

Eosinophilic Gastrointestinal Diseases (EGIDs)

EGIDs Working Group: ¶Glenn T. Furuta, ††David Forbes, ‡‡Chris Boey, †C. Dupont,
§§Phil Putnam, ¶¶S.K. Roy, *Aderbal Sabrá, ‖Anadina Salvatierra, §Yuichiro Yamashiro, and
**S. Husby

*†Department of Paediatrics and Nutrition, Hospital Saint Vincent de Paul, Paris, France, ‡International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, §Probiotics Research Laboratory, Juntendo University School of Medicine, Tokyo, Japan, ¶University of Colorado School of Medicine, Denver, **Department of Paediatrics, Odense University Hospital, Odense, Denmark, ††School of Paediatrics and Child Health, University of Western Australia, Perth, ‡‡Pediatric Gastroenterology and Hepatology, Department of Pediatrics, University of Malaya Medical Centre, Kuala Lumpur, Malaysia, and §§Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH

Eosinophilic gastrointestinal diseases (EGIDs) are a heterogeneous group of diseases (eosinophilic esophagitis [EoE], eosinophilic gastroenteritis, and eosinophilic colitis) characterized by gastrointestinal symptoms and increased eosinophils in the intestinal mucosa; more important, other causes of gastrointestinal eosinophilia must have been ruled out for the diagnosis of EGIDs to be confirmed. Original descriptions of EGIDs divided patients into subtypes with respect to the anatomical location affected by eosinophilia; ie, mucosal (diarrhea and bleeding), muscular (obstruction), and serosal (ascites) disease. Recent descriptions characterize the mucosal forms in more detail; patients affected by mucosal EGIDs present with a diverse set of symptoms that reflect the organ-specific section of the intestinal tract that is affected. EoE may present with feeding intolerance, vomiting, food impaction, and dysphagia. Patients with eosinophilic gastroenteritis develop vague symptoms including abdominal pain, diarrhea, and bleeding. Eosinophilic colitis typically presents with diarrhea and lower abdominal pain. In the most clearcut circumstances, this categorization will provide specificity for the tissue involved, but in clinical practice a wide variety of symptoms have been attributable to EGIDs. Thus, an open mind should be maintained when these diseases are suspected.

A number of reasons have led to a lack of clarity defining the histopathology associated with EGIDs. The

rarity of the diseases limits well-designed studies and precludes consensus on histological features; in fact, only recently have studies explored the normal numbers of eosinophils in the different part of the gastrointestinal tract (1,2). A gradient exists with respect to the normal number of eosinophils per high power field (eos/HPF) in the gastrointestinal (GI) tract starting with the esophagus, where there are none, and advancing to the terminal ileum, where more than 30 eos/HPF have been documented. In most studies, specimens examined have been derived from mucosal pinch biopsies that are limited to 2 to 3 mm in depth, sections that typically only allow examination of only the superficial mucosa; deeper eosinophilic infiltration likely occurs in certain circumstances but is unaccounted for presently. Geographic variation likely exists with respect to the number of eosinophils in the GI tract of healthy individuals, a feature suggesting a role in host health and constitutive immune defense. Finally, most analyses examining histological features use only hematoxylin and eosin staining with little attention to other immunohistochemical methods of assessment. Thus, the histological assessment of the tissue is limited to a statement indicating increased numbers of eosinophils in the lamina propria and or intraepithelial layer; the interpretation of this finding is restricted to a small amount of data interpreting normal values and individual pathologist experience within defined geographic locations.

ISSUES OF CONTROVERSY

With these initial descriptions in mind, a number of specific areas of controversy exist that continue to perplex practitioners and scientists alike.

Address correspondence and reprint requests to Glenn T. Furuta, MD, Section of Pediatric Gastroenterology, Hepatology, and Nutrition, The Children's Hospital Denver, University of Colorado Denver, School of Medicine, 13123 E 16th Ave, B290, Aurora, CO 80045 (e-mail: furuta.glenn@tchden.org).

The authors report no conflicts of interest.

What Are the Best Diagnostic Criteria for These Diseases?

Because the normal values across the world have yet to be defined, the establishment of diagnostic criteria for EGIDs continues to pose challenges. Several studies in North America have identified ranges of normal numbers of mucosal eosinophils, but broader definitions that encompass more diverse settings are lacking. In addition, reports focus primarily on the enumeration of eosinophils and little data exist characterizing distribution within the mucosa. For instance, is it normal for eosinophils to reside directly adjacent to epithelial cells? If the paradigm for histological assessment of polymorphonuclear cells in the classical inflammatory bowel disease is adopted, the answer is no, but this issue has not been fully addressed in the healthy intestinal mucosa. Because eosinophils are normal residents of the intestinal mucosa, whereas polymorphonuclear cells are not, significant differences likely exist. In addition, a full consideration of all diagnostic possibilities for pathological intestinal eosinophilia always must be considered. Currently, the finding of mucosal eosinophilia is met with the frequent assumption that it is secondary to food allergy or parasitic infection, but a number of other diseases have been associated with this finding.

What Is the Epidemiology of the EGIDs and Why Are They Seemingly Increasing, at Least in Certain Geographic Locations?

Because diagnostic criteria are lacking, answers remain elusive. The absolute number of eos/HPF may indeed vary in different geographic environments, making absolute threshold numbers for the diagnostic evaluation difficult to establish.

Because EGIDs are rare, scant population-based data are available on incidence, prevalence, and racial diversity of EGIDs, and most knowledge has been accumulated from isolated reports occurring in children and adults (3). The best-documented and most-studied EGID is EoE. The rapid rise in prevalence of EoE has been documented in several populations and is consistent with changing environmental exposure in vulnerable individuals. EoE has been reported in North America, South America, Europe, Asia, the Pacific, and the Middle East (4,5), and EoE was reported with a prevalence of 0.05 rising to 0.89/10,000 children in Australia between the years 1995 and 2004 (6). Most investigations so far have not been population based. Rather, they have originated in academic centers and urban settings, reflecting a potential bias and making it unknown whether less populated or rural environments are represented; a recent report suggests that EoE occurs in a broader context. In a population-based study of adults in Sweden, it was

estimated that esophageal eosinophilia is present in about 1% of the population (7). Whether the emergence of EoE represents increased recognition or increasing incidence is still uncertain, although the data from Western Australia suggests that this is a new disease, accompanied by more severe inflammation in the mucosa.

With respect to other EGIDs, the data are less clear. Katz et al (8) reported 12 children with peripheral eosinophilia, iron deficiency anemia because of blood loss in the stools, protein-losing enteropathy, and eosinophilic infiltration of the stomach and small intestine, what today would be called eosinophilic gastroenteritis. These patients were divided into 2 groups. In the first group, the disease presented under the age of 1 year and responded to the exclusion of milk from the diet. The second group consisted of patients whose disease started later in childhood and who did not respond to dietary changes. They had atopy and immunoglobulin (Ig)E-mediated immediate hypersensitivity reactions to food. This report and others suggest that specific phenotypes may exist within patient populations with EGIDs.

Few natural history data are published examining the long-term outcome of EGIDs in children or adults. Clinical observation suggests that the condition may resolve permanently with time, or more likely is characterized by recurrent relapses. For instance, allergic eosinophilic proctocolitis and/or food-induced proctocolitis are significant causes of lower gastrointestinal bleeding in infants. It is thought that milk proteins are the etiologic agent inducing these findings but little has been done to determine the natural history or potential complications of these conditions. In fact, some patients may have a relatively benign disorder called neonatal transient eosinophilic colitis (9).

The rising prevalence reported of eosinophilic esophagitis mirrors the rise in allergic disease that has been occurring for the past 4 decades, probably reflecting an increasing vulnerability to antigen sensitization (3). The increases in allergic disorders parallel a declining incidence of infectious diseases. This gradient from infectious to allergic disease correlates with gradients from low to high socioeconomic status, large to small family size, and increasing body weight, and also with early day care attendance, exposure to animals, and the patterns of gut microflora. Helminth exposure appears to be an important mirror, and possibly a determinant of these changes. It has been proposed that the orientation of the immune system can be changed by the nature of environment, and that an overly hygienic environment predisposes to allergic type immune responses (10). The influence of TH₂ cells, important in the development of IgE responses and eosinophilia, normally wanes over the first 2 years of life in nonallergic individuals, possibly secondary to TH₁ stimulation that occurs in association with bacterial infection. It has been more particularly demonstrated that parasite-driven immune responses are associated with a lower risk

of development of skin test reactivity to aeroallergens (11). Furthermore, interleukin (IL)-10, which has a counter-regulatory role across the immune system, is less likely to be produced under conditions of a hygienic lifestyle, and it is the absence of this signal that leads to persistence of TH₂ skewing of immune responses and predisposition to allergic-type responses (10). It has been suggested that the orientation of the immune system to TH₂- or TH₁-dominated responses may be determined antenatally with both antigen exposure and heredity speculated to have an effect on this outcome (12).

How Do Eosinophils Traffic to the Intestine and What Is Their Role in GI Dysfunction?

Eosinophils are white blood cells that probably participate in the control of infection by parasites and in the mechanisms associated with asthma, food allergy, and other types of inflammatory diseases. These granulocytes are produced and matured in the bone marrow and differentiate under the influence of the cytokines IL-3, IL-5, and granulocyte macrophage colony-stimulating factor. After maturation, they gain access to the peripheral circulation and migrate to mucosal surfaces or to sites of helminth infections.

The TH₂-related cytokine IL-5 is the single most important factor for the release of eosinophils from the bone marrow into the bloodstream. IL-5 is a crucial factor for esophageal eosinophilic accumulation in an experimental model of food allergy. Several cytokines and chemokines are able to regulate eosinophilic accumulation in the gastrointestinal mucosa; however, in murine studies IL-5 and the chemokine eotaxin-1 display a high degree of eosinophilic selectivity. In humans, eotaxin-3 has convincingly been demonstrated to be the main chemoattractant in selected children with EoE (13).

During inflammatory conditions, marked increases of eosinophils occur not only in the lamina propria but also in Peyer patches, the outer cortex, and interfollicular regions (14). It is commonly believed that this infiltration may be induced by food allergens that cross the intestinal mucosa and trigger an inflammatory response leading to mast cell degranulation and eosinophilia. The pathophysiology is unclear, but the possibility relates to a mixed IgE and non-IgE mediated food allergy, with TH₁ and TH₂ cytokines involved.

Abundant evidence suggests that EoE is associated with food allergy. A family or personal history of atopy is associated with up to 50% to 90% of cases, and dietary antigens are the most frequently identified trigger in the pathogenesis of EoE (15). Identification of positive skin prick or patch test reactions to specific food allergens and their subsequent dietary elimination results in improvement in esophageal mucosal biopsies in up to 77% of patients (16,17). Murine studies show that sensitization via inhaled antigens and via damaged skin can lead to

esophageal eosinophilia (18). An overlap with gastroesophageal reflux disease and EoE has been suggested, and they may represent a continuum. As a causative explanation, it has been suggested that damage to the stratified squamous mucosa of the esophagus allows enhanced access of antigens to the immune system, eliciting an allergic reaction (19–21).

In the GI tract, eosinophils may have many effector roles as determined by their cationic granule proteins, reactive oxygen species such as superoxide, lipid mediators (eicosanoids), growth factors (transforming growth factor- β), and cytokines (14). In addition, eosinophils may be involved in other processes by virtue of their proposed antiviral activity, antihelminth colonization, and more recently by their antigen presentation activity to T cells. Basic studies examining intestinal function and speculation from studies focusing on other organ systems suggest a pathological role in barrier dysfunction, neuronal activation, smooth muscle contraction, and cytokine secretion (4). On the effector side, intestinal mucosal damage induced by eosinophils is mediated by at least 4 different granular proteins: major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin. Besides various cytotoxic effects, major basic protein and eosinophil peroxidase both exert a direct effect on smooth muscle tone. A functional interaction between eosinophils and nerve fibres was seen in a mouse model of gastrointestinal eosinophilia. After sensitisation to ovalbumin, a TH₂-associated eosinophilic inflammation involving the esophagus, stomach, and the small intestine was observed by Hogan et al (22). In morphological studies, damaged enteric nerve endings in close approximation with eosinophils were observed by electron microscopy. A loss of intracellular organisation of the nerve fibres indicated axonal necrosis and thereby disruption of GI motility induced by the eosinophils. However, it is unknown if these observations also may be seen in human tissues.

The pathogenesis of stricture formation that occurs in EE recently has received attention (23). It has been shown that biopsies from a small group of patients with EoE have increased expression of the fibrogenic factor transforming growth factor₁, its downstream effector molecule phospho-SMAD2/3, and the vascular cell adhesion molecule VCAM-1 in comparison with patients with reflux esophagitis and normal controls. Increased fibrosis is present even early in the disease and in the absence of overt features of stricturing. Eosinophils are pivotal to the similar process that is known to occur in airways.

What Are Effective Treatment Strategies for These Diseases?

Nutritional exclusion and corticosteroids have formed the mainstay of treatments (15). Only one multicenter,

randomized, placebo-controlled study has been performed determining the impact of topical corticosteroids and demonstrating that significant issues with compliance and side effects exist for both treatment modalities (24). Resources to support nutritional management may not be available in all parts of the world. In addition, less well-documented treatments such as mast cell stabilizer and leukotriene antagonist have been reported in small, uncontrolled trials. Experimental treatment with anti-IL-5 seems in general to be the most promising and is a putative treatment for severe or therapy-resistant EGID.

CONSENSUS STATEMENTS

Diagnostic Criteria for EGIDs

EoE is the only EGID with reasonably well-defined diagnostic criteria. A goal of the recent First International Gastrointestinal Eosinophil Research Symposium was to determine criteria based on the current literature (4). Upon review of the literature to September 2006, the following diagnostic guidelines for EoE were established (15):

1. Symptoms associated with esophageal dysfunction
2. Epithelial eosinophilia greater than 15 eos/HPF
3. Exclusion of other causes for eosinophilia, especially gastroesophageal reflux disease (lack of clinicopathological response to treatment with high-dose proton pump inhibitor or normal pH monitoring of the distal esophagus)

The diagnosis of the remaining EGIDs is based on organ-specific symptoms, associated laboratory findings, and histopathology of the intestinal tissues demonstrating increased eosinophils. The determination of what defines increased eosinophils has not been standardized and is dependent on pathologist experience, geographic variations, and patterns of infiltration.

Epidemiology

EoE has emerged as the most common EGID and has a widespread geographic and age distribution. The epidemiology of other EGIDs is unknown and data are limited to case reports and small series.

Pathophysiology

Basic and limited clinical studies suggest an immune mechanism for eosinophilic esophageal inflammation with a potential role for food allergens and a critical role for the cytokines IL-5 and IL-13. An allergic etiology is present in many but not all patients affected by EoE.

Treatment Strategies

Nutritional management with either dietary elimination or an elemental diet is effective treatment in selected patients with EoE and some patients with EGIDs. Compliance, cost, availability, and appropriate testing to determine specific allergens can pose significant problems with this treatment approach. Corticosteroids (systemic and topical in EoE) also are effective in inducing clinicopathological remission.

Initial treatment of EoE remains a highly individualized process. Dietary antigen elimination is appropriate for those individuals with EoE who have evidence for atopy including history of food allergy, asthma, eczema, and chronic rhinitis. The options include directed dietary antigen elimination based on the results of allergy skin testing, the so-called 6-food elimination diet, or total antigen elimination with replacement of the diet with an elemental formula. After clinicopathological remission is established, planned reintroduction of selected dietary antigens is appropriate to restore the diet to one that permits the child to eat the foods to which there is not an adverse response. For nonatopic individuals and for individuals who fail dietary antigen elimination, swallowed fluticasone or budesonide offered twice per day can be used. Maintenance therapy is necessary in most children, as the recurrence rate upon withdrawal of topical steroids or resumed ingestion of offending food antigens is extremely high in clinical practice.

RESEARCH AGENDA

Below are EGID research topics that are focused on the previously discussed controversial issues. Current needs include the following.

Diagnostic Criteria

1. Evaluation of histological gastrointestinal specimens from well-defined geographic locations focusing on the number and distribution of eosinophils in a range of geographic sites, plus the patterns of eosinophilic inflammation and associated immunological features
2. Correlation of histological and immunological analyses with clinical phenotype of patients

Epidemiology and Clinical Features of EGIDs

1. Development of international registry of well-characterized patients as determined by above diagnostic criteria

2. Multidisciplinary (allergy/immunology, gastroenterology, pathology, epidemiology) assessment of environmental factors associated or not associated with EGIDs
3. Long-term outcomes for children with EGIDs

Pathophysiological Role of Eosinophils in GI Disease

1. Translational studies linking immunohistochemical analysis with clinical phenotype
2. Methodological development of noninvasive measurements of eosinophilic inflammation
3. Basic studies developing novel murine models and in vitro systems to define pathophysiological role of eosinophils in GI dysfunction
4. Determination of how eosinophils target the intestine and colon during pregnancy
5. Identification of various pathogenetic mechanisms leading to eosinophilic inflammation

Treatment of EGIDs

1. Multicenter, blinded, placebo-controlled studies examining effectiveness of nutritional treatment and/or corticosteroids and eventually biological reagents such as anti-IL-5
2. Multicenter studies determining the impact of disease and treatment on quality of life
3. Development of effective, nontoxic, and easily administered novel treatments
4. Identification of maintenance medications

REFERENCES

1. Lowichik A, Weinberg A. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol* 1996;9:110–4.
2. DeBrosse CW, Case JW, Putnam PE, et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol* 2006;9:210–8.
3. Nielsen RG, Husby S. Eosinophilic oesophagitis: epidemiology, clinical aspects, and association to allergy. *J Pediatr Gastroenterol Nutr* 2007;45:281–9.
4. Liacouras C, Bonis PA, Putnam PE, et al. Summary of First International Gastrointestinal Eosinophil Research Symposium. *J Pediatr Gastroenterol Nutr* 2007;45:370–91.
5. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940–1.
6. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 2006;91:1000–4.
7. Ronkainen J, Talley NJ, Aro P, et al. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 2006;56:615–20.
8. Katz AJ, Twarog FJ, Zeiger RS, et al. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984;74:72–8.
9. Ohtsuka Y, Shimizu T, Shoji H, et al. Neonatal transient eosinophilic colitis causes rectal bleeding in early infancy. *J Pediatr Gastroenterol Nutr* 2007;44:501–5.
10. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001;1:69–75.
11. Lynch NR, Hagel I, Perez M, et al. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. *J Allergy Clin Immunol* 1993;92:404–11.
12. Prescott SL. Early origins of allergic disease: a review of processes and influences during early immune development. *Curr Opin Allergy Clin Immunol* 2003;3:125–32.
13. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116:536–47.
14. Hogan SP, Rothenberg ME. Eosinophil function in eosinophil-associated gastrointestinal disorders. *Curr Allergy Asthma Rep* 2006;6:65–71.
15. Furuta GT, Liacouras C, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342–63.
16. Spergel JM, Brown-Whitehorn T. The use of patch testing in the diagnosis of food allergy. *Curr Allergy Asthma Rep* 2005;5:86–90.
17. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;109:363–8.
18. Mishra A, Hogan SP, Brandt EB, et al. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83–90.
19. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol* 2007;102:1301–1306.
20. Ngo P, Furuta GT, Antonioli DA, et al. Eosinophils in the esophagus—peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006;101:1666–70.
21. Genta RM, Jon Spechler S, Souza RF. The twentieth eosinophil. *Adv Anat Pathol* 2007;14:340–3.
22. Hogan S, Mishra A, Brandt E, et al. A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nat Immunol* 2001;2:353–60.
23. Aceves SS, Newbury RO, Dohil R, et al. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:206–12.
24. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381–91.