Food Allergy and Eosinophilic Gastrointestinal Disorders: Guiding Our Diagnosis and Treatment

C. Allan Pratt, MD,[a] Jeffrey G. Demain, MD,[b] and Melinda M. Rathkopf, MD[b]

Eosinophilic gastrointestinal disorders are a new spectrum of diseases with an old history. Many causes of eosinophilic infiltration of the gut have long been recognized (Table 1). Most of these conditions are autoimmune or primary eosinophilic disorders. The focus of this review is the role of food allergy in the pathophysiology of eosinophilic gastrointestinal disorders.

The incidence of atopy, including food allergy, has been on the rise over the past three decades and the association between food allergy and eosinophilic gastrointestinal disorders is becoming better recognized.[1-5] It is now accepted that allergic diseases have reached near epidemic proportions, inflicting nearly 30% of the population.[6] Asthma has risen 160%; atopic dermatitis has risen threefold, and food allergy has more than doubled since accurate records of these conditions have been kept.[7]

Whether from increased recognition or increased incidence, the identification of food allergy is now estimated to affect between 2 and 8% of children and 2% of adults,[4] but eosinophilic diseases of the intestines are still poorly recognized and considered rare by some.[8,9] When Kaijser first described eosinophilic gastrointestinal disorders in 1937,[10] the significance of this disorder, which was considered exceptionally rare, was not appreciated. Esophageal eosinophilia was first reported by Dobbins and coworkers in 1977,[11] but the connection to possible food allergy was not identified. Food allergy, and its role in eosinophilic gastrointestinal disorders, was first described by Kelly and coworkers in 1995[1] but was largely ignored by the general medical community. At the same time that technological advances such as magnetic resonance imaging and advanced interventional techniques were being widely adopted, the fact that patients could have debilitating symptoms as a result of reactions to foods was largely ignored.

This is a disorder that is becoming increasingly better recognized. According to PubMed, there were 301 articles published in the 40 years between 1950 and 1990 on eosinophilic esophagitis or eosinophilic gastroenteritis. Between 1990 and 2007, 802 articles were published on the same topics. Although few studies have been done specifically to evaluate the prevalence of eosinophilic esophagitis in children, it appears that during the past decade the prevalence has been increasing. A review of patients 20 years and younger with biopsy-confirmed eosinophilic esophagitis at Cincinnati Children's Hospital Medical Center showed that the prevalence rose from 1 in 10,000 children in 2000 to 4 in 10,000 children in 2003.[12] More recently, Prasad and coworkers[13] reported that 15% of adults ages 18-20 years presenting with dysphagia had biopsy-confirmed eosinophilic esophagitis.

Definitions

An adverse food reaction is an aberrant reaction after ingestion of a food or food additive. Adverse food reactions can be divided into food aversions, food poisoning, and food intolerances. Food aversions are general dislikes to texture or taste or perceptions that a food is somehow offensive. These are not typically reproducible reactions. Food intolerances are reproducible, specific reactions to foods. They can be non-immunologic, as in lactose intolerance, or immunologic, as in food allergies and celiac disease. The focus of this article is on immunologic food reactions. These are reactions by the immune system against

From [a]Pediatric Gastroenterology of Alaska, Anchorage, Alaska; and the [b]Allergy, Asthma, and Immunology Center of Alaska, Anchorage, Alaska.

There was no funding for the authorship of this study. The authors have no commercial associations that might create a real or perceived conflict of interest.

Curr Probl Pediatr Adolesc Health Care 2008;38:170-188

1538-5442/$ - see front matter

doi:10.1016/j.cppeds.2008.03.002

TABLE 1. Etiologies of intestinal eosinophilia

Esophagus
Gastroesophageal reflux
Allergy to inhaled pollens
Food allergy
Celiac disease
Crohn's disease
Intestinal tract
Food allergy
Autoimmune eosinophilic gastroenteritis
Celiac disease
Crohn's disease
Ulcerative colitis
Parasites—particularly worms
Graft versus host disease
Collagenous colitis
Posttransplant enteritis

ingested foodstuffs, largely proteins. The reactions may be pure non-IgE-mediated reactions as in celiac disease; they may be pure IgE-mediated reactions as in anaphylaxis, or they may be mixed reactions as in eosinophilic gastrointestinal disorders. To understand this complex system and how it goes awry, we review normal intestinal physiology and the complex relationship between the intestinal mucosa and the immune system.

Pathophysiology

The two chief functions of the intestinal mucosa are to digest and absorb nutrients necessary for maintenance of metabolism and growth and to act as a defense to the "outside" environment. In its role as the first line of defense from the outside world, the gut-associated lymphoid tissue must process and appropriately react to numerous different substances. These include food antigens—either innate to the food itself or antigens that have been altered by preparation such as digestive enzymes, or medications. An example of such medications would be acid-suppression medications, histamine receptor antagonists or proton pump inhibitors, or artificially produced pancreatic enzymes. The gut-associated lymphoid tissue also must process swallowed aeroallergens and react appropriately to both normal and pathologic microorganisms. Because of the varied interactions between a large number of immune-regulating cells and typically very large antigen loads, the intestinal mucosa is predisposed to hypersensitivity reactions. There is a complex interaction between digestion, absorption, and antigen recognition. This tight control of reactions to antigen regulation may become ineffective and may explain some food "intolerances"—that is, symptoms related to foods despite negative allergy testing.

All eosinophilic gastrointestinal disorders are not necessarily secondary to allergy, as discussed later, but discussion of other causes of these conditions is beyond the scope of this review. Therefore, we describe the basic types of allergic reactions and the mechanisms that drive them.

Immunologic Food Reactions—Allergy

There are four generally recognized types of immune mediated (or hypersensitivity) reactions, referred to as Gel and Coombs Type I-IV. Food reactions can also be classified into one of these types. Gel and Coombs type I reactions are IgE-mediated reactions that are responsible for immediate hypersensitivity reactions—as in anaphylaxis. These reactions stem from a failure of oral tolerance to food antigens resulting in the production of excessive food-specific IgE antibodies. The specific IgE antibodies then bind to the Fc receptors on basophils and mast cells. Food proteins can then act as antigens that bind the Fab fragment of the IgE antibodies, resulting in the release of proinflammatory cytokines, chemokines, and preformed mediators such as histamine.

With exposure to food antigens (protein fragments) there is often the production of IgG antibodies. In fact, many researchers have questioned the utility of food-specific IgG measurements in evaluating adverse food reactions. Currently, there is insufficient evidence that the presence or quantity of food allergen-specific IgG produced as a result of natural exposure is related to allergic disease.[14] Additionally, the roles of specific IgG as diagnostic or prognostic indicators of clinical allergy have not been substantiated.[15,16]

Type II hypersensitivity reactions are non-IgE-mediated reactions, commonly referred to as antibody-dependent cytotoxic reactions. During type II reactions, specific antibodies bind to surface tissue antigens and induce complement activation. These reactions stimulate the release of inflammatory mediators, which leads to tissue damage. Examples of type II reactions include milk-induced thrombocytopenia and food-induced pulmonary hemosiderosis, also known as Heiner syndrome.

Type III reactions are driven by the formation of antigen-antibody immune complexes. These complexes activate complement, which leads to the re-

cruitment and activation of inflammatory cells, predominately neutrophils. The neutrophils then cause direct tissue injury. Examples include serum sickness and Arthus reactions (in situ formation of antigen/antibody complexes after the intradermal injection of an antigen).[17] IgG, IgM, or IgA antibodies can also form specific immune complexes with food antigens that have been absorbed across the intestinal mucosa. Elevated food antigen–antibody complexes have been measured in the serum of individuals with a variety of clinical presentations including food hypersensitivity; however, these complexes have also been found in the sera of normal individuals,[18] making interpretation of their presence uncertain and controversial. Antigen–antibody complexes to lactoglobulin, in fact, have been found 1 to 3 hours after milk ingestion in the sera of normal, asymptomatic children and adults.[19]

Finally, type IV reactions are T-cell-mediated allergic responses. Normally, T-cells become sensitized after contact with a specific antigen. On re-exposure to that antigen, they are activated and can directly damage tissue or release proinflammatory cytokines. Type IV responses are implicated in food reactions with delayed onset of symptoms and likely contribute to a number of gastrointestinal disorders and atopic dermatitis. Although this is perhaps the least understood of the food allergic reactions, the ingestion of sensitizing antigens is clearly linked to mucosal lesions and eosinophilia.[20]

The four types of immunologic reactions to foods are important to understand but are not the most clinically useful way to look at the connection between a patient's symptoms and what he or she is eating. From a clinical standpoint, we feel it is easiest to classify food reactions as predominately IgE-mediated, non-IgE-mediated, or mixed IgE/non-IgE and then to classify the reactions according to where they occur within the gastrointestinal tract.

IgE-mediated reactions are characterized by a temporal relationship between exposure to the food and the reaction. Reactions may be generalized, as in anaphylaxis, or localized to a specific organ. IgE-mediated food reactions include urticaria, angioedema, acute rhinoconjunctivitis, bronchospasm, oral allergy syndrome (pruritis and tingling in the mouth after an ingestion of an allergen), and anaphylaxis. Examples of these are the anaphylactic reactions to nuts, shellfish, or egg antigen. Allergy of this type is life-threatening and requires complete avoidance of the offending allergen and, if encountered, is treated with injectable epinephrine, steroids, and antihistamines. Pure IgE-mediated reactions do not typically cause abdominal pain without other systemic manifestations.

Non-IgE-mediated reactions are T-cell-mediated and, hence, typically take days to fully develop and weeks to completely resolve. Cutaneous reactions include contact dermatitis, an example of which is the typical reaction to poison ivy, or the nickel-induced dermatitis seen commonly on the suprapubic area of the abdominal wall secondary to the metal in snaps or belt buckles. Another example of this type of reaction is dermatitis herpetiformis—a chronic vesicular skin rash so strongly associated with gluten sensitivity that it is now generally accepted that this reaction is a manifestation of celiac disease.[21]

In the gastrointestinal tract, cell-mediated reactions are not as well understood and are classified according to the location of the reaction in the gastrointestinal tract for clinical purposes. These reactions include food protein-induced enterocolitis, food protein-induced proctocolitis, and food protein-induced enteropathy syndrome. Food protein-induced proctocolitis is the most common of these reactions. It is seen in otherwise well infants who have small amounts of blood and mucous in the stool. It is commonly due to milk protein in the formula or in the mother's diet if the infant is breastfeeding. Food protein-induced enterocolitis often presents in young infants but can occur at any age. Patients typically present with chronic emesis, diarrhea, and failure to thrive, along with pallor and diaphoresis. Reintroduction of the offending protein after a period of avoidance may result in violent emesis and, in 20% of cases, hypovolemic shock.[22] Celiac disease (gluten-sensitive enteropathy) is an example of a food protein-induced enteropathy. In this case, the reaction is stimulated by gliadin, the alcohol-soluble portion of gluten found in wheat, rye, and barley, and involves both T-cell responses and IgA antibodies.

More vexing to the pediatrician than the purely IgE- or non-IgE-mediated reactions in the gut are the mixed IgE and cell-mediated allergic reactions. These conditions may be difficult to diagnose, as symptoms of these conditions tend to be less specific and, as mentioned above, may not have the immediate temporal relationship seen in pure IgE-mediated reactions. Patients often present with nonspecific abdominal pain, excessive gassiness, or symptoms consistent with gastroesophageal reflux that are recalcitrant to standard reflux treatment. The medical community is well

versed in recognizing mixed IgE and cell-mediated reactions in the lungs, such as asthma, or in the skin, such as atopic dermatitis. In the gastrointestinal tract these reactions cause allergic eosinophilic esophagitis, eosinophilic gastroenteritis, and allergic eosinophilic proctocolitis.

Eosinophilic Gastrointestinal Disorders

The pathophysiology of the eosinophilic gastrointestinal disorders has not been completely worked out, but both genetic and environmental factors are important. Approximately 10% of patients with this disorder have an immediate family member with eosinophilic gastrointestinal disorders as well, and this number is probably an underestimation.[23] This fact, however, suggests eosinophilic gastrointestinal disorders stem from genetic predisposition, common environmental factors, or, most likely, a combination of the two. Interestingly, only 50 to 70% of patients with eosinophilic gastrointestinal disorders have other recognized atopic disorders, so one cannot rely wholly on the recognition of an atopic profile before considering this diagnosis.[20,24,25]

Recent efforts have identified the cellular and humoral responses that lead to the symptoms of eosinophilic gastrointestinal disorders. Eosinophilic granules release proinflammatory mediators, such as cationic proteins, leukotrienes, and prostaglandins and have cytotoxic effects by producing oxygen-free radicals and peroxidase.[24] Work by Blanchard and coworkers[26] identified markedly elevated eotaxin-3, a chemokine for eosinophils, in the mucosa of eosinophilic esophagitis. Additionally, elevated levels of IL-5, IL-4, and IL-13 have been identified in eosinophilic esophagitis and support a Gel and Coombs type I, Th2 IgE-mediated immune process.[27] This results in upregulation and proliferation of eosinophils, recruiting them to the affected tissue. Eosinophilic esophagitis is considered a mixed immune response consisting of both a type I, IgE-mediated response and a non-IgE-mediated or cell-mediated (type IV) response. Evidence for cell-mediated reactions is demonstrated by the utility of atopic patch testing in identifying offending foods.[4,28-31]

Eosinophilic Esophagitis

Case 1. An 18-year-old male with a 9-year history of gastroesophageal reflux disease repeatedly described regurgitation, heartburn, acid-brash (tasting acid in the mouth), and, occasionally, difficulty swallowing. He had minimal improvement in his symptoms with the use of acid-reducing therapy including H2-blockers and proton pump inhibitors. He additionally had seasonal oculonasal symptoms, including sneezing, rhinorrhea, and oculonasal itching. He also had a strong history of atopy in the paternal side of his family. In 2006, he had an episode of acute food impaction and underwent upper endoscopy with biopsy. During the endoscopy numerous white papules and linear furrowing were identified in the esophagus. Eosinophilic esophagitis was suspected based on these findings and biopsies were taken from the distal and mid-esophagus. The biopsies from the distal esophagus showed 52 eosinophils per high powered field in the greatest concentration with "focal clustering" [of eosinophils] and "degranulation." The mid-esophageal biopsies showed up to 180 eosinophils per high powered field with "aggregates" and degranulation of the eosinophils. He was started on fluticasone 440 micrograms, to be puffed and swallowed, twice daily and referred for allergy evaluation. Epicutaneous testing was significantly positive for food (cow's milk) and aeroallergens (grasses, cottonwood, weeds, and outdoor molds). Atopic patch testing was negative for additional foods. All cow's milk products were withdrawn from his diet. After 2 weeks of therapy he felt much better and discontinued the fluticasone. On a milk avoidance diet he had complete resolution of his symptoms, including heartburn, regurgitation, and dysphagia. He then began slowly introducing more dairy into his diet and felt that it was well tolerated. Five months later, he presented to the emergency room with another food impaction and biopsies taken at the time of the impaction removal again confirmed the diagnosis of eosinophilic esophagitis. He resumed a strict cow's milk free diet and has remained asymptomatic.

Eosinophils within the esophagus were originally thought to reflect gastroesophageal reflux or primarily inflammatory conditions such Crohn's disease.[24] In 1982, Winter and coworkers strongly correlated the presence of eosinophils in the esophagus with acid reflux and, in fact, suggested their presence should be part of the diagnostic criteria for pathologic gastroesophageal reflux.[32] In this study, intraepithelial eosinophils in the esophagus correlated with prolonged clearance of acid in the esophagus and basal cell hyperplasia seen on biopsy—interpreted at the time as a histologic feature typical of reflux-induced esophagitis.[32] Later studies in adults supported the correlation of intraepithelial eosinophils with reflux esophagitis when their presence was identified in patients who also had abnormal pH probe results.[33,34] Based on these and similar studies, children with reflux-like

symptoms were treated with aggressive acid blockade therapy.[24]

There are, however, other recognized causes of esophageal eosinophilia (Table 1). Many of the conditions are rare or have other symptoms that suggest their diagnosis. Symptomatic gastroesophageal reflux is very common and occurs in approximately 7% of adults and is even more common in infants and children.[35,36] In 1995, Kelly and coworkers described esophageal eosinophilia in 10 patients who were unresponsive to aggressive reflux treatment but responded well to an elimination diet.[1] In this study 8 of 10 children had resolution of symptoms and there was significant improvement in the other two. Kelly allowed these patients to drink clear liquids and foods from apple or corn. Corn, however, has been identified as one of the most commonly identified allergens associated with eosinophilic gastrointestinal disorders.[2] Kelly's study was the first study to suggest that esophageal eosinophilia may be secondary to conditions other than gastroesophageal reflux. Finally, eosinophilic esophagitis can occasionally be a subset of the more diffuse eosinophilic gastroenteritis and therefore be associated with lower gastrointestinal tract symptoms.[37]

Allergic eosinophilic esophagitis often presents with symptoms that strongly suggest gastroesophageal reflux disease such as vomiting, regurgitation, heartburn, acid brash, and epigastric pain, in addition to dysphagia and food impaction[24,25,38] (Table 2). One report even described significant airway inflammation that included laryngeal edema and subglottic stenosis associated with esophageal eosinophilia.[38] Classically, eosinophilic esophagitis in children presents more commonly in males (often teenagers) with gastroesophageal reflux-like symptoms that are only partially responsive to antireflux or acid-controlling medications.[24,25,38] Acid blockade therapy can reduce reflux symptoms associated with eosinophilic esophagitis somewhat, and this leads to diagnostic challenges among clinicians. In eosinophilic esophagitis esophageal pH monitoring often reveals frequent, brief reflux episodes, but normal esophageal acid clearance and reflux index.[24] The esophageal inflammation caused by allergy and infiltration of eosinophils may either prevent the lower esophageal sphincter from having its normal tone or cause increased transient lower esophageal sphincter relaxations. The diagnosis of eosinophilic esophagitis should also be strongly suspected when patients present with dysphagia or with food impaction in the esophagus. Food impaction tends to be more common in the older pediatric patient or adolescent and reflux symptoms predominate in younger children.[39] Eosinophilic esophagitis occurs in children and adults, but only rarely in infants and there is a predominance of boys over girls.[24,25]

TABLE 2. Features of gastroesophageal reflux versus eosinophilic esophagitis (EE)

	GER	EE
Symptoms		
Heartburn	+++	+++
Regurgitation	+++	+++
Dysphagia	+	+++
Food impaction (Esophagus)	+	+++
Abdominal pain	++	++
History of atopy	–	++
Testing		
Abnormal pH-metry	+++	+
Biopsy results		
Eosinophil density	+	+++
Eosinophilic abscesses	–	++
Basal cell hyperplasia	++	++
Subepithelial fibrosis	++	++
Treatment		
Response to acid suppression	+++	+
Response to fluticasone	+	+++

Eosinophilic esophagitis is associated with both type I (IgE-mediated) and type IV (cell-mediated) allergy and therefore is associated with atopic disease. In one study, 80% of patients with eosinophilic esophagitis had other forms of allergy compared with only 29% in the gastroesophageal reflux disease group.[40] Like all gastrointestinal allergic diseases, eosinophilic esophagitis requires a thorough gastrointestinal and allergy evaluation. The allergy evaluation is critical even though a classic paper on the subject suggests that medicinal therapy alone for 6 weeks can eliminate symptoms and significantly reduce the eosinophilic inflammation in the esophagus.[41] Additionally, the authors described that eosinophilic inflammation did not return during the follow-up period. This has not been our experience. In contrast, Spergel[3] reported resolution of symptoms in addition to reduced or resolved tissue eosinophilia following removal of offending food(s). By removing the stimulus for the reaction, the assumption is that the eosinophilic infiltrate and symptoms will not return, although this has not yet been subjected to a randomized controlled trial.

A limited number of studies and case reports have looked at the role of aeroallergen sensitivity in eosinophilic gastrointestinal diseases, most notably in eosinophilic esophagitis. As mentioned, the majority of

patients with eosinophilic esophagitis are atopic, with 50 to 80% having coexistent asthma, allergic rhinitis, and/or atopic dermatitis.[5] In a model of experimentally induced esophagitis, mice challenged with *Aspergillus fumigatus* developed marked levels of esophageal eosinophils.[6] Most notable, however, was that the eosinophilic infiltrate found in the mouse esophagus occurred from inhalational exposure but not from oral or intragastric administration of the allergen. The researchers therefore concluded that the eosinophilic esophagitis occurred as a result of allergen sensitization in the respiratory tract followed by topical delivery of allergen to the esophagus. This appears to establish a causal link between the development of allergic hypersensitivity in the respiratory tract and the development of allergy in the esophagus. The first case report suggesting an etiologic role of pollen sensitization in the development of eosinophilic esophagitis in humans was published in 2003.[42] This 21-year-old female, with allergic rhinitis, asthma, and known eosinophilic esophagitis, experienced clear exacerbations of her esophagitis symptoms during the pollen season. There was also an association identified between the pollen season and her level of esophageal eosinophilia. Similarly, in a report by Onbasi and coworkers, 38 patients with allergic rhinitis (with or without asthma) who were symptomatic during the grass pollen season showed evidence of eosinophils in the esophagus at this time.[43] These patients, however, did not complain of gastrointestinal symptoms and did not meet diagnostic criteria for eosinophilic esophagitis.

Simon and coworkers investigated the association of eosinophilic esophagitis with other allergic diseases.[44] They examined 31 patients with previously diagnosed eosinophilic esophagitis and reported concomitant atopic diseases in 68%. Seventy-seven percent had sensitization to aeroallergens. In this study, allergic rhinitis and asthma preceded the eosinophilic esophagitis, again supporting the notion that initial sensitization might take place in the airways. In the adult patients of this study, a high frequency of sensitization to plant-derived food allergens that cross-react with pollens, such as wheat and rye with grass pollens, was particularly noted.

As a result of the strong association between atopic disease and eosinophilic gastrointestinal diseases, and with evidence of the etiologic role of aeroallergens, a recent expert panel concluded that patients identified with eosinophilic esophagitis should also have a complete evaluation for other allergic diseases.[45] Allergy evaluation for eosinophilic esophagitis needs to address aeroallergens as well as food allergens through epicutaneous (prick) testing. Food allergens are also tested for by atopy patch testing, described below.

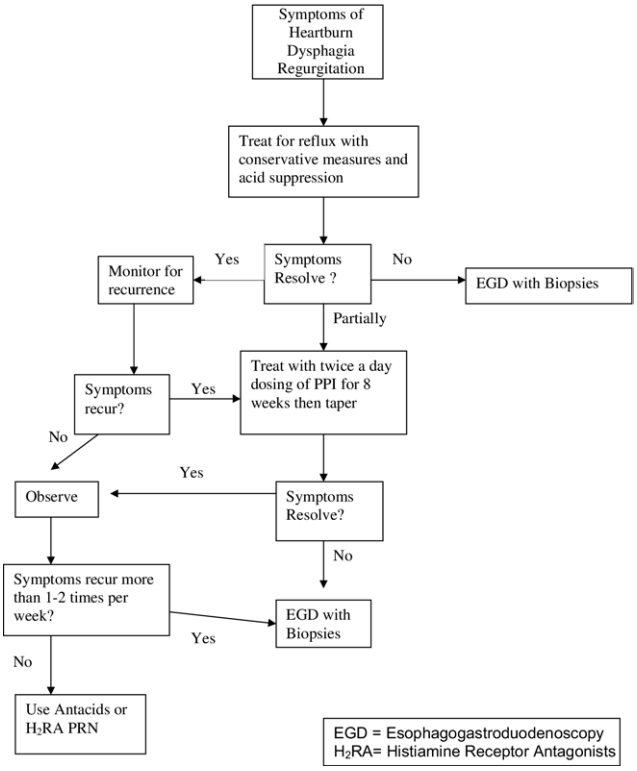

FIG 1. An approach to GER versus eosinophilic esophagitis.

While allergy to food or inhaled allergens can now be accurately and precisely diagnosed with a thorough history and appropriate testing, it remains true that, like all eosinophilic gastrointestinal disorders, eosinophilic esophagitis can only be definitively diagnosed by biopsy. Care must be taken to eliminate as much inflammation secondary to acid reflux as possible, and therefore, reduce confusion in interpreting the esophageal biopsies. Based on this important fact, the diagnostic plan proposed by Liacouras[24] suggests "preparing" patients for biopsies with aggressive acid reduction therapy. Patients are treated with 6 to 8 weeks of high-dose proton pump inhibitor therapy and then tapered off medicines over 2 to 3 weeks. This allows for the possibility of resolving esophagitis secondary to acid reflux and the associated esophageal dysmotilities, and the expectation is that the usual symptoms of heartburn, regurgitation, or dysphagia will also resolve. If a patient's symptoms return on

tapering off the acid blockade medicine or do not completely resolve during the treatment period, then the medications are restarted (typically twice daily dosing) and endoscopy is performed. During endoscopy multiple biopsies are taken from both the distal and proximal esophagus, looking specifically for evidence of eosinophilic esophagitis. A summary of this approach is found in Figure 1.

A review of 10 years experience with eosinophilic esophagitis from the Children's Hospital of Philadelphia reported that gross abnormalities of the mucosa were recognized during endoscopy 68% of the time.[5] There have also been several attempts to define eosinophilic esophagitis by objective criteria applied to the pathologic specimens from endoscopic biopsies.[46] The first attempt was in 1993 in a landmark paper that compared the number of eosinophils in the esophageal mucosa in patients with gastroesophageal reflux disease versus those with classic features of eosinophilic esophagitis: dysphagia, atopy, and normal pH studies.[47]

At this time it is well established that esophageal biopsies should be evaluated by counting the number of eosinophils in the greatest density in any high powered field of the microscope and by looking for stereotypical patterns.[24] Until recently, 20 eosinophils per high powered field was considered adequate to establish the diagnosis of eosinophilic esophagitis.[25,40,48] Current evidence suggests that 15 to 17 eosinophils per high powered field is more precise, especially in patients who have undergone acid reduction therapy with a proton pump inhibitor.[48,49] Eosinophils deeper than the mucosal layer (in the muscularis mucosae for example) and eosinophilic abscesses are also important clues to the diagnosis as described below.[24] Finally, to differentiate inflammation caused by gastroesophageal reflux from inflammation secondary to swallowed allergens, biopsies in the distal esophagus are compared with biopsies taken in the mid- or proximal esophagus. In eosinophilic esophagitis the inflammation, although often a patchy distribution, is nearly equal throughout the esophagus.[24] With gastroesophageal reflux the inflammation is greater in the distal esophagus (where there is more acid exposure) when compared with the proximal esophagus. The protocol to pretreat patients with acid reduction makes the interpretation of the biopsies much clearer since there should be essentially no inflammation from acid after appropriate blockade.[5] If a patient with significant eosinophilia on biopsies subsequently has negative allergy evaluation or does not respond to elimination of the allergens identified, it is then reasonable to proceed with pH or impedance probe monitoring to ensure that the acid blockade is complete throughout the day.

The key to treatment of eosinophilic esophagitis consists of allergen avoidance.[1,24,49] The most common causative foods have been identified as egg, milk, soy, corn, and wheat.[2] However, many other foods have been recognized as allergens, including beef, pork, chicken, barley, rice, oat, garlic, and legumes. With appropriate elimination, symptoms may take up to 3 to 6 weeks to fully resolve. If the offending allergen is not eliminated, symptoms return 90% of the time once medicines are stopped.[50] The patient (case 1) described earlier experienced symptomatic relief within 3 weeks of beginning the elimination diet and the improvement in symptoms correlated well with improvement in the esophageal eosinophilia.

Consider prescribing swallowed fluticasone when symptoms are severe, need to be controlled sooner, or appropriate allergens cannot be identified and the esophageal eosinophilia is not felt to be secondary to ongoing acid reflux from the stomach.[51] This is administered via a metered-dose inhaler without the use of a spacer and without the usual methods intended to deliver the medicine to the lower airway.[52] In fact, the patient uses the inhaler in a way such that they deliberately allow the medicine to be sprayed to the back of the throat or tongue and then swallowed. The patient should not eat or drink anything for 30 minutes unless old enough to rinse the mouth and spit out without swallowing. This method allows the steroid to be applied "topically" to the inflamed esophagus. This is done twice daily for 6 weeks and works very well in decreasing the inflammation and resolving the patient's symptoms.[51,52] As with any inhaled or swallowed steroids, be aware of the possibility of oral or esophageal candidiasis.

In resistant cases, eosinophilic esophagitis can also be treated with budesonide. Budesonide is used in its liquid form (intended for nebulization) that is then mixed with sucralose (one ampule mixed with five packets of Splenda®) to form a slurry.[53] This is taken orally up to four times a day. Dosing regimes for budesonide have been developed at the Children's Hospital of Philadelphia.[51] This is strictly off-label and patients and their families must know that this use of the medication for this purpose is not approved by the U.S. Food and Drug Administration. It does,

however, work very well with few side effects. Systemic steroids have also been used with good success, particularly in the early history of treatment evolution and before our current understanding of the disorder.[51]

Finally, a strictly elemental diet (so-called since the diets contain no intact protein, but rather the basic "elements" of protein, amino acids), using only liquid formula for 4 to 6 weeks can be used.[24] This is typically reserved for the most difficult to control cases as it is a very difficult task for patients to undertake and compliance long term is problematic. Whatever treatment is chosen, it is important to recognize that not treating eosinophilic inflammation is probably unwise. Eosinophilic esophagitis has been linked to stricture development and eosinophilic abscess formation with perforation of the esophagus as well as advanced esophageal dysfunction.[52] In the case of mechanical esophageal abnormalities, specifically, stricture, dilation is performed, but often requires multiple treatments.[52]

Eosinophilic Gastroenteritis

Case 2. A 3-month-old male with cystic fibrosis and a strong family history of atopy developed meconium ileus at 21 days of age for which he underwent a small bowel resection with formation of a double barrel ileostomy. He was started on a diet of Pregestamil® and received pancreatic replacement enzymes sprinkled on applesauce. One week after discharge he was rehospitalized with fever, suspected abdominal pain, and diarrhea. Endoscopy and biopsy of the stomas revealed "sheets of eosinophils." Inflammation secondary to inspissated meconium was considered, as was small bowel bacterial overgrowth. He did not respond to the usual treatments for these disorders or to several formula changes. Allergy evaluation included epicutaneous testing for foods that was significantly positive for cow's milk, beef, and pork. ImmunoCap® assay was also positive for pork (class 2). The patient was changed to an amino acid formula, Neocate®, with marginal improvement. He was then started on intrastomal beclomethasone again with marginal improvement. Gastrocrom®, an oral form of Chromolyn sodium, was added without significant benefit. Epicutaneous testing was performed using the patient's pancreatic enzymes (Creon®), which was positive at 1:10 concentration. Since all commercially available pancreatic enzymes are porcine-based, enzyme supplementation was discontinued and he was continued on an elemental formula with additional medium chain triglyceride (MCT) oil added. Within 2 weeks of withdrawing pancreatic enzymes, the mucosal eosinophilia was completely resolved. Reanastomosis of his double barrel ileostomy was then completed successfully.

TABLE 3. Symptoms of eosinophilic gastroenteritis by subtype

Mucosal
Abdominal pain
Cramping
Nausea
Vomiting
Diarrhea
Excess gassiness
Bloating
Anemia
Hematachezia
Mucous in stool
Protein losing enteropathy
Food refusal
Failure to thrive (infants)
Muscular
Abdominal pain
Gastric outlet obstruction
Intestinal strictures
Serosal
Abdominal pain
Bloating
Ascites

Eosinophilic gastroenteritis is a condition marked by eosinophilic inflammation in the bowel wall distal to the esophagus and can involve the entire remainder of the gastrointestinal tract.[54,55] By accepted definition, eosinophilic gastroenteritis is marked by the presence of gastrointestinal symptoms, a predominant eosinophilic infiltrate on biopsy, and exclusion of other causes of eosinophilia.[9,20] It is typically divided into three categories depending on the depth of inflammation, each category with overlapping but different presenting symptoms (Table 3).

These subtypes are mucosal (the most common subtype), muscular (occurring in 13-70% of cases), and serosal. The mucosal form has been reported to occur in 25 to 100% of cases and typically presents with abdominal pain, nausea, vomiting, and diarrhea, each of which occur in nearly 50% of patients,[20,56] and occult blood loss, anemia, and protein-losing enteropathy.[9,57] Allergic eosinophilic gastrointestinal disorders can cause failure to thrive or food refusal in infants and toddlers.[58] In this form, peripheral eosinophilia occurs in 50 to 65% of cases and the sedimentation rate is elevated in approximately 25% of cases,[9,20,24,57,58] both of which return to normal with treatment.[9,55] The abdominal pain is typically

quite generalized throughout the abdomen and may be more severe after eating. Eosinophilic gastroenteritis can also be associated with villus blunting and subsequent maldigestion or malabsorption. This leads to excessive gassiness and cramping.[9,59] Many patients are well in between spells of pain and this can lead to months or years of on and off symptoms before evaluation is sought.[59] This is particularly true if the patient has very few allergens or ones that are not ingested daily.

Muscular involvement can also cause colicky abdominal pain and has been recognized as a cause of gastric outlet or intestinal obstruction secondary to inflammation, swelling, or stricture within the muscular layer of the intestine.[59] This can be confused with infantile pyloric stenosis.

Finally, serosal involvement with eosinophils presents with bloating and occasionally ascites.[8,57,60] It is also associated with a higher peripheral blood eosinophilia and responds quite well to treatment with systemic steroids.[8,57,58] Patients' symptoms typically subside within 2 weeks, although the majority feel much improved after just a few days of appropriate therapy.[60]

Eosinophilic gastroenteritis and eosinophilic esophagitis affect all ages with a slight male predominance.[24] These conditions are typically secondary to mixed IgE and non-IgE allergic reactions resulting in increased levels of interleukin-3, interleukin-5, and granulocyte/monocyte-colony stimulating factor—all strongly proinflammatory cytokines. A complete blood count can give clues to the diagnosis of eosinophilic gastroenteritis. In extreme cases, the total white blood cell is elevated, but usually the only clue to the diagnosis is an elevation of the percentage of eosinophils. In all eosinophilic gastrointestinal conditions studied, the eosinophilic percentage of the total white blood cell count is elevated in approximately 50% of cases.

Other markers of intestinal inflammation such as stool tests for white blood cells, stool for alpha-1-antitrypsin (a marker of excessive enteric protein loss), or stool guaiac tests may be helpful. A lactulose/mannitol excretion test for intestinal permeability may be helpful as well but is difficult to perform and rarely used clinically. We are evaluating serum markers of eosinophilic gastroenteritis and particularly markers of the associated intestinal inflammation. In our experience, elevated levels of antigliadin IgG antibodies can be quite helpful as a marker of gut inflammation (unpublished). This is distinguished from celiac disease in that antireticulum, anti-endomysial and tissue transglutamase antibodies are not elevated. As with eosinophilic esophagitis, eosinophilic gastroenteritis is best diagnosed by evaluation of endoscopic biopsies.

The objective data used to identify an excess concentration of eosinophils in the setting of eosinophilic gastroenteritis are not strong. This is still an area that needs more study and biopsies must be interpreted with caution, as few normal standards exist. While there is no generally agreed on pathologic number of eosinophils in the mucosa of the small bowel and colon,[61] eosinophils do not typically occur in groups in the submucosa, muscularis, or serosa. A few studies have attempted to identify norms for mucosal eosinophil concentrations, with varied results. One hallmark study published in 1996[62] based on autopsies of children who died of traumatic, nonallergic causes found essentially no eosinophils in the fundus or antrum of the stomach, leading to the conclusion that the presence of eosinophils in these locations is pathologic. This study also found up to 24 eosinophils per high powered field in the duodenum and up to 30 eosinophils per high powered field in the terminal ileum and cecum. Up to 30 eosinophils per high powered field were also found in the terminal ileum and cecum of children hospitalized for chronic abdominal pain and the authors therefore concluded that eosinophil counts in the lower gastrointestinal tract are unlikely to be useful. This conclusion is questionable, however, since the children included with chronic abdominal pain could have been suffering from undiagnosed food allergy. We use 30 eosinophils per high powered field in the cecum as the upper limit of normal, but just as importantly, we look for the lack of the usual pattern of decreasing eosinophil concentration as one moves distally through the colon as further evidence of eosinophilic gastroenteritis or allergic proctocolitis.

The treatment for eosinophilic gastroenteritis is the same as for eosinophilic esophagitis: avoidance of food allergens and, if needed, an elemental diet to eliminate all dietary proteins. If an elemental diet is not chosen, not accepted by the patient, or is too difficult to sustain, other treatment options must be sought. Montelukast has been used in eosinophilic gastroenteritis with some success. Cromolyn sodium (Gastrocrom®) given orally four times daily has been beneficial in the management of some patients in our experience. The use of Gastrocrom® for eosinophilic gastroenteritis was reported in 2003 by Suzuki.[103] The use of Gastrocrom® will be further discussed below. Occasionally, there is also the need to use steroids (such as oral budesonide) or even systemic steroids to

get symptoms under control. We use the nebulizable form of budesonide as is used for eosinophilic esophagitis. With eosinophilic gastroenteritis, however, we do not add Splenda® as it is not necessary to obtain a slurry consistency and we often encounter patients with corn allergy for which this sweetener would be contraindicated. Budesonide also comes in a time released oral form called Entocort®, but, according to the manufacturer, this delivers medicine only to the terminal ileum and right side of the colon, clearly limiting its effectiveness in small bowel disease. More recently, we have used ketotifen, 1 milligram twice daily, as an adjunct to therapy in particularly difficult cases of eosinophilic gastroenteritis and have found this to be beneficial. Ketotifen is a unique medication, not approved for oral use by the U.S. Food and Drug Administration; however, it is widely used outside the United States. Ketotifen has both antihistamine and anti-inflammatory properties. Finally, in extreme cases, immunomodulators such as 6-mercaptopurine, tacrolimus, or cyclosporine have been used.

Eosinophilic Proctocolitis

Case 3. A 6-week-old infant girl born at 35 weeks gestation had a neonatal course complicated by respiratory distress requiring admission to the NICU for 5 days. She was breast fed and supplemented with cow's milk formula. At 4 weeks of age she developed bloody stools and apparent abdominal discomfort that included crying and arching. She continued to breast feed; however, her formula was switched to a hydrolyzed cow's milk based formulation (Nutramigen®). She remained symptomatic. When she continued to have daily rectal bleeding, a flexible sigmoidoscopy with biopsies was undertaken. This showed moderate eosinophilia with 14 eosinophils per high powered field in greatest density and moderate lymphonodular hyperplasia. She was referred for allergy evaluation. Epicutaneous allergy testing was negative. Atopic patch testing was positive for egg, pork, and peanut. These foods were removed from the mother's diet and within a few days the infant's symptoms resolved completely.

Eosinophilic proctocolitis is a form of eosinophilic gastroenteritis with a unique yet common presentation. This condition is also known as eosinophilic colitis or milk-protein colitis. The condition was originally described in breastfed infants,[63] although we still regularly encounter the community opinion that an infant cannot be "allergic to breast milk." The provider may initially assume that the infant has an internal anal fissure.[64] Since the initial report of allergic proctocolitis, there have been many reports of infants with bleeding associated with both breast milk and a wide variety of proteins found in commercial formulas.[55,65,66] Milk-protein colitis is the most common cause of rectal bleeding in infants generally, presenting between 2 and 4 months of age.[55,64]

Milk-protein colitis is usually secondary to a mixed type I and type IV allergic reaction to cow's milk, soy, corn, or dietary proteins found in maternal breast milk (often from the same protein sources).[22,67,68] Infants typically present with diarrhea, mucousy and bloody stools, and occasionally, fussiness and perceived abdominal pain. It is not unusual for the infant to be completely asymptomatic except for mucousy or bloody stools.[22] The infant is nearly always thriving and significant anemia is not seen.[64] The condition is often diagnosed based on history alone and appropriate dietary changes are instituted. These include removing the allergens from the infant's and breastfeeding mother's diet and occasionally the use of elemental or hydrolysate formulas.

Confirmatory testing may be necessary and typically includes an unsedated or minimally sedated flexible sigmoidoscopy with biopsies[55,63,66,69] or a trial of elemental formula for 3 to 4 days to see if symptoms resolve.[64] On endoscopic evaluation, focal erythema, erosions, and nodularity consistent with lymphonodular hyperplasia may be seen.[70,71] On histologic examination of biopsy specimens, eosinophil concentration is typically in excess of six per high powered field, with degranulated eosinophils, crypt hyperplasia, crypt abscesses, and giant cells seen with variable frequency.[63,69,72] Eosinophils may be clustered in proximity to lymphoid aggregates, which suggests they play a role in antigen or antigen–antibody complex uptake.[64] For unknown reasons, eosinophilia and the changes consistent with milk-protein colitis are limited to the rectum and sigmoid colon.[70] Complete blood counts are not routinely done in cases of suspected eosinophilic proctocolitis since they are moderately traumatic and painful for the infants and add little to sorting through the differential diagnosis. The confirmatory sigmoidoscopy is more helpful in narrowing the differential diagnosis by ruling out anatomic abnormalities such as arteriovenous malformations, rectal ulcers, or polyps.

When the offending protein is removed from the infant's diet, either by an elimination diet in a breast-

feeding mother or by a trial of a hydrolysate or amino-acid-based formula, the symptoms frequently resolve within 96 hours.[63] At the end of this trial period, the parents may wish to continue using hydrolyzed formula (Alimentum®, Nutramigen®, Pregestamil®) or elemental formula (Elecare®, Neocate®) or reinstitute breastfeeding with the mother's diet altered. In anticipation of this possibility, mothers should be counseled to eliminate allergens from their diet during the 3- to 4-day trial period of formula use so that at the end of this time the offending antigens have been eliminated from her breast milk. In our experience, approximately 50% of the time the symptoms will still return when the baby begins nursing again and further elimination from mother's diet, guided by allergy test results on the baby, is necessary. Rechallenging the infant with the offending protein within 6 months typically triggers recurrence of the symptoms within 3 to 4 days but by 1 year of age infants routinely tolerate an unrestricted diet.[64] It is not unusual for a mother to continue to breastfeed despite seeing occasional blood in the infant's stool.[65] We are unaware of any reported long-term consequences of allowing the allergic reaction to continue except for occasional mild anemia.[67,68]

Evaluation

There are few laboratory tests that will suggest the diagnosis of eosinophilic gastrointestinal disorders. The diagnosis of eosinophilic gastroenteritis or eosinophilic esophagitis is dependent on endoscopic biopsy results with attention to the quantity, location, and characteristics of the eosinophilic inflammation.[23] Eosinophilic esophagitis may appear grossly as white papules (actually eosinophilic abscess when viewed under the microscope), linear furrows, or circular rings—often referred to as "tracheization."[25,50,73,74] Increased thickness of the esophageal wall has been noted by barium swallow[75] or endoscopic ultrasound.[76] With eosinophilic gastroenteritis, edema, erythema, and erosions may be seen in the antrum of the stomach or duodenum.[59] Rarely, ulcers[77-79] or pseudopolyps may be found[80] but typically the mucosa appears normal.[81]

When evaluating biopsy specimens, eosinophils are counted in the high powered field of the microscope (×400) with the highest concentration of these cells. In the esophagus 17 eosinophils per high powered field from any location of the esophagus is indicative of eosinophilic esophagitis, although until recently 20 eosinophils per high powered field was the accepted upper limit of normal.[39,41,43,47,82] Normally, the esophagus is void of eosinophils.[83] As mentioned above, any eosinophils in the stomach, greater than 20 per high powered field in the duodenum and greater than 30 in the terminal ileum or cecum, is suggestive of eosinophilic gastroenteritis, although these numbers are uncertain.[62,84] It is also important to look closely for the normal distribution of eosinophils in the colon—decreasing from the cecum to no greater than 5 eosinophils per high powered field in the rectum.[62]

Due to the uncertainty about the normal density of eosinophils in different locations within the gastrointestinal tract, recent work has moved away from using the absolute number of eosinophils for diagnosis. Eosinophilic abscesses and groups of eosinophils in the muscularis or serosa are considered abnormal.[62,84] There is also strong support that the presence of major basic protein (MBP) on biopsies, as a marker of eosinophilic degranulation, is highly suggestive of eosinophilic esophagitis,[27,39] as is the presence and degranulation of mast cells.[74,85] The same work has not yet been performed with eosinophilic gastroenteritis. Even though thickening of the basal layer of the esophageal mucosa has classically been considered an important change associated with gastroesophageal reflux,[86,87] this thickening has now been shown to be even more prominent and suggestive of eosinophilic esophagitis.[50,74,88] Finally, there is some evidence that subepithelial fibrosis is not only prevalent on histologic examination of esophageal biopsies from patients with eosinophilic esophagitis but may be specific for this condition.[74] Chehade and coworkers suggest that this fibrosis may cause a dysmotility and account for the dysphagia and high incidence of food impaction in adolescents with eosinophilic esophagitis.[74]

Only 50% of patients with eosinophilic esophagitis or eosinophilic gastroenteritis are found to have peripheral eosinophilia, so a CBC may not be helpful due to the patchy nature of the eosinophilic infiltrates, the diagnostic findings can be missed even on biopsy specimens in up to 15% of cases.[57] Checking the stool for leukocytes is helpful, but fecal smears for eosinophils specifically are routinely negative and therefore of limited value.[65] This illustrates the importance of maintaining a high index of suspicion for food allergies and assessing the patient's test results in light of the history and physical examination. The differential diagnosis for eosinophilic gastroenteritis is broad and includes parasitic infections, inflammatory bowel disease, connective tissue diseases, malignancy, and the effects of drugs.[20] In the setting of suspected infantile

milk-protein colitis, radiographs of the abdomen may also be needed to rule out necrotizing enterocolitis and obstructive colitis associated with Hirschprung disease.[64] Combinations of epicutaneous skin testing, atopy patch testing, and in vitro assays (RAST® and ImmunoCap®) have been used to identify the specific food allergens involved.

Food-specific IgE antibodies are tested for by either skin prick testing or serum assays. The use of serum assays are complicated by a number of factors, including different manufacturers, different specific substrates, and variation in measures of reporting results.[89] The traditional serum IgE assay is known as the radioallergergosorbant test (RAST®). Currently the ImmunoCap® assay or CAP-RAST® is utilized more widely. The RAST® tests and even ELISA-based assays remain available but are less sensitive and less specific than the ImmunoCap® assays. Both of these tests have excellent negative-predictive values, up to 95%, and are therefore useful for ruling out IgE-mediated reactions. They have somewhat lower positive-predictive values (approximately 50%) and are not generally recommended for screening purposes.[22] False-negative tests are also more common in CAP-RAST® than in skin testing.

We suggest initially performing skin prick testing and following up with CAP-RAST® if necessary. Current recommendations include a combination of skin prick testing and CAP-RAST® tests for IgE-mediated reactions.[2,4,5,28] Skin prick testing for mixed disorders, such as eosinophilic esophagitis, is thought to be superior to in vitro testing. Most published studies on skin prick testing in eosinophilic gastrointestinal disorders are focused on eosinophilic esophagitis or the mucosal form of eosinophilic gastroenteritis. The usefulness of these tests in other forms of eosinophilic gastrointestinal disorders has not been carefully evaluated.

While most allergy centers studying eosinophilic gastrointestinal disorders use epicutaneous skin testing, disagreement exists regarding the utility of atopy patch testing. The essential question with any set of allergy tests is, "How accurate is allergy testing in guiding diet elimination once the diagnosis has been confirmed with endoscopic biopsies?" Spergel and coworkers published one of the first studies that attempted to answer this question utilizing both prick and patch testing in 2002.[28] He prospectively studied 26 patients with biopsy-confirmed eosinophilic esophagitis. Patients underwent both skin prick testing and patch testing to a standard panel. Positive skin prick tests were found in 19 patients and positive patch tests were found in 21 patients. Four patients had pure IgE reactions with only positive prick tests; 5 had pure non-IgE with only positive patch tests, and 15 patients had mixed reactions with both positive prick and patch tests. Elimination diets based on this testing resulted in a reduction in eosinophil count from a mean of 55.8 eosinophils per high powered field to 8.4 eosinophils per high powered field. Eighteen patients had resolution of symptoms; 6 had partial improvement, and 2 were lost to follow-up. Milk and egg were the most commonly identified food triggers. An expanded follow-up study that also included the original cohort was published in 2005.[2] By this time, the investigators had evaluated 146 patients with eosinophilic esophagitis with skin prick and atopy patch testing. Clinical results after elimination diets based on prick and patch testing divided the patients into three groups: responders, nonresponders, and those with partial response. One hundred twelve patients (77%) demonstrated resolution on their eosinophilic esophagitis (follow-up biopsy revealed <5 eosinophils per high powered field) on dietary restriction therapy only. Thirty-nine of these patients were rechallenged with the foods for which they had tested positive and had recurrence of their eosinophilia. Fifteen patients (10%) were considered nonresponders, with no change in their eosinophil levels after an appropriate elimination diet. The remaining 19 patients had partial response with reduction in eosinophil count from a mean of 68.8 to 12 per high powered field. In this study, egg, milk, and soy were identified most frequently with skin prick testing, and with corn, soy, and wheat being identified most frequently with atopy patch testing. This study concluded that in more than 75% of patients with eosinophilic esophagitis, both symptoms and esophageal inflammation can be significantly improved with dietary elimination of foods and that skin prick and atopy patch testing together can help identify the offending foods in most patients. In fact, either test alone had a poor sensitivity for identifying offending allergens.

A basic understanding of what skin prick and patch testing are and how they are performed is important. There are multiple devices available for skin prick testing. Food skin prick testing is an epicutaneous test, not an intradermal one. Intradermal testing is not recommended due to an increase in nonspecific results and an increase in the risk of systemic reactions. A negative control (glycerinated diluent) is used to rule out irritant or dermatographic responses. A positive

TABLE 4. Foods included in standard Atopy Patch Test

Cow's milk
Chicken egg
Beef
Chicken
Turkey
Pork
Green bean
Pea
Soy
Wheat
Rye
Barley
Oat
Corn
Potato
Rice
Garlic
Peanut
Sesame

TABLE 5. Modified Spergel Grading Scale for Atopy Patch Test reactions

Score	Reaction
Trace	Slightly raised erythematous macule
1+	Erythema, at least seven papules, slight induration
2+	Erythema, vesicles, numerous papules
3+	Ulcerative lesion

control (histamine) is used to rule out the presence of antihistamines in the body and to ensure appropriate technique. Erythema and wheal size are measured 15 to 20 minutes after application of a suspected allergen. A wheal diameter that is at least 3 mm larger than the negative control is considered positive.

The patch test is performed on skin uninvolved with rashes or marking. Usually it is applied on the back. The foods are used in their native state, either from dry powdered formulations or single-ingredient baby foods. One gram of the dried food is mixed with 1 milliliter of saline to make a paste. The foods are placed in 12-mm aluminum cups, called Finn chambers, and are applied to the skin. The array of chambers is then secured to the skin with Scanpor® tape (hypoallergenic) to decrease the risk of contact dermatitis from the adhesive. We use a standard panel of 19 foods (Table 4) plus others elicited by history and a negative saline control. For milk, a concentration of 3 grams per milliliter of saline is used since a concentration of 1 gram per milliliter was found to have a low sensitivity.[31] The chambers are left in place for 48 hours and are then removed. An initial reading is done at this time and then again at 72 hours post application. The area that each chamber covered is inspected and graded according to a modified Spergel scale, created by Dr. Jonathan Spergel at Children's Hospital of Philadelphia.[2,28] This scale includes 1+ to 3+ reactions (Table 5). We have modified it to include "trace" reactions. We feel inclusion of these reactions increases the sensitivity of the testing but clearly lowers the specificity and, in fact, these reactions are difficult to correlate with clinical symptoms, although may lower the specificity. A recent consensus report on eosinophilic esophagitis concluded that the combination of skin prick tests and atopy patch test has been successful at one center and is being examined at other centers.[89]

The understanding of eosinophilic disorders is rapidly expanding. Further research needs to be done to help in the accurate diagnosis and treatment of eosinophilic gastrointestinal disorders. Unique approaches have included colonoscopic antigen provocation, in which a wheal and flare reaction correlating to mast cell and eosinophil activation is evaluated after injection of an antigen into the colonic mucosa.[90] This is comparable to a skin prick test in the colon. There have also been attempts to look for inflammatory mediators in intestinal lavage fluid[91] or stool samples.[92] Finally, there is interest in looking at antigliadin antibodies as markers of intestinal inflammation resulting from eosinophilic esophagitis or eosinophilic gastroenteritis.

Treatment

In general, treatment for eosinophilic gastrointestinal disorders can be divided into elimination diets, systemic steroids, inhaled steroids, leukotriene receptor antagonists, and other anti-inflammatory agents.[8,20,56,59,60,82] Most research has been done in eosinophilic esophagitis and may not apply to the other eosinophilic gastrointestinal disorders. Treatments unique to the specific subtypes are discussed above. To summarize, elimination diets directed by skin prick tests and atopy patch tests have been shown to lead to improvement and resolution of symptoms as well as decreases in tissue eosinophilia.[5] The removal of appropriate dietary antigens significantly improved patient symptoms and esophageal eosinophilia in 98% of patients reported in one large study[5] and 90% in another.[2] Elemental diets have also been used in studies where prick or patch testing was not utilized or found not useful.[1]

Several studies have looked at the usefulness of systemic steroids. In one study oral steroids were given to 20 children with eosinophilic esophagitis.[50] Patients with eosinophilic gastroenteritis or gastro-

esophageal reflux disease were excluded. Thirteen patients became asymptomatic and 6 showed marked improvement after 4 weeks. When they underwent a second biopsy, the number of eosinophils per high powered field decreased from an average of 34.2 to 1.5. One year later, half the patients were still asymptomatic and two patients required additional systemic steroids. Another large series[5] showed a good response to corticosteroids in patients with biopsy-confirmed eosinophilic esophagitis, but relapse was likely following their withdrawal of the steroid. Systemic steroids should be reserved for refractory cases given the poor long-term outcome and the side effects of this class of medication.

Topical application of steroids in the esophagus has also been widely used. Protocols have utilized either inhaled formulations or steroid suspensions. With the inhalers, the patient activates the metered-dose inhaler without a spacer and then swallow the medication after oral deposition. Studies have used both fluticasone and beclomethasone.[41,49,52,53] In a representative study, Konikoff and coworkers showed the efficacy of swallowed fluticasone in reducing symptoms and eosinophilic inflammation in a recent double-blind placebo-controlled trial.[93] A budesonide suspension has also been used and may be helpful in patients unable to coordinate the puff and swallow sequence.[53] Importantly, no abnormalities in patients' morning cortisol levels were found in one study using topical budesonide administered twice daily for 3 months. Topical steroids may prove most beneficial when used in conjunction with dietary management.

Other less studied treatments include leukotriene receptor antagonists, oral disodium cromoglycate, and ketotifen. Leukotriene receptor antagonists such as montelukast have been reported in a few, small studies. Several case series reported improvement in eosinophilic gastroenteritis in children[94-96] and adults[97,98] following treatment with montelukast. Friesen and coworkers studied 40 children and adolescents with dyspepsia and duodenal eosinophilia who did not respond to acid suppression and treated them with montelukast.[99] Using post treatment pain assessment, an improvement in clinical response was seen in 62% treated with the drug versus 32% receiving placebo. Additionally, improvement in swallowing function was reported in six of eight adult patients reported by Atwood and coworkers in 2003.[100] There are also several reports of patients in whom montelukast did not improve symptoms.[99,101,102]

A single case report was published in 2003 wherein a patient with eosinophilic gastroenteritis was treated with oral disodium comoglycate and ketotifen.[103] Disodium comoglycate is a mast cell stabilizer that has been used in allergic rhinitis, allergic conjunctivitis, and asthma. Ketotifen is a benzocycloheptathiophene derivative that is an antihistamine and a mast cell stabilizer. It is widely used in other countries as an oral agent for the management of bronchial asthma and other allergic disorders; however, ketotifen is only available in the United States as an ophthalmic preparation.

Even more novel therapies are being studied in light of recent advances in monoclonal antibody development. A recently published study evaluated the efficacy of anti-IgE therapy in eosinophilic gastrointestinal disorders.[104] Nine subjects with eosinophilic gastrointestinal disorders received omalizumab, an anti-IgE monoclonal antibody, every 2 weeks for 16 weeks, while other therapies were held constant. Several outcome measurements, including absolute eosinophil count, free IgE levels, and basophil and dendritic cell IgE receptor levels decreased. Tissue eosinophil counts in the duodenum and gastric antrum also decreased, but the difference between cases and controls was not statistically significant. Esophageal eosinophilia appeared unaffected by this treatment and, in fact, counts were unchanged from pretreatment.

Many other recent treatment developments are still under study. These generally target the eosinophilic inflammatory pathway. Anti-IL-5 or IL-5 gene deletion blocks induction of experimentally induced eosinophilic esophagitis in mice.[90] Garrett and coworkers published a case study showing the effectiveness of anti-IL-5 in an adolescent male with hypereosinophilic syndrome and esophageal eosinophilia.[105] Another study demonstrated decreases in tissue eosinophilia and improved clinical outcomes as well, this time in four adult patients with eosinophilic esophagitis treated with an anti-IL5 antibody preparation.[106] Larger clinical studies are underway to verify the clinical usefulness and safety of this drug. Other possibilities for drug development include agents that target eotaxin-3 and IL-13, but detailed discussions of these agents are beyond the scope of this review.

In addition to drug development, some attention has been given to the development of treatment protocols to facilitate logical, clear approaches to the eosinophilic intestinal disorders. Ngo and Furuta published a treatment protocol for eosinophilic esophagitis in 2005.[107] This protocol suggests that adult and pediatric patients experiencing upper intestinal symptoms,

including food impaction, vomiting, abdominal pain, or dysphagia, that is not clearly from another source should undergo biopsy with histopathologic analysis of the distal and proximal esophageal mucosa. If the diagnosis of eosinophilic esophagitis is made, patients should seek the consultation of the allergist in an effort to identify possible food sensitivities. If the allergic evaluation identifies a specific food, this food should be strictly avoided as a first-line treatment, as there are well-documented treatment failures if medicinal therapy is not accompanied by removal of the offending antigen.[51] If a food allergy is not identified, an elemental formula should be used to induce a remission. If an elemental diet cannot be used, topical steroids are effective in inducing a remission. Given the lack of prognostic data, the use of systemic corticosteroids should be reserved for severe cases when dietary elimination or topical steroids are ineffective. To date, diet restriction has been identified as the only effective and reasonable maintenance treatment, but montelukast and topical cromolyn may also offer benefit.[108]

Patients with eosinophilic gastrointestinal disease who have other allergic diseases might benefit from control of allergen exposure and from therapeutic intervention directed against their allergies.[109] An expert panel has concluded that reducing exposure to inhaled indoor allergens can improve asthma control and therefore recommended evaluating the role of aeroallergens in patients with persistent asthma.[110] The use of environmental controls has been extensively reviewed in other references and is beyond the scope of this article. However, it is interesting to speculate that allergy testing may likewise predict the response to pharmacotherapy or dietary avoidance in patients with eosinophilic gastrointestinal diseases. This idea is in need of further evaluation.[45]

Prevention

There have been a few novel approaches to the prevention of eosinophilic gastrointestinal disorders in young children and infants, particularly those at high risk secondary to family history of atopy or eosinophilic esophagitis/eosinophilic gastroenteritis. A Cochrane review of studies comparing human breast milk, cow's milk formula, and hydrolysate formula given to high-risk infants for the prevention of food allergies showed no benefit of formula over human breast milk, but some improvement in the incidence of food allergies up to 5 years of age when hydrolysate formulas were given in place of standard cow's milk formulas.[111] Elimination of specific foods will not prevent the development of food allergy. Data suggests that eczema improved with the early introduction of probiotics to infants, but this did not prevent food allergies.[112] A few studies suggest that an increase in omega-3-fatty acid (fish oil) reduced atopic disease.[113] Additional research on dietary medication and supplements is needed.

Prognosis

Eosinophilic gastrointestinal disorders are becoming more commonly recognized and the pathophysiologic changes are beginning to be better understood. Still, very little is known about the long-term consequences of this disease. We are unaware of any studies specifically addressing the prognosis of any of the eosinophilic gastrointestinal disorders. With identification of offending allergens, elimination of these allergens from the diet, and subsequent healing of the intestinal mucosa, children with this condition do tend to improve. Essential to the prognosis is minimizing intestinal permeability and allowing enough time for the patients to "outgrow" their allergies. Only when the patient has developed tolerance to all of the allergens does the condition resolve. We eagerly await studies on the long-term consequences of untreated eosinophilic inflammation in the gut as well. We have reported here incidences of stricture formation and perforation of the gastrointestinal tract thought to be secondary to eosinophilic infiltration, but no case series have studied this in detail. Current discussion in the scientific community also includes the possibility of untreated eosinophilia in the intestinal tract leading to the development of malignancy.

Summary

The diagnosis of eosinophilic gastrointestinal disorders is made through a thorough history, including a family or personal history of atopy and a detailed dietary history. When confirmation or further evaluation is needed, endoscopic biopsies should be evaluated. Total IgE and peripheral eosinophil counts may be useful. Diagnostic criteria have been proposed, but no consistent laboratory test or radiographic finding has been found to be pathognomonic for this condition. Diagnosis requires gastrointestinal symptoms and biopsy-confirmed eosinophilic infiltration of the gas-

trointestinal tract. Treatment is primarily based on dietary elimination of offending food allergens as guided by a combination of skin prick and patch testing. Elimination diets are rarely helpful without the results of allergy testing as a guide. In our experience, dietary elimination has been effective in eliminating symptoms approximately 80-85% of the time and, when not effective, medications were helpful and generally well tolerated. Treatment may also involve a strict elemental diet, but it is often difficult to achieve patient compliance. After elimination of offending allergens, symptomatic relief occurs within 3 weeks, although many patients appreciate benefit within 3 to 4 days. Histological improvement is seen in 4 weeks. After 1 year, offending foods are retested. If repeat tests are negative, the food can be reintroduced to the diet by controlled challenge. Only one food should be reintroduced at a time with a 2- to 3-week interval in between new foods so that a developing reaction will be recognized in time to avoid confusion as to its cause. It is useful to include consultation with a nutritionist in the treatment plan.

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