagnosed as EGE, routine surveillance of the cardiopulmonary and gastrointestinal systems is important. We present a patient who demonstrates the variability of presentation and treatment response in this multifaceted disease. The fact that he has apparently entered remission also makes his an uncommon presentation of EGE.

Index Entries

Eosinophilia; abdominal pain; grapefruit-induced urticaria.

*Author to whom all correspondence and reprint requests should be addressed. E-mail: megershwin@ucdavis.edu.

**These two authors contributed equally to this manuscript.

Introduction

A 46-year-old male presented with 2 mo of nonbloody, loose bowel movements (16/d) with abdominal cramping and nausea without emesis. He denied dysphagia, abdominal distention, heartburn, fevers, rigors, or weight loss. He had no rash, urticaria, angioedema, flushing, or syncope. He had recovered from pneumococcal pneumonia after taking oral antibiotics 2 mo prior to the onset of the gastrointestinal (GI) symptoms. He denied foreign travel and had not eaten any new or unusual foods prior to onset of symptoms. He had not drunk water from streams or wells. He was not on medications, vitamins, or supplements. His review of systems was otherwise negative.

Past Medical History

The patient had two episodes of pneumonia in the past, which responded well to routine treatment. He had no other infections suggestive of immunodeficiency. He had a lifelong history of mild seasonal allergic rhinitis treated as needed with oral antihistamines, but did not suffer from it currently. He had been diagnosed approx 10 yr prior with citrus fruit-dependent, exercise-induced anaphylaxis. Lemon or grapefruit consumption followed by exercise caused urticaria and wheezing but not GI symptoms. He has completely avoided citrus fruits since then. His surgical history includes a vasectomy.

Family and Social History

There is no family history of GI malignancy, inflammatory bowel disease (IBD), atopic disorders, or other GI problems. He has no known drug allergies. He is a married physician with four healthy children. He does not smoke or use drugs and rarely consumes alcohol.

Physical Examination

His vital signs were normal. He was a well-developed, well-nourished male in no distress. The oropharynx was clear. His abdomen was soft, flat, and nontender with hyperactive

bowel sounds and no hepatosplenomegaly. No lymphadenopathy was appreciated. His cardiac, pulmonary, neurological, musculoskeletal, endocrine, and skin exams were unremarkable. Stool was soft and guaiac was negative.

Initial Laboratory and Pathology Results

The patient's leukocyte count was 16,400/ μ L, with 33% neutrophils, 45.3% lymphocytes, 3.2% monocytes, 18% eosinophils, and 0.5% basophils. The absolute eosinophil count was 2940/ μ L. The hemoglobin was 14.0 g/dL and the platelet count was 281,000/ μ L. The erythrocyte sedimentation rate was 11 mm/h. Basic chemistry and liver enzyme panels were normal. The serum albumin was 3.6 g/dL and total protein was 6.3 g/dL. Serum immunoglobulin (Ig)E was reported at more than 2000 kU/L. Other Igs, C3 and C4 levels, and serum B12 level were normal. Anti-nuclear antibody was negative. Stool cultures, stool *Clostridium difficile* toxin assay, and stool for ova and parasite examination were negative; however, moderate numbers of red and white blood cells were seen. Colonoscopy showed terminal ileitis, and pancolonial decreased vascular markings suggesting chronic inflammation. Histology revealed acute colitis and ileitis with gland dropout, cryptitis, and villous blunting. There were more than 1000 eosinophils per high-power field seen intra-epithelially, in the lamina propria, in the muscularis mucosa, and in the submucosa (Figs. 1 and 2). Neutrophilia was lacking. Computed tomography scan of the abdomen revealed colonic, ileum, and duodenal wall thickening (Fig. 3). Small bowel follow-through was normal.

Questions

Given the Patient's Chronic Diarrhea With Peripheral and GI Eosinophilia, What Is the Differential Diagnosis?

The differential diagnosis includes the following:

- Drug-related colitis or hypersensitivity.

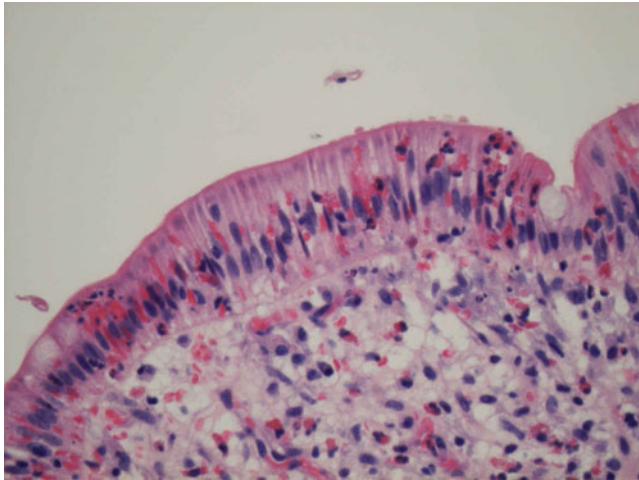


Fig. 1. Abundant intraepithelial eosinophils in the terminal ileum (hematoxylin-eosin, original magnification $\times 60$).

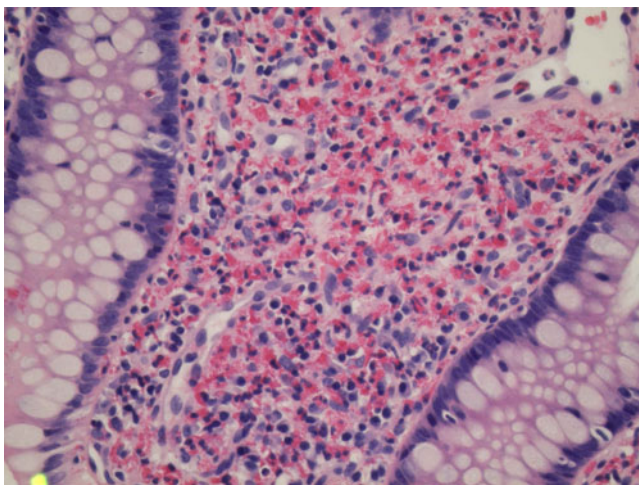


Fig. 2. Sheets of eosinophils in the lamina propria of the right colon (hematoxylin-eosin, original magnification $\times 60$).

- Infectious colitis (parasitic, bacterial, fungal).
- IgE-mediated food allergy.
- IBD.
- Celiac disease.
- Celiac disease co-presenting with IBD.
- Primary eosinophilic GI disorders (EGIDs) (eosinophilic gastroenteritis, colitis).
- GI malignancy.
- Vasculitis (polyarteritis nodosa, Churg-Strauss vasculitis).

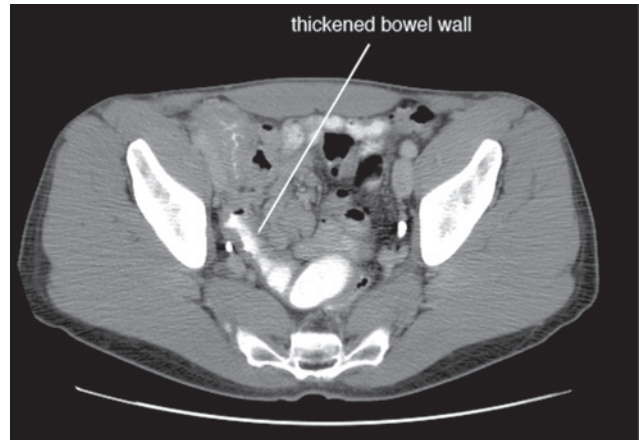


Fig. 3. Computed tomography scan of abdomen/pelvis with thickened bowel wall.

- Systemic mastocytosis.
- Histiocytosis X.
- Hypereosinophilic syndrome (HES).
- Chronic granulomatous disease.

This patient had recently been on antibiotics for pneumonia, making *C. difficile* colitis a possibility. However, repeated stools showed no *C. difficile* toxin. Because he was not taking other medications, drug hypersensitivity was excluded. An IgE-mediated food allergy was considered, but this was unlikely because he was not consuming any known citrus fruit, he denied other classic IgE-mediated symptoms, and there was no relationship of symptoms to meals. Infectious colitis was not likely with normal stool cultures and without a supporting travel history. Also, histological exam of bowel specimens did not identify eggs, erosions, or channels in the tissue from parasites (1). We still considered celiac disease a possibility as it can present with diarrhea, villous blunting, and tissue eosinophilia, and has rarely been described in association with concomitant IBD, which could account for the pancolonic involvement. However, this degree of tissue eosinophilia would be unusual (2,3). Ulcerative colitis alone was excluded given the ileal involvement. The florid tissue eosinophilia and the lack

of tissue neutrophilia and other histological features of Crohn's disease made this disease unlikely. Primary EGIDs can present with non-specific GI symptoms, peripheral and tissue eosinophilia, elevated IgE, leukocytosis, and thickening of bowel walls on imaging, all of which were seen in this patient. EGIDs, however, require exclusion of other known causes of eosinophilia. Vasculitides, such as polyarteritis nodosa and Churg-Strauss syndrome, were not likely given the lack of perivascular inflammation on biopsies and the lack of any other systemic manifestations, asthma, or sinusitis (1). Systemic mastocytosis presents in most adults with urticaria pigmentosa, which was not seen in our patient, nor did he have symptoms of mast cell mediator release, such as flushing, hypotension, or headaches. Finally, the mucosal biopsy in systemic mastocytosis usually only shows mild eosinophilia in the lamina propria with increased numbers of mast cells in the submucosal or serosal layers (4). Histiocytosis X is a rare disease seen usually in smokers and can cause tissue eosinophilia (1), but it has a granulomatous appearance on biopsy. Chronic granulomatous disease was excluded because the patient did not have a history of recurrent infections. HES was also considered in our patient. A GI malignancy was considered less likely given the lack of significant weight loss and histological evidence of malignancy.

What Additional Diagnostic Information Would Be Helpful?

Serological evaluation for celiac disease was negative, with negative IgA anti-tissue transglutaminase antibodies and negative IgA anti-endomysial antibodies. Biopsy specimens were further evaluated with immunostains for CD20, CD79a, CD3, and CD45RO. This demonstrated a mixture of B- and T-cells with follicular architecture, favoring a reactive rather than malignant lymphoid infiltrate. HES is defined by peripheral eosinophilia greater than 1500/ μ L for 6 mo, eosinophilic infiltration

and dysfunction of often multiple organ systems, and absence of another cause of eosinophilia. Within 1 mo of the initial labs, our patient's absolute eosinophil count dropped to 1300/ μ L. Also, he lacked fevers and sweats, as well as cardiopulmonary, neurological, or renal involvement commonly seen in HES (5). Based on these factors, these diagnoses were excluded and the diagnosis of eosinophilic gastroenteritis (EGE) was made.

Clinical Course

In as many as half of patients with EGE, there is associated food allergy, although not necessarily associated with IgE (6). Our patient underwent screening for specific IgE against foods, but patch testing was not available at the time. His tests returned positive for IgE toward lemon (>100 kU/L), grapefruit (27.4 kU/L), tomato (0.39 kU/L), carrot (0.43 kU/L), potato (0.43 kU/L), coconut (1.79 kU/L), banana (2.23 kU/L), parsley (0.72 kU/L), yeast (0.84 kU/L), garlic (0.75 kU/L), onion (0.52 kU/L), hazelnut (2.68 kU/L), peanut (0.45 kU/L), sesame (1.97 kU/L), and corn (0.45 kU/L). IgE assays toward other common ingestants were negative. Elimination of the positive foods did not result in clinical improvement, and the patient was not interested in a trial of an elemental diet (7–9). He was treated with non-enteric-coated budesonide and mesalamine with relief. Budesonide has been effective in cases of EGE (10). Follow-up colonoscopy revealed much less tissue eosinophilia; however, peripheral eosinophilia persisted. Based on promising case report data, montelukast was initiated (11,12). He was able to use both the budesonide and montelukast intermittently with relief of symptoms. However, 1 yr after diagnosis, he had a significant flare-up of symptoms that was unresponsive to these medications. A brief course of prednisone rapidly resolved his symptoms. Since this flare, the patient has been asymptomatic off medication for nearly 1 yr. Such remission after steroid therapy is not common in EGE (13). Follow-up colonoscopy 16 mo after

diagnosis and an esophagogastroduodenoscopy showed resolution of tissue eosinophilia. His peripheral eosinophil count had also normalized. Finally, computed tomography scan of the abdomen showed improvement in the intestinal wall thickening. Notably, his diet did not change.

Discussion

In 1937, Kaijser described the first known case of primary eosinophilic gastroenteropathy and coined the term “eosinophilic gastroenteritis” (14), referring to patients with nonspecific GI signs and symptoms and abnormal eosinophilic infiltration of the stomach or small intestines in the absence of other causes of eosinophilia. EGE now refers to a spectrum of disorders marked by GI symptoms combined with abnormal eosinophilic infiltration of the esophagus, stomach, small bowel, colon, or a combination of these. However, if esophageal or colonic involvement occur alone, the terms eosinophilic esophagitis (EE) or eosinophilic colitis (EC) are used; the disorders are thought to be distinct, except for EC occurring in adults, which seems to be a subset of EGE (5). Table 1 highlights the fact that the EGIDs can have similar presentations, may be associated with atopy, and that some EGIDs (such as EE and EC of infancy) are felt to be caused by allergic responses to food. In fact, even eosinophilic gastritis, eosinophilic enteritis, and EGE are likely distinct diseases, but are often grouped together given their clinical similarity and our incomplete understanding of their pathophysiology (5).

What is the Epidemiology of EGE?

Much of the data that describes EGE and the other eosinophilic gastroenteropathies is in the form of case reports, with only several hundred cases reported. However, an increasing number of cases, especially of EE, have been reported in the last 10 yr (15). The overall prevalence of EGIDs may be higher than that

of IBD (5). EGE is seen in patients of all ages, with males affected slightly more often than females (13). In adults, disease usually presents in the second to sixth decade of life (16). Most cases are sporadic, but there have been reports of a familial form (5).

How Is EGE Classified?

In 1970, Klein proposed a classification scheme dividing EGE into mucosal, muscularis, or serosal groups based on which tissue layer was predominantly infiltrated by eosinophils (7). Of the seven patients he studied, those with mucosal-predominant EGE had hypoproteinemia owing to protein-losing enteropathy, iron-deficiency anemia, and loss of weight secondary to malabsorption (7). Muscularis layer involvement usually resulted in obstructive symptoms, such as abdominal pain and vomiting owing to development of a thickened, rigid gut. Patients in the serosal EGE group presented with abdominal distention caused by eosinophilic ascites. Although Klein’s classification is cited in the literature today (17–19), its utility and validity require reexamination. Talley evaluated 40 patients with EGE, analyzing numerous clinical and laboratory parameters relative to layer of involvement (20). Only high peripheral eosinophilia, bloating, and dramatic response to steroids were statistically different among the three layer-defined groups; these findings were associated with serosal EGE. This study did not identify other variables that distinguished any of the layer-defined groups (21). Furthermore, probably because of referral bias, the prevalence of each of the Klein subtypes is not known, with surgical series reporting more muscularis disease, and medical series reporting more mucosal cases (20,22).

What Are the Clinical Manifestations of EGE and How Is it Diagnosed?

Symptoms and signs are typically subacute or chronic and can include dysphagia, nausea, vomiting, dyspepsia, regurgitation, bloating, diarrhea, weight loss, peripheral edema, mel-

Table 1
Features of the Different EGIDs

EGID type	Ages affected	Common presentation	Prevalence of atopy	Relationship to food hypersensitivity
EGE	Children and adults (second to sixth decade in adults)	Nausea, abdominal pain, diarrhea, malabsorption, weight loss, ascites	High (up to 50%)	Majority has positive skin tests to food antigens, but few have food anaphylaxis; elimination of suspect foods rarely helpful
EE	Children and adults	Emesis, dysphagia, epigastric or chest pain, heartburn, feeding problems (all unresponsive to acid suppression and mimicking severe GERD)	Very high (50%)	Majority has food sensitivity by skin-prick, RAST, or patch testing. Only a minority have a history of food anaphylaxis; elimination of offending food typically reverses the disease process
EC	Adolescents and young adults	Diarrhea, abdominal pain, weight loss, anorexia	Variable	Food triggers rarely identified
EC of infancy	Infants at about 60 d old	Bloody stools in a healthy appearing baby	Variable	Caused by allergic response to specific food proteins, commonly those in cow's milk or soy; resolves with elimination of offending protein, usually tolerant of that protein by age 1–3 yr

Adapted from refs. 5 and 13.

EC, eosinophilic colitis; EE, eosinophilic esophagitis; EGE, eosinophilic gastroenteritis; GERD, gastroesophageal reflux disease; RAST, radioallergosorbent test.

ena, and failure to thrive (23). In Naylor's 1990 review of 220 cases, the most common symptoms were episodic abdominal pain (77%) and diarrhea (42%) (24). Subsequent studies have also found abdominal pain, diarrhea, vomiting, and nausea to be the most frequent complaints (19,25). There are also numerous cases reported with atypical presentations, including acute appendicitis (26), bowel obstruction (27,28), gastric outlet obstruction (29), intussusception and bowel perforation in a neonate (30), duodenal strictures (31), biliary disease

(32,33), pancreatic disease (34), and abdominal distention owing to ascites (35).

The initial step in diagnosis is to consider clinical and epidemiological factors in the history that may suggest an EGID. A family history of eosinophilic gastroenteropathy may identify those with the familial EGE subtype (5). About half of patients in some series have atopic diseases (19,20). In extremely rare cases, development of EGE has been associated with initiation of a medication with resolution of symptoms upon discontinuation (36–38).

Physical examination by itself cannot distinguish EGE. Thus, the second criterion in diagnosing EGE is documenting eosinophilic infiltration in the GI tract. This usually requires esophagogastroduodenoscopy with gastric and small bowel biopsies (39), but lower (20,39) endoscopic biopsy of the small or large bowel may be required. Open or laparoscopic full-thickness biopsies are sometimes needed to diagnose muscularis (39) or serosal disease (13). Tissue eosinophilia is normal in the GI tract, except for the esophagus, where eosinophilia always indicates pathology, be it EE, EGE, gastroesophageal reflux disease, or another disorder (40). Baseline tissue eosinophilia in the rest of the gut makes it more difficult to diagnose EGE (1,41). It is often necessary for the pathologist to compare eosinophil counts at each area of the gut with normal values at their hospital (5). They may also be able to identify eosinophils located abnormally in the intraepithelial, superficial mucosal, or intestinal crypt regions, as in our patient (42). Immunohistochemistry may reveal increased extracellular eosinophil granule products, such as myelin basic protein (42) or eosinophilic cationic protein (43). Also, noting the absence of neutrophilia associated with IBD or the vascular inflammation found in vasculitis is critical (5).

A third requirement for diagnosis of EGE is exclusion of other known causes of tissue eosinophilia. Eosinophils may accumulate in the blood and tissues during numerous disease states including atopic conditions, parasitic infections, vasculitides, HES, connective tissue disorders, drug hypersensitivity reactions, and malignancies (5). In addition, eosinophils accumulate in the GI tissues in disorders, such as IgE-mediated food allergy, gastroesophageal reflux disease, IBD, and in the eosinophilic gastroenteropathies (13).

Laboratory and imaging studies aid in diagnosis. Stool analysis for ova and parasites is mandatory. Serological titers against specific parasites or colonoscopic aspirates for exami-

nation can also be obtained. This is especially important in patients living on farms or drinking from wells. Peripheral eosinophilia has been reported in 20–90% of cases but is not required for diagnosis (19,20). Elevated total IgE level or food-specific IgEs are variably present and may help identify those with an atopic or food-induced component, or prompt further search for an occult parasitic infection (5). The erythrocyte sedimentation rate is usually normal (20). In serosal EGE, ascitic fluid analysis usually reveals a markedly elevated eosinophil count. Barium studies may show mucosal irregularities, wall thickening, luminal stenosis, or ulceration but have poor sensitivity and specificity in EGID (44). In patients with hypereosinophilia, additional tests may include bone marrow biopsy, vitamin B₁₂ level, serum tryptase, echocardiogram, genetic analysis for the FIP1L1-PDGFR α fusion, and biopsy of any other potentially involved tissue (5).

What Is the Pathogenesis of EGE?

Although EGE is considered idiopathic, clinical and epidemiological data suggest that an allergic component is involved in at least a subset of patients with EGID. Half or more of patients in some series have atopic diseases (19,20,45,46). The majority of such patients have elevated IgE to specific foods and high total serum IgE (5,45,47,48). Allergen-free diets have been effective in decreasing symptoms in most patients with EE when food allergens were identified by both prick and patch tests (49). Also, evidence of mast cell degranulation has been documented in EGID tissue specimens (50,51). Finally, a murine model of delayed EGE has recently been developed by exposing sensitized mice to oral allergens (52).

EGIDs with an atopic component are considered mixed IgE and non-IgE mediated disorders (5,53). Rothenberg places EGE and the other EGIDs somewhere in the middle of a spectrum of inflammatory GI disorders between

IgE-mediated problems, such as food anaphylaxis, and more cell-mediated hypersensitivity disorders, such as celiac disease (5).

Most would agree that eosinophils play an important role in EGE. Eosinophils are formed in the bone marrow and mature there for 8 d, with their development promoted by activation of the transcription factors GATA-1, GATA-2, and c/EBP (54,55). Interleukin (IL)-3, IL-5, and granulocyte macrophage-colony stimulating factor (GM-CSF) act as permissive growth factors for eosinophils (5). IL-5 is the most specific growth factor to the eosinophil line, causing selective expansion of eosinophils, allowing their release into the blood, and prolonging their survival (56,57). Different mediators play a role in the accumulation of eosinophils in particular tissues. IL-3, IL-5, and GM-CSF promote eosinophil development, migration, and effector function (58). Of the many mediators involved in eosinophil accumulation, only IL-5 and the eotaxin chemokines are relatively specific for eosinophils (59). In addition, eotaxin 1 has been shown to be vital for eosinophil accumulation in the gut in a tissue-specific manner (60). At baseline, constitutive expression of eotaxin 1 causes specific localization of eosinophils to the GI tract (5). Here, the eosinophils can defend the host against parasites, but also regulate immune responses by interacting with T-lymphocytes in a bidirectional manner. T-cells release IL-5, promoting eosinophil growth and survival (13). At the same time, eosinophils can present antigens (61) to T-cells and can secrete various cytokines, including IL-2, IL-4, IL-5, IL-12, GM-CSF, and several interferons, which can direct T-cell proliferation and maturation along T-helper (Th)1 or Th2 paths (5).

Eosinophilic infiltration in EGE is a major cause of tissue damage (20). In the small bowel of patients with EGE, extracellular myelin basic protein and eosinophilic cationic protein deposits have been demonstrated (42,43); there is a correlation between tissue eosinophilia and the severity of disease (43). Also, Charcot-Leyden crystals, which are remnants of eosinophil

degranulation, are often found in EGE patients' stools (46). Finally, in a study utilizing multiple biopsies from patients with EGE and controls with irritable bowel syndrome, eosinophils were present in higher numbers in the intestinal mucosa of patients with EGE and these patients had IL-3, IL-5, and GM-CSF localized in eosinophilic granules in their intestinal biopsy samples, whereas none of the control patients did. This not only suggests that eosinophils are increased in number in EGE, but also that activated eosinophils can produce cytokines to upregulate their own proliferation and differentiation (62).

Despite such evidence that shows that eosinophils are present and have degranulated in areas of GI tissue damage in EGE, there is some controversy as to the role played by this cell. Namely, is the eosinophilic infiltrate a secondary response to an unknown primary pathological process? Kelly, in his 2000 review of EGE, suggests that the tissue eosinophilia in EGE may be a manifestation of inflammation and not the primary effector mechanism of disease (21). Jaffe showed that peripheral blood T-cells in patients with atopic EGE secrete higher amounts of IL-4 and IL-5 compared with controls (63). These cytokines may then be responsible for increased eosinophilopoiesis and IgE production in this EGE subgroup. Finally, Beyer was able to show that in children with milk-related EGE and milk-induced enteropathy, milk-specific intestinal mucosal T-cells displayed a Th2 cytokine profile after stimulation with milk protein (64). This suggests that a hypersensitivity response to foods at the T-cell level may explain part of the inflammatory changes in some patients.

How Is EGE Managed?

The literature on EGE is dominated by case reports or small retrospective series and lacks any prospective, randomized trials regarding therapy. In mild disease, some doctors recommend symptomatic treatment with antidiarrheal medications, such as loperamide (65).

Because food allergy likely plays a role in a subset of patients, some support initial treatment with elimination diets (5,13). This involves eliminating foods identified by any form of allergy testing (specific IgE in vitro, skin-prick test, patch test). In patients who are not sensitized to any foods by the methods used, or who are sensitized to too many foods to eliminate, systematic exclusion of the most likely allergenic foods is recommended. If this plan induces remission of disease, specific foods may be reintroduced at approx 3-wk intervals (or longer) while monitoring for remission using endoscopic and clinical criteria. Unfortunately, this approach results in remission in only a small number of patients with EGE, unlike in EE (7–9). Alternatively, an elemental diet can be instituted to see if there is any possibility of a food allergy contribution. An elemental diet has been shown to be effective in treating severe cases of steroid-dependent EGE (9).

In patients who fail dietary restriction, in those for whom this therapy is not feasible or accepted, or in those who have severe symptoms or evidence of malabsorption, most support the judicious use of systemic or topical corticosteroids (5,13,17). It is, of course, important that *Strongyloides* infestation be ruled out by stool ova and parasite examination owing to the risk of inducing systemic strongyloidiasis with the initiation of oral steroids. Corticosteroids have been shown to be effective in achieving remission in patients who have significant symptoms, usually within 2 wk, regardless of which tissue layer is involved (19,46). Wallace recommends 20–40 mg of prednisone per day, with a rapid taper over 2 wk (17). However, duration of remission is variable and often not long, requiring more prolonged or repeated steroid therapy (13). Attempts to minimize side effects of systemic steroids have led to “less systemic” steroid regimens, including non-enteric coated budesonide (10).

Other agents have been used in case reports or small series, but are not routinely recom-

mended (5,13). Montelukast, a leukotriene inhibitor, was successful as a steroid-sparing agent in two reports (11,12) but not in a third (66). Oral cromolyn has similarly been effective in several cases (67–73) but not in others (74,75). The mast cell-stabilizer ketotifen is not available in the United States but has been used in some cases (76–78). Suplatast tosilate, a novel anti-allergic drug known to inhibit T-cell production of IL-4 and IL-5, appeared to be useful in treating EGE in one patient but is not commercially available (79). Also, an anti-IL 5 antibody has been used in a pilot study at the National Institute of Health to treat four patients with EGE refractory to other treatments (80), resulting in reduced blood and tissue eosinophilia, but no change in symptoms.

References

1. Blackshaw, A. J. and Levison, D. A. (1986), *J Clin Pathol.* **39**, 1–7.
2. Talley, N. J., et al. (1992), *Gastroenterology* **103**, 137–145.
3. Yang, A., et al. (2005), *Inflamm Bowel Dis* **11**, 528–532.
4. Ammann, R. W., et al. (1976), *Gut* **17**, 107–112.
5. Rothenberg, M. E. (2004), *J Allergy Clin Immunol* **113**, 11–28; quiz 29.
6. Liacouras, C. A. (2003), *J Pediatr Gastroenterol Nutr* **37(Suppl 1)**, S23–S28.
7. Klein, N. C., et al. (1970), *Medicine (Baltimore)* **49**, 299–319.
8. Leinbach, G. E. and Rubin, C. E. (1970), *Gastroenterology* **59**, 874–889.
9. Justinich, C., et al. (1996), *J Pediatr Gastroenterol Nutr* **23**, 81–85.
10. Tan, A. C., Kruimel, J. W., and Naber, T. H. (2001), *Eur J Gastroenterol Hepatol* **13**, 425–427.
11. Schwartz, D. A., Pardi, D. S., and Murray, J. A. (2001), *Dig Dis Sci* **46**, 1787–1790.
12. Neustrom, M. R. and Friesen, C. (1999), *J Allergy Clin Immunol* **104**, 506.
13. Liacouras, C. and Markowitz, J. E. (2003), in *Pediatric Allergy: Principles and Practice*, vol. 1, Leung, D., ed., Mosby, St. Louis, MO, pp. 518–528.
14. Kaijser, R. (1937), *Arch Klin Chir* **188**, 36–64.
15. Bates, B. (2000), *Pediatric News* **34**, 4.
16. Edelman, M. J. and March, T. L. (1964), *Am J Roentgenol Radium Ther Nucl Med* **91**, 773–778.
17. Wallace, M. B. and Apstein, M. D. (2003), *UpToDate Online*, 1–8.
18. Matsushita, M., et al. (1995), *Am J Gastroenterol* **90**, 1868–1870.

19. Lee, C. M., et al. (1993), *Am J Gastroenterol* **88**, 70–74.
20. Talley, N. J., et al. (1990), *Gut* **31**, 54–58.
21. Kelly, K. J. (2000), *J Pediatr Gastroenterol Nutr* **30**(Suppl), S28–S35.
22. Ureles, A. L., et al. (1961), *Am J Med* **30**, 899–909.
23. Heine, R. G. (2004), *Curr Opin Allergy Clin Immunol* **4**, 221–229.
24. Naylor, A. R. (1990), *Scott Med J* **35**, 163–165.
25. Guajardo, J. R., et al. (2002), *J Pediatr* **141**, 576–581.
26. Tran, D., et al. (2000), *Am Surg* **66**, 990–992.
27. Alexander, P., Jacob, S., and Paul, V. (2003), *Trop Gastroenterol* **24**, 97–98.
28. Uenishi, T., et al. (2003), *Dig Surg* **20**, 326–329.
29. Chaudhary, R., et al. (2001), *Indian J Gastroenterol* **20**, 110.
30. Siahianidou, T., et al. (2001), *J Pediatr Gastroenterol Nutr* **32**, 335–337.
31. Tan, H. L., et al. (2003), *Pediatr Surg Int* **19**, 562–563.
32. Whitaker, I. S., et al. (2004), *Eur J Gastroenterol Hepatol* **16**, 407–409.
33. Jimenez-Saenz, M., et al. (2003), *Dig Dis Sci* **48**, 624–627.
34. Polyak, S., Smith, T. A., and Mertz, H. (2002), *Dig Dis Sci* **47**, 1091–1095.
35. Santos, J., et al. (1995), *Eur J Gastroenterol Hepatol* **7**, 675–678.
36. Ravi, S., et al. (1993), *Am J Gastroenterol* **88**, 612–613.
37. Lee, J. Y., Medellin, M. V., and Tumpkin, C. (2000), *South Med J* **93**, 807–808.
38. Barak, N., Hart, J., and Sitrin, M. D. (2001), *J Clin Gastroenterol* **33**, 157–158.
39. Katz, A. J., Goldman, H., and Grand, R. J. (1977), *Gastroenterology* **73**, 705–709.
40. Rothenberg, M. E., et al. (2001), *J Allergy Clin Immunol* **108**, 891–894.
41. Lowichik, A. and Weinberg, A. G. (1996), *Mod Pathol* **9**, 110–114.
42. Torpier, G., et al. (1988), *Clin Exp Immunol* **74**, 404–408.
43. Keshavarzian, A., et al. (1985), *Gastroenterology* **88**, 1041–1049.
44. MacCarty, R. L. and Talley, N. J. (1990), *Gastrointest Radiol* **15**, 183–187.
45. Caldwell, J. H., et al. (1979), *Gastroenterology* **77**, 560–564.
46. Cello, J. P. (1979), *Am J Med* **67**, 1097–1104.
47. Verdaguer, J., et al. (1993), *Allergy* **48**, 542–546.
48. Scudamore, H. H., et al. (1982), *J Allergy Clin Immunol* **70**, 129–138.
49. Spergel, J. M., et al. (2002), *J Allergy Clin Immunol* **109**, 363–368.
50. Bischoff, S. C. (1996), *Baillieres Clin Gastroenterol* **10**, 443–459.
51. Oyaizu, N., et al. (1985), *Acta Pathol Jpn* **35**, 759–766.
52. Hogan, S. P., et al. (2000), *Proc Natl Acad Sci USA* **97**, 6681–6686.
53. Sampson, H. A. (1999), *J Allergy Clin Immunol* **103**, 717–728.
54. Kulesa, H., Frampton, J., and Graf, T. (1995), *Genes Dev* **9**, 1250–1262.
55. Hirasawa, R., et al. (2002), *J Exp Med* **195**, 1379–1386.
56. Wardlaw, A. J. (1999), *J Allergy Clin Immunol* **104**, 917–926.
57. Shalit, M. (1997), *Allergy Immunol (Paris)* **29**, 7–10.
58. Rothenberg, M. E. (1998), *N Engl J Med* **338**, 1592–1600.
59. Jose, P. J., et al. (1994), *J Exp Med* **179**, 881–887.
60. Matthews, A. N., et al. (1998), *Proc Natl Acad Sci USA* **95**, 6273–6278.
61. Lucey, D. R., Nicholson-Weller, A., and Weller, P. F. (1989), *Proc Natl Acad Sci USA* **86**, 1348–1351.
62. Desreumaux, P., et al. (1996), *Gastroenterology* **110**, 768–774.
63. Jaffe, J. S., et al. (1994), *J Clin Immunol* **14**, 299–309.
64. Beyer, K., et al. (2002), *J Allergy Clin Immunol* **109**, 707–713.
65. Lee, M., et al. (1996), *South Med J* **89**, 189–194.
66. Daikh, B. E., Ryan, C. K., and Schwartz, R. H. (2003), *Ann Allergy Asthma Immunol* **90**, 23–27.
67. Heatley, R. V., Harris, A., and Atkinson, M. (1980), *Dig Dis Sci* **25**, 470–472.
68. Martin, D. M., et al. (1981), *Gastroenterology* **80**, 1567–1570.
69. Perez-Millan, A., et al. (1997), *Dig Dis Sci* **42**, 342–344.
70. Van Dellen, R. G. and Lewis, J. C. (1994), *Mayo Clin Proc* **69**, 441–444.
71. Di Gioacchino, M., et al. (1990), *Allergy* **45**, 161–166.
72. Moots, R. J., Prouse, P., and Gumpel, J. M. (1988), *Gut* **29**, 1282–1285.
73. Gilinsky, N. H. and Kottler, R. E. (1982), *Postgrad Med J* **58**, 239–243.
74. Robert, F., Omura, E., and Durant, J. R. (1977), *Am J Med* **62**, 139–143.
75. Elkon, K. B., Sher, R., and Seftel, H. C. (1977), *S Afr Med J* **52**, 838–841.
76. Melamed, I., et al. (1991), *Am J Med* **90**, 310–314.
77. Katsinelos, P., et al. (2002), *Am J Gastroenterol* **97**, 1072–1074.
78. Suzuki, J., et al. (2003), *Asian Pac J Allergy Immunol* **21**, 193–197.
79. Shirai, T., et al. (2001), *J Allergy Clin Immunol* **107**, 924–925.
80. Prussin, C., James, S. P., and Huber, M. M. (2003), *J Allergy Clin Immunol* **11**, 1.