

Molecular mechanisms in allergy and clinical immunology

Series editors: William T. Shearer, MD, PhD, Lanny J. Rosenwasser, MD, and Bruce S. Bochner, MD

Eosinophilic gastrointestinal disorders (EGID)

Marc E. Rothenberg, MD, PhD *Cincinnati, Ohio*

This activity is available for CME credit. See page 41A for important information.

Primary eosinophilic gastrointestinal disorders are defined as disorders that selectively affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia (eg, drug reactions, parasitic infections, and malignancy). These disorders include eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis and are occurring with increasing frequency. Significant progress has been made in elucidating that eosinophils are integral members of the gastrointestinal mucosal immune system and that eosinophilic gastrointestinal disorders are primarily polygenic allergic disorders that involve mechanisms that fall between pure IgE-mediated and delayed T_H2-type responses. Preclinical studies have identified a contributory role for the cytokine IL-5 and the eotaxin chemokines, providing a rationale for specific disease therapy. An essential question is to determine the cellular and molecular basis for each of these clinical problems and the best treatment regimen, which is the main subject of this review. (*J Allergy Clin Immunol* 2004;113:11-28.)

Key words: Eosinophil, gastrointestinal, inflammation, pathogenesis, therapy

OVERVIEW OF EOSINOPHILIC GASTROINTESTINAL DISORDERS

Eosinophil accumulation in the gastrointestinal tract is a common feature of numerous gastrointestinal disorders, including classic IgE-mediated food allergy,^{1,2} eosinophilic gastroenteritis,^{3,4} allergic colitis,⁵⁻⁷ eosinophilic esophagitis (EE),⁸⁻¹⁰ inflammatory bowel disease (IBD),¹¹⁻¹³ and gastroesophageal reflux disease (GERD).¹⁴⁻¹⁸ In IBD eosinophils usually represent only a small percentage of the infiltrating leukocytes,^{11,19} but

Abbreviations used

ECP:	Eosinophil cationic protein
EDN:	Eosinophil-derived neurotoxin
EE:	Eosinophilic esophagitis
EGID:	Eosinophilic gastrointestinal disorder
EPO:	Eosinophil peroxidase
GERD:	Gastroesophageal reflux disease
HES:	Hypereosinophilic syndrome
hpf:	High-powered field
IBD:	Inflammatory bowel disease
LT:	Leukotriene
MAdCAM:	Mucosal addressin cell adhesion molecule
MBP:	Major basic protein
MCP:	Monocyte chemoattractant protein
PDGFRA:	Platelet-derived growth factor α
VLA:	Very late antigen

their level has been proposed to be a negative prognostic indicator.^{19,20} Primary eosinophilic gastrointestinal disorders (EGIDs; eg, EE, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis) are defined as disorders that primarily affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia (eg, drug reactions, parasitic infections, and malignancy). Patients with EGIDs have a variety of problems, including failure to thrive, abdominal pain, irritability, gastric dysmotility, vomiting, diarrhea, and dysphagia.^{21,22} Evidence in support of the concept that EGIDs arise as a result of the interplay of genetic and environmental factors is accumulating. Notably, a large percentage (approximately 10%) of patients with EGIDs have an immediate family member with an EGID.²¹ Additionally, several lines of evidence support an allergic cause, including the finding that approximately 75% of patients with EGIDs are atopic,²³⁻³⁰ the finding that the severity of disease can sometimes be reversed by institution of an allergen-free diet,²⁹⁻³¹ and the common finding of mast cell degranulation in tissue specimens.^{32,33} Importantly, our recent models of EGIDs support a potential allergic cause for these disorders.¹⁸ Interestingly, despite the common finding of food-specific IgE in patients with EGIDs, food-induced anaphylactic responses only occur in a minority of patients.^{3,34} Thus EGIDs have properties that fall between pure IgE-mediated food allergy and cellular-mediated hypersensitivity disorders (eg, celiac disease; *Fig 1*).³⁴

From the Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center.

Supported in part by the Burroughs Wellcome Fund, the Human Frontier Science Program RG 264/99, the International Life Science Institute, National Institutes of Health/National Institutes of Allergy and Infectious Disease R01 AI42242 and AI45898, and the kind support of Martin Schlaff.

Disclosure of potential conflict of interest: M. E. Rothenberg has a consultant arrangement with Cambridge Antibody Technology and receives grants/research support from Burroughs Wellcome.

Received for publication October 10, 2003; revised October 15, 2003; accepted for publication October 20, 2003.

Reprint requests: Marc E. Rothenberg, MD, PhD, Cincinnati Children's Hospital Medical Center, Division of Allergy and Immunology, Department of Pediatrics, 3333 Burnet Ave, MLC 7028, Cincinnati, OH 45229-3039.

0091-6749/\$30.00

© 2004 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2003.10.047

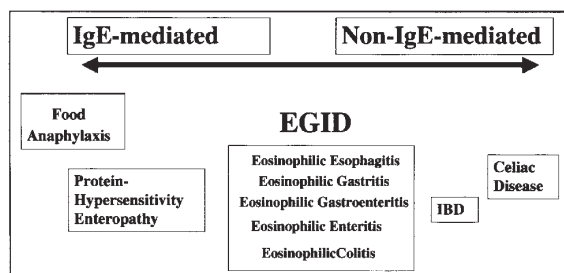


FIG 1. The spectrum of gastrointestinal inflammatory disorders involving eosinophils. Gastrointestinal eosinophils accumulate in a variety of disorders with variable dependence on IgE, ranging from predominant IgE dependence (food anaphylaxis) to non-IgE dependence (celiac disease), and IBD. Adapted with permission from Rothenberg et al.¹⁸

Although the incidence of primary EGIDs has not been rigorously calculated, a miniepidemic of these diseases (especially EE) has been noted over the last decade.^{9,35} One group of investigators has found that 1% of their pediatric patients with GERD have EE.¹⁵ Another group of investigators has reported that 6% of their patients with esophagitis have EE.⁹ Finally, we have estimated that one type of EGID, EE, occurs in approximately 2 of 10,000 children in the geographic region of our medical center in Cincinnati (Richard Noel, Phil Putnam, and Marc Rothenberg, unpublished findings). Collectively, these epidemiologic results indicate that the EGIDs are not an uncommon group of diseases and might have a combined prevalence even higher than that of IBD.

EGIDs typically occur independent of peripheral blood eosinophilia (>50% of the time), indicating the potential significance of gastrointestinal-specific mechanisms for regulating eosinophil levels; indeed, our work has demonstrated the importance of the eotaxin pathway in this process. However, some patients with EGIDs (typically those with eosinophilic gastritis) can have substantially increased levels of peripheral blood eosinophils and meet the diagnostic criteria for the idiopathic hyper-eosinophilic syndrome (HES). This syndrome is defined by sustained severe peripheral blood eosinophilia (>1500 cells/mm²) and the presence of end-organ involvement (in the absence of known causes for eosinophilia).³⁶⁻³⁸ Notably, although HES commonly involves the gastrointestinal tract, the other end organs typically associated with HES (eg, heart and skin) are uncommonly involved in EGIDs. Recently, it has been appreciated that a subset of patients with HES have a microdeletion on chromosome 4 that generates an activated tyrosine kinase susceptible to imatinib mesylate therapy³⁹; the possible occurrence of this and other genetic events in patients with EGIDs, especially those with significant circulating eosinophilia, is currently being investigated.

EOSINOPHIL GROWTH AND DEVELOPMENT

The eosinophil is formed in the bone marrow, where it spends about 8 days maturing under the regulation of the transcription factors GATA-1, GATA-2, and c/EBP (Fig

2).⁴⁰⁻⁴² Notably, GATA-1 and GATA-2 overexpression are sufficient signals for promoting eosinophil development in avian, murine, and human systems. Additionally, mice with a targeted genetic deletion in the high-affinity GATA site present in the GATA-1 promoter are selectively deficient in the eosinophil lineage.⁴¹ These transcription factors provide “instructional” signals that cooperate with the “permissive” eosinophil growth factors IL-3, IL-5, and GM-CSF. IL-5 is the most specific to the eosinophil lineage and is responsible for the selective expansion of eosinophils and their release from the bone marrow.⁴³ Eosinophils subsequently relocate into the peripheral circulation for 8 to 12 hours and finally traffic to specific tissues, predominantly the gastrointestinal tract, where they reside for at least 1 week.⁴⁴ The critical role of IL-5 in the production of eosinophils is best demonstrated by genetic manipulation of mice. Overproduction of IL-5 through a variety of approaches, including transgenic overexpression in enterocytes, results in profound eosinophilia and deletion of the *IL5* gene causes a marked reduction of eosinophils in the blood, lungs, and gastrointestinal tract after allergen challenge.⁴⁵⁻⁴⁹

REGULATION OF EOSINOPHIL TISSUE ACCUMULATION

Numerous inflammatory mediators have been implicated in regulating eosinophil accumulation, including IL-1, IL-3, IL-4, IL-5, IL-13, and GM-CSF and the chemokines RANTES, monocyte chemoattractant protein (MCP) 3, MCP-4, macrophage inflammatory protein 1 α , and eotaxin 1, eotaxin 2, and eotaxin 3.^{44,50,51} IL-3 and GM-CSF, in association with IL-5, enhance eosinophil development, migration, and effector function, whereas IL-1, IL-4, IL-13, and TNF- α regulate eosinophil trafficking by promoting adhesive interactions with the endothelium.^{44,52} In collaboration with IL-5, chemokines and lipid mediators (platelet-activating factor and cysteinyl leukotriene [LT] C₄) induce eosinophil trafficking by promoting chemoattraction. Of the mediators implicated in modulating eosinophil accumulation, only IL-5 and the recently described subfamily of eotaxin chemokines are relatively specific for eosinophils.⁵³ Recent studies suggest that eotaxin 1 has a key role in the modulation of eosinophil accumulation in the gastrointestinal tract and that its effect is primarily tissue specific.⁵⁴ For example, eotaxin 1-deficient mice have a defect in eosinophil trafficking to the gastrointestinal tract and are protected from experimental oral antigen-induced gastrointestinal pathology.⁵⁵ In contrast, IL-5-deficient mice fail to mount expansion of eosinophils in the bone marrow and blood and have markedly impaired eosinophil accumulation in the allergen-challenged lung.⁴⁶ These studies have identified IL-5 as a critical eosinophil growth factor and the eotaxins as critical tissue recruitment factors.

Although the adhesion processes involved in eosinophil tissue accumulation have not been extensively elucidated in the gastrointestinal tract, they have been

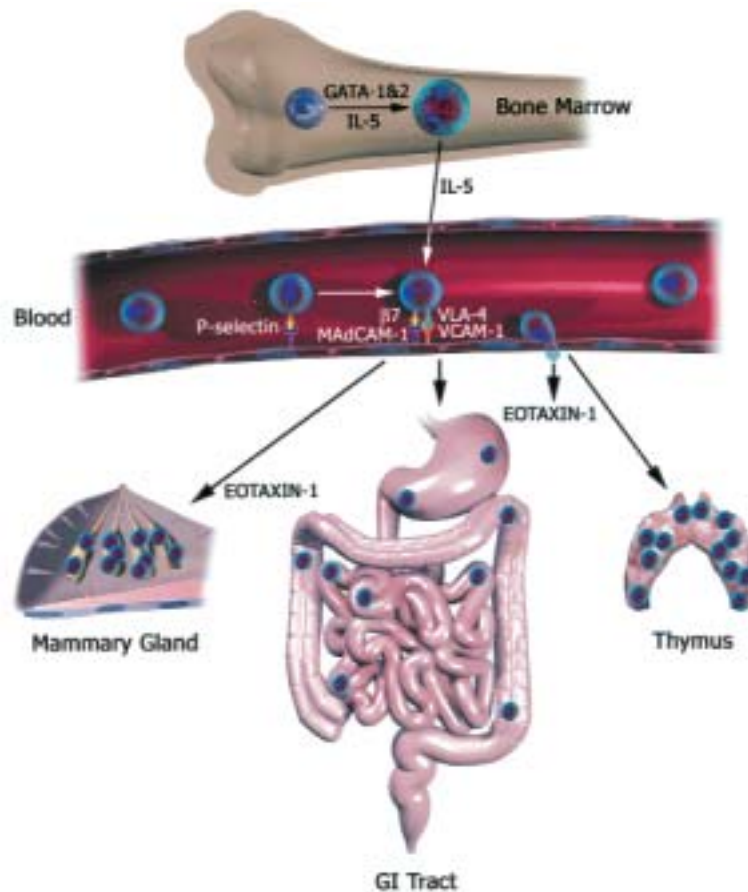


FIG 2. Eosinophil development and tissue localization. The eosinophil is formed in the bone marrow under the regulation of the transcription factors GATA-1, GATA-2, and *c/EBP*. With the influence of IL-5, adhesion molecules, and eotaxin 1, eosinophils subsequently relocate into the peripheral circulation and finally traffic to specific tissues, predominantly the gastrointestinal (GI) tract, thymus, hematopoietic organs, and mammary gland (during pubertal development).

examined in vitro and in the lung.⁵⁶ Reversible interactions between eosinophils and endothelial cells are primarily mediated by selectins; eosinophils express the ligands (eg, sialylated Lewis-X antigen) for E and P selectins (Fig 2). The integrins expressed by eosinophils include members of the $\beta 1$ (eg, very late antigen [VLA] 4), $\beta 2$ (eg, CD18 family of molecules), and $\beta 7$ families (eg, $\alpha 4\beta 7$ molecule).⁵⁷ The CD18 family of molecules includes lymphocyte function antigen 1 and Mac-1, which both interact with endothelial cells through intercellular adhesion molecule; the VLA-4 integrin binds to vascular cell adhesion molecule 1. These adhesion interactions have been shown to be important for eosinophil recruitment into the lung and skin, but their role in eosinophil recruitment to the gastrointestinal tract has not been extensively evaluated.^{56,58,59} The $\alpha 4\beta 7$ molecule, which is coexpressed on lymphocytes and eosinophils, might be the most important integrin for gastrointestinal eosinophils. This integrin binds to mucosal addressin cell adhesion molecule 1 (MAdCAM-1), a major adhesion molecule expressed on high endothelial venules in the intestinal lamina propria,

lymph nodes, and Peyer's patches.^{60,61} Importantly, extensive studies focused on inhibiting the $\beta 7$ /MAdCAM-1 interaction with neutralizing antibodies or with $\beta 7^{-/-}$ mice have supported a central role for this pathway in regulating lymphocyte and mast cell progenitor cell homing into the intestine.⁶²⁻⁶⁴ The findings that eotaxin 1-induced eosinophil recruitment to the lung and eotaxin 1-mediated chemoattraction in vitro are dependent on VLA-4 ($\alpha 4\beta 1$)⁶⁵ suggests that the other $\alpha 4$ -associated integrins on eosinophils (eg, $\alpha 4\beta 7$) might also be involved in eotaxin-mediated events. Consistent with this, there is delayed intestinal hypersensitivity (including lymphocyte and eosinophil infiltrations) in response to intestinal infection with *Trichinella spiralis* in $\beta 7$ -deficient animals.⁶⁶ Determining the role of the $\alpha 4$ and $\beta 7$ integrins on gastrointestinal eosinophils has important therapeutic implication for EGIDs because there are several clinical agents that block these molecules⁶³; in particular, a recent study has shown a beneficial effect of anti- $\alpha 4$ integrin in patients with IBD.⁶⁷ Notably, recent studies have shown that eotaxin-induced gastrointestinal eosinophilia is dependent on the interaction of the

eosinophil adhesion molecule $\alpha 4\beta 7$ and the endothelial receptor MADCAM-1.⁶⁸ Finally, eosinophils express several other adhesion receptors, including CD44, a receptor for hyaluronan, and the sialic acid-binding immunoglobulin-like lectin protein 8 (siglec-8), both of which have been shown to regulate multiple eosinophil responses.⁶⁹⁻⁷¹

EOTAXIN SUBFAMILY OF CHEMOKINES

Eotaxin was initially discovered by using a biologic assay in guinea pigs designed to identify the molecules responsible for allergen-induced eosinophil accumulation in the lungs.⁵³ A partial amino acid sequence facilitated the genetic cloning of the genes and cDNA for guinea pig, murine, and human eotaxin, which led to the identification of eotaxin as a member of the CC chemokine family most homologous to the MCP subfamily,⁷²⁻⁷⁶ all being present in the same genetic locus (human 17q11). By using genomic analyses, rather than biologic assays, 2 additional chemokines have been identified in the human genome that encode for CC chemokines with eosinophil-selective chemoattractant activity and have hence been designated eotaxin 2 and eotaxin 3⁷⁷⁻⁸⁰; the mouse genome was shown to only contain eotaxin 1 and eotaxin 2.⁸¹ Eotaxin 2 and eotaxin 3 are only distantly related to eotaxin 1 because they are only approximately 30% identical in sequence and are located in a different chromosomal position (human 7q11.23).⁸⁰⁻⁸² The specific activity of all eotaxins is mediated by the selective expression of the eotaxin receptor CCR3, a 7-transmembrane-spanning G protein-coupled receptor primarily expressed on eosinophils.⁸³⁻⁸⁵ CCR3 is a genetically polymorphic promiscuous receptor that interacts with multiple ligands, including MCP-2, MCP-3, MCP-4, RANTES, and HCC-2 (macrophage inflammatory protein 5, Leukotactin); however, the only ligands that signal exclusively through this receptor are the eotaxin chemokines, accounting for the cellular selectivity of the eotaxins.^{86,87} Interestingly, other cells involved in allergic responses (eg, T_H2 cells, basophils, mast cells, dendritic cells, and airway epithelial cells) also express CCR3 at variable levels⁸⁸⁻⁹²; however, the significance of CCR3 expression on these cells has been less clearly demonstrated than on eosinophils. Notably, human gastrointestinal mast cells have also been shown to express CCR3⁹³; recently, mast cell CCR3 has been shown to predominantly exist in an intracellular location.⁹⁴

Mice deficient in both eotaxin 1 and IL-5 have a synergistic deficiency of allergen-induced lung eosinophilia and airway hyperreactivity, providing compelling evidence that both of these cytokines work together to elicit and regulate eosinophilia.⁹⁵ In addition to having a role in the respiratory tract, the eotaxin chemokines are involved in regulating eosinophils in other tissues. Under baseline conditions, eotaxin 1 and eotaxin 2 are constitutively expressed in a variety of tissues, with especially high levels in the gastrointestinal tract and thy-

mus.^{48,72,74,81} Analysis of eotaxin 1^{-/-} mice has revealed that the constitutive expression of this chemokine is critically involved in regulating the baseline homing of eosinophils, especially in the intestine (Fig 2).^{48,54} Additionally, induction of experimental gastrointestinal allergy in eotaxin 1^{-/-} mice has revealed an essential role for eotaxin 1 in regulating eosinophil-associated gastrointestinal pathology.^{55,96} Recently, CCR3^{-/-} mice have been developed and have been shown to have a decreased level of jejunal eosinophils at baseline and after *T spiralis* infection.⁹⁷⁻⁹⁹ The finding that gene targeting of the CCR3 locus (a locus not genetically linked to eotaxin 1) induces a phenotype similar to that of eotaxin 1^{-/-} mice, definitively links the eotaxin/CCR3 pathway as a prime regulator of gastrointestinal eosinophils. However, in contrast to the eotaxin 1^{-/-} mice (that have normal levels of splenic eosinophils), CCR3^{-/-} mice have increased levels (approximately 5-fold) of splenic eosinophils^{97,99} that appear to be a result of cell recruitment rather than eosinophilopoiesis.⁹⁹ These results indicate that CCR3 ligands, in addition to eotaxin 1, are likely to be uniquely regulating eosinophil tissue localization.

There is now substantial preclinical evidence supporting a role for eotaxins in human disease. For example, there are markedly increased levels of eotaxin 1 mRNA in the lesions of patients with IBD.⁷⁴ Additionally, experimental induction of cutaneous and pulmonary late-phase responses in human subjects has revealed that the eotaxin chemokines are produced by tissue resident cells (eg, respiratory epithelial cells and skin fibroblasts) and allergen-induced infiltrative cells (eg, macrophages and eosinophils). Several studies have reported baseline and allergen-induced increases in eotaxin 1 levels in the bronchoalveolar lavage fluid of asthmatic subjects compared with control individuals.¹⁰⁰⁻¹⁰⁴ Further support for an important role of eotaxin 1 in human asthma is derived from analysis of a single nucleotide polymorphism in the gene encoding eotaxin 1. A naturally occurring mutation encoding for a change in the last amino acid in signal peptide (alanine→threonine) results in less effective cellular secretion of eotaxin 1 in vitro and in vivo.¹⁰⁵ Notably, this polymorphism is associated with reduced levels of circulating eotaxin 1 and eosinophils and improved lung function (eg, FEV₁).¹⁰⁵ Recently, the activity of eotaxin 1 and eotaxin 2 in human subjects has been investigated by injection of these chemokines into the skin of human subjects; both eotaxin 1 and eotaxin 2 induced an immediate wheal-and-flare response associated with mast cell degranulation and subsequent infiltrations by eosinophils, basophils, and neutrophils.¹⁰⁶ The infiltration by neutrophils is likely to be mediated indirectly by the mast cell degranulation. These results provide substantial evidence that the biologic activities attributed to eotaxins in animals are conserved in human subjects.

Collectively, these studies have provided the impetus for the development of therapeutic agents aimed at blocking the action of eotaxins, CCR3, or both. Indeed, small-molecule inhibitors of CCR3 and a humanized anti-human eotaxin 1 antibody have been developed.^{86,87,107}

Early results with a phase I trial of humanized antieotaxin 1 in patients with allergic rhinitis have shown no serious adverse responses after intravenous or intranasal administration.^{108,109} Notably, antieotaxin 1 has been shown to lower levels of eosinophils in nasal wash samples and nasal biopsy specimens and to improve nasal patency.^{108,109} These early results have substantiated a role for eotaxin 1 in human allergic disease.

CONSTITUTIVE GASTROINTESTINAL EOSINOPHILS

Eosinophils have been noted to be present at low levels in numerous tissues. When a large series of biopsy and autopsy specimens were analyzed, the only organs that demonstrated tissue eosinophils (at substantial levels) were the gastrointestinal tract, spleen, lymph nodes, and thymus (Fig 2).¹¹⁰ Interestingly, eosinophil infiltrations were only associated with eosinophil degranulation in the gastrointestinal tract. Examination of eosinophils throughout the gastrointestinal tracts of conventional healthy mice (untreated mice maintained under pathogen-free conditions) has revealed that eosinophils are normally present in the lamina propria of the stomach, small intestine, cecum, and colon.⁴⁸ Notably, unlike intestinal lymphocytes and mast cells, eosinophils are not normally present in Peyer's patches or intraepithelial locations, although they commonly infiltrate these regions in patients with EGIDs.¹⁷ Interestingly, prenatal mice have eosinophils located in similar regions and concentrations as observed in adult mice,⁴⁸ providing evidence that eosinophil homing into the gastrointestinal tract occurs independent of endogenous flora. Indeed, germ-free mice⁴⁸ and mice deficient in innate signaling responses (MyD88 deficient) have normal levels of gastrointestinal eosinophils (Anil Mishra and Marc Rothenberg, unpublished findings). These data suggest that eosinophils respond to distinct stimuli compared with other intestinal leukocytes; indeed, constitutive expression of eotaxin 1 has been demonstrated to provide the unique signal that promotes localization of eosinophils into the gastrointestinal tract at baseline.

ROLE OF BASELINE EOSINOPHILS

The beneficial function of eosinophils has been primarily attributed to their ability to defend the host against parasitic helminths. This is based on several lines of evidence, including (1) the ability of eosinophils to mediate antibody-dependent (or complement-dependent) cellular toxicity against helminths *in vitro*,^{111,112} (2) the observation that eosinophil levels increase during helminth infections and that eosinophils aggregate and degranulate in the local vicinity of damaged parasites *in vivo*, and (3) the results in experimental parasite-infected mice that have been depleted of eosinophils by means of IL-5 neutralization, gene targeting, or both.¹¹³ In addition to having a role in antiparasite immunity, the

localization of gastrointestinal eosinophils in juxtaposition with lymphocytes suggests a functional interaction between these 2 leukocytes. Although most studies have focused on the role of T cells in the regulation of eosinophils (eg, through IL-5), it is likely that eosinophils might also regulate lymphocytes. Consistent with this finding, eosinophils are known to express the necessary cellular machinery for antigen presentation, such as MHC class II and costimulatory molecules (eg, B7.1 and B7.2; Fig 3).¹¹⁴⁻¹¹⁶ Eosinophils are also known to express a variety of cytokines that can induce the proliferation, maturation, or both of T cells (eg, IL-2, IL-4, and IL-12). Furthermore, preliminary investigations with human eosinophils *in vitro* have shown that eosinophils have the capacity to present antigen to T cells.^{114,115} Recent studies have shown that eosinophils isolated from the mouse lung can present antigen to T cells when adoptively transferred to naive animals.¹¹⁷ In addition, it has been proposed that lymph node eosinophils in patients with Hodgkin's disease might provide cellular ligands for TNF superfamily receptors and CD30, thereby transducing proliferation and anti-apoptotic signals.^{118,119} Additional support for an interaction between eosinophils and T cells has recently been derived from analysis of thymic eosinophils. As mentioned earlier, the thymus is a primary site for eosinophils under healthy conditions (Fig 2). In young mice thymic eosinophils are primarily located in the corticomedullary region, express IL-4 and IL-13, and are positive for CD11b and CD11c (similar to dendritic cells).¹²⁰ In adult mice eosinophils traffic to the medulla under the regulation of eotaxin 1.⁵⁴ During experimental induction of tolerance, the level of thymic eosinophils increases, and their location correlates with areas of active T-cell apoptosis. Taken together, these studies indicate that regulation of T-cell responses might be one of the physiologic functions of eosinophils. Finally, mice deficient in both eotaxin 1 and IL-5 not only have reduced eosinophils but also have an intrinsic defect in T-cell production of IL-13,⁹⁵ substantiating a role for eosinophils in regulating T helper function.

The finding that eosinophils home into the gastrointestinal tract during gestational development⁴⁸ suggests that eosinophils might have a role in tissue or organ development. A role for eosinophils in developmental processes in the gastrointestinal tract has not yet been identified. However, a physiologic function for eosinophils in postnatal mammary gland development has been proposed recently (Fig 2).¹²¹ The important role for leukocytes in mammary gland development was demonstrated by depleting hematopoietic precursors by means of whole-body γ -irradiation. After γ -irradiation, ductal outgrowth was impaired, and this abnormality was reversed by bone marrow transplantation. Interestingly, the level of eotaxin 1 and eosinophils in the mammary gland increased with the development of the mammary gland during puberty. Furthermore, eotaxin 1-deficient mice had a near complete loss of mammary gland eosinophils, and this was associated with a decreased

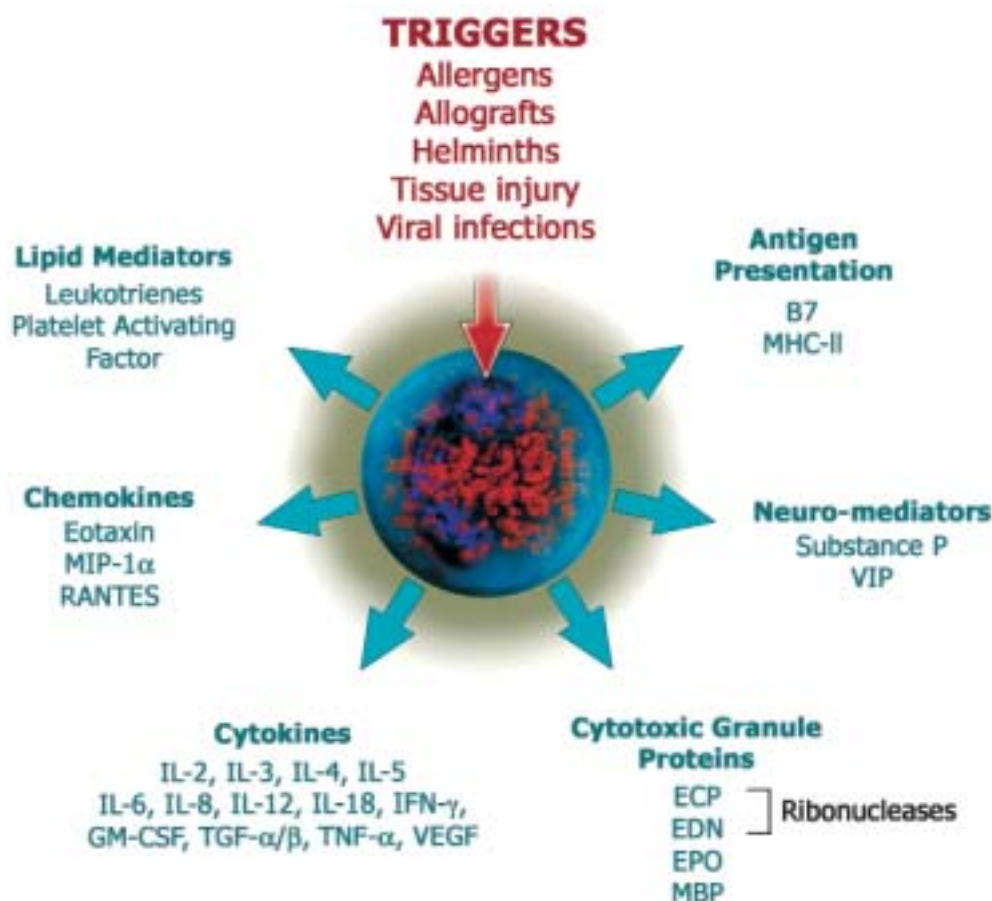


FIG 3. Schematic diagram of an eosinophil and its pleiotropic effects. Eosinophils release their preformed secondary granule constituents, most notably 4 cytotoxic cationic proteins designated EPO, MBP, ECP, and EDN. ECP and EDN are also ribonucleases. Eosinophils also release a variety of cytokines and neuromediators and generate large amounts of lipid mediators. Lastly, eosinophils can be induced to express MHC class II and costimulatory (eg, B7) molecules and might be involved in propagating immune responses by presenting antigen to T cells.

number of ductal branches and a defect in terminal end bud formation. Taken together, these data establish that eosinophils are critically involved in the branching morphogenesis of the mammary gland. The presence of constitutive eotaxin 1 and eosinophils in other endocrine organs (eg, uterus),¹²²⁻¹²⁴ as well as in the gastrointestinal tract, suggests that the involvement of tissue eosinophils in developmental processes is not likely to be restricted to the mammary gland.

PRO-INFLAMMATORY ROLE OF EOSINOPHILS IN EGIDs

Eosinophils are pleiotropic cells stimulated by a variety of triggers (Fig 3). In vitro studies have shown that eosinophil granule constituents are toxic to a variety of tissues, including intestinal epithelium.¹²⁵ Eosinophil granules contain a crystalloid core composed of major basic protein (MBP) 1 (and MBP-2) and a matrix composed of eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase

(EPO; Fig 3).¹²⁶ These cationic proteins share certain pro-inflammatory properties but differ in other ways. For example, MBP, EPO, and ECP have cytotoxic effects on epithelium in concentrations similar to those found in biologic fluids from patients with eosinophilia. Additionally, ECP and EDN belong to the ribonuclease A superfamily and possess antiviral and ribonuclease activity.^{127,128} ECP can insert voltage-insensitive, ion-nonspecific toxic pores into the membranes of target cells, and these pores might facilitate the entry of other toxic molecules.¹²⁹ MBP directly increases smooth muscle reactivity by causing dysfunction of vagal muscarinic M2 receptors.¹³⁰ MBP also triggers degranulation of mast cells and basophils. Triggering of eosinophils through engagement of receptors for cytokines, immunoglobulins, and complement can lead to the generation of a wide range of inflammatory cytokines, including IL-1, IL-3, IL-4, IL-5, IL-13, GM-CSF, transforming growth factors, TNF- α , RANTES, macrophage inflammatory protein 1 α , vascular endothelial cell growth factor, and eotaxin 1, indicating that they have the potential to modulate multiple

aspects of the immune response.¹³¹ In fact, eosinophil-derived transforming growth factor β is linked with epithelial growth, fibrosis, and tissue remodeling.^{132,133} Eosinophils express MHC class II molecules and relevant costimulatory molecules (CD40, CD28, B7.1, and B7.2) and secrete an array of cytokines capable of promoting lymphocyte proliferation, activation, and T_H1 or T_H2 polarization (IL-2, IL-4, IL-6, IL-12, and IL-10).^{95,114,117,131,134} Further eosinophil-mediated damage is caused by toxic hydrogen peroxide and halide acids generated by EPO and by superoxide generated by the respiratory burst oxidase enzyme pathway in eosinophils. Eosinophils also generate large amounts of cysteinyl LTC₄, which is metabolized to LTD₄ and LTE₄. These 3 lipid mediators increase vascular permeability and mucus secretion and are potent stimulators of smooth muscle contraction.¹³⁵ Clinical investigations have demonstrated extracellular deposition of MBP and ECP in the small bowel of patients with eosinophilic gastroenteritis^{3,4,13,136,137} and have shown a correlation between the level of eosinophils and disease severity.^{136,138} Electron microscopy studies have revealed ultrastructural changes in the secondary granules (indicative of eosinophil degranulation and mediator release) in duodenal samples from patients with eosinophilic gastroenteritis.³ Furthermore, Charcot-Leyden crystals, remnants of eosinophil degranulation, are commonly found on microscopic examination of stools obtained from patients with eosinophilic gastroenteritis.^{24,139}

CLINICAL EVALUATION FOR EGIDs

Patients with EGIDs present with a variety of clinical problems, most commonly failure to thrive, abdominal pain, irritability, gastric dysmotility, vomiting, diarrhea, dysphagia, microcytic anemia, and hypoproteinemia.²¹ A diagnostic evaluation for EGIDs should be performed on all patients with these refractory problems, especially in individuals with a strong history of allergic diseases, peripheral blood eosinophilia, and/or a family history of EGIDs (Table I). Depending on the intestinal segment involved, the frequency of specific symptoms varies (eg, abdominal pain and dysphagia are most common in eosinophilic gastroenteritis and EE, respectively), but there are no pathognomonic symptoms or blood tests for diagnosing EGIDs. Notably, blood eosinophil counts are normal in the majority of patients. If an EGID is suspected (on the basis of clinical presentation or evaluation of endoscopic biopsy specimens), then additional testing should be considered to rule out the possibility that there might be another primary disease process, such as drug hypersensitivity, collagen-vascular disease, malignancy, or infection (Table I).

The evaluation for EGIDs starts with a comprehensive history and physical examination. Evaluation for intestinal parasites through examination of stool samples, intestinal aspirates obtained during colonoscopy, or specific blood antibody titers should be performed, especially when patients have high-risk exposure (eg, living on

TABLE I. Diagnostic work-up for EGIDs

General
Complete blood count and differential
Total IgE
Erythrocyte sedimentation rate
Skin prick tests and IgE RASTs
Infection work-up (stool and colonic aspirate analysis)
Upper and lower gastrointestinal endoscopy with biopsies (pH probe and skin patch testing)
In the presence of hypereosinophilia
Bone marrow analysis
Serum tryptase
Vitamin B12
Echocardiogram
Genetic analysis for <i>FIP1L1-PDGFR</i> fusion (evaluation and biopsy of any other potentially involved tissue)

farms or drinking well water). For example, in one series of patients with eosinophilic enteritis, the common dog hookworm *Ancylostoma caninum* (identified by endoscopic detection) was shown to be the cause of eosinophilic enteritis in 10 of 79 patients,¹⁴⁰ raising the possibility that other occult infections might be involved in the pathogenesis of other apparent cases of EGIDs. As a precaution, before using systemic immunosuppression for EGIDs, infection with *Strongyloides stercoralis* should be ruled out because this infection can become life-threatening in the setting of systemic immunosuppression.¹⁴¹ The evaluation of total IgE levels has significance in stratifying patients with atopic variants of EGIDs or suggesting further consideration for occult parasitic infections. Notably, skin prick testing with a panel of food and aeroallergens helps to identify sensitizations to specific allergens. Indeed, patients with the atopic variant of EGIDs have evidence of IgE sensitization to a mean of 14 different food groups.²¹ A preliminary study has suggested a value for delayed cutaneous hypersensitivity testing (skin patch testing) for specific food antigens in further identifying allergic variants of EE.³⁰

The diagnosis of an EGID is dependent on the microscopic evaluation of endoscopic biopsy samples, with careful attention to the quantity, location, and characteristics of the eosinophilic inflammation. It is not uncommon for the endoscopic appearance of the gastrointestinal tract to be normal, and thus microscopic evaluation of biopsy samples is essential. Furthermore, the disease often has patchy involvement, necessitating the analysis of multiple endoscopic biopsy specimens from each intestinal segment.¹⁴² Because no widely accepted diagnostic criteria has been established for EGIDs, the diagnosis is dependent on the expertise of the physicians involved in the evaluation of the biopsy samples. Although the normal esophagus is devoid of eosinophils, the rest of the gastrointestinal tract contains readily detectable eosinophils. Thus differentiation of EGIDs from the normal condition relies on several factors, including (1) eosinophil quantification (and comparisons with normal values at each medical center), (2) the location of eosinophils (eg, their presence in abnormal positions such as the intraepithelial, superficial

mucosal, and intestinal crypt regions), (3) the presence of extracellular eosinophilic staining constituents (often free granules), (4) associated pathologic abnormalities (eg, epithelial hyperplasia as in the case of EE), and (5) the absence of pathologic features suggestive of other primary disorders (eg, neutrophilia associated with IBD or vasculitis associated with Churg-Strauss syndrome). On the basis of these criteria, patients often have symptoms for an extended period of time (mean of 4 years) before a bonafide diagnosis of an EGID is established.²¹

EVALUATION FOR HES IN PATIENTS WITH APPARENT EGIDs

The term HES was introduced by Anderson and Hardy¹⁴³ in 1968 to designate patients with marked eosinophilia. They reported 3 patients, all men between the ages of 34 and 47, who had cardiopulmonary symptoms, fever, sweats, weight loss, and marked eosinophilia. Two of the patients died, and at autopsy, their hearts were enlarged and showed mural thrombi. Chusid and associates¹⁴⁴ formulated the diagnostic criteria for HES to include (1) persistent eosinophilia of at least 1500 cells/mm² for a minimum of 6 months, (2) lack of known causes for eosinophilia (eg, parasitic or allergic triggers), and (3) symptoms and signs of organ system involvement. On the basis of these diagnostic criteria, patients with EGIDs and blood eosinophil counts of greater than 1500/mm² meet the diagnostic criteria. However, patients with EGIDs generally do not have the high risk of life-threatening complications associated with classic idiopathic HES (ie, cardiomyopathy or central nervous system involvement). Notably, considerable heterogeneity among patients with HES has been recognized. For example, T-cell clones producing the characteristic T_H2 cytokines IL-4 and IL-5 have been found in patients satisfying the diagnostic criteria for HES.^{38,145} The treatment for HES is similar to those used for patients with chronic myelogenous leukemia, including prednisone, hydroxyurea, and IFN- α . Perhaps the most striking advance in our understanding of HES has come about after treatment of patients with HES with the tyrosine kinase inhibitor imatinib mesylate.^{39,146-149} Imatinib was introduced for the treatment of chronic myelogenous leukemia and has had a remarkable effect in that disease. Treatment of many patients with HES with imatinib mesylate causes a dramatic reduction of peripheral blood and bone marrow eosinophils, suggesting that certain patients with HES express a novel kinase sensitive to imatinib mesylate. Further investigation of the ability of imatinib mesylate to treat patients with HES revealed the existence of an 800-kb deletion in chromosome 4, bringing together an upstream DNA sequence homologous to a yeast protein, referred to as FIP1 and designated as like FIP1 or FIP1L1, and the gene for the cytoplasmic domain of the platelet-derived growth factor α (PDGFRA) receptor.^{39,150} This fusion gene is transcribed and translated, yielding a novel kinase referred to as FIP1L1-PDGFRA; FIP1L1-PDGFRA is exquisitely sensitive to imatinib *in vitro*, thus explaining the remarkable sensitivity of patients

with HES to this drug. The patients responsive to imatinib are those most characteristic of "classic" HES, namely male subjects between the ages of 20 and 50 years who present clinically with marked peripheral blood eosinophilia. Recently, these patients have been shown to meet minor criteria for systemic mastocytosis, having increased levels of serum mast cell tryptase and high numbers of dysplastic mast cells in the bone marrow.^{151,152} These patients go on to have eosinophilic endomyocardial disease with embolization to peripheral organs, including the extremities and the brain, and they strikingly resemble the patients originally designated by Anderson and Hardy.¹⁴³ However, it appears that any disease that results in prolonged and marked eosinophilia can be associated with endomyocardial disease. For example, endomyocardial disease has occurred during the course of helminth infections and also in various malignancies associated with marked eosinophilia.¹⁵³⁻¹⁵⁵ Thus, patients with marked eosinophilia are at risk for the development of cardiac disease, regardless of the underlying cause of the eosinophilia. Accordingly, routine surveillance of the cardiorespiratory system (eg, echocardiograms and plethysmography) in patients with EGIDs and peripheral blood eosinophilia is warranted. On the basis of these concerns, the diagnosis of HES in patients with EGIDs should always be considered, especially in patients who have extragastrointestinal manifestations (eg, splenomegaly, or cutaneous, cardiac, or respiratory systems). As such, additional diagnostic testing for HES should be considered, including bone marrow analysis (searching for evidence of myelodysplasia), serum mast cell tryptase and vitamin B12 levels (both moderately increased in classic HES), and genetic analysis for the presence of the FIP1L1-PDGFRA fusion event (Table I).¹⁵¹

EOSINOPHILIC ESOPHAGITIS

The esophagus is normally devoid of eosinophils, and therefore the finding of esophageal eosinophils denotes pathology.^{9,10} It is now appreciated that many disorders are accompanied by eosinophil infiltration in the esophagus, such as EE, eosinophilic gastroenteritis, GERD, recurrent vomiting, parasitic and fungal infections, IBD, HES, esophageal leiomyomatosis, myeloproliferative disorders, carcinomatosis, periarteritis, allergic vasculitis, scleroderma, and drug injury.^{10,156} Eosinophil-associated esophageal disorders are classified into primary and secondary subtypes. The primary subtype includes the atopic, nonatopic, and familial variants, and the secondary subtype is divided into 2 groups, one composed of systemic eosinophilic disorders (HES) and the other of noneosinophilic disorders (Table II). Of note, primary EE has also been called idiopathic EE or allergic esophagitis. The familial form of EE follows autosomal dominant penetrance and is seen in approximately 10% of patients (unpublished findings).²¹

Cause of EE

The cause of EE is poorly understood, but food allergy has been implicated. In fact, the majority of patients

have evidence of food and aeroallergen hypersensitivity, as defined by skin prick tests, RASTs, or both; however, only a minority have a history of food anaphylaxis.⁹ It has also been suggested that esophageal eosinophilic inflammation is mechanistically linked with pulmonary inflammation. This latter theory is based on the finding that repeated delivery of specific allergens or the T_H2 cytokine IL-13 to the lung of mice induces experimental EE.^{49,157} In addition, patients with EE commonly report seasonal variations in their symptoms. In addition to eosinophils, T cells and mast cells are increased in esophageal mucosal biopsy specimens, suggesting a chronic T_H2-associated inflammation.^{29,158} Consistent with this view, overexpression of IL-5 induces EE, and neutralization of the T_H2 cytokine IL-5 completely blocks allergen-induced or IL-13-induced EE in mice.^{49,157,159}

Clinical and diagnostic studies for EE

Patients with primary EE commonly report symptoms that include vomiting, epigastric or chest pain, dysphagia, and respiratory obstructive problems.^{29,160} Patients are predominantly young males^{29,160} and have relatively high levels of eosinophils (>20-24 eosinophils/high-powered field [hpf])^{10,161} in the esophageal mucosa, extensive epithelial hyperplasia, and a high rate of atopic disease when compared with patients with GERD.¹⁶¹ The distinguishing features between GERD and EE are presented in Table III. The number and location of eosinophils is helpful when trying to differentiate EE from GERD. Up to 7 eosinophils/hpf (400×) is most indicative of GERD, 7 to 20 to 24 eosinophils/hpf likely represents a combination of GERD and food allergy, and more than 20 to 24 eosinophils/hpf is characteristic of EE.^{10,161} The anatomic location of eosinophils to both the proximal and distal esophagus denotes EE, whereas the accumulation of eosinophils mainly in the distal esophagus is characteristic of GERD.⁹ In addition, esophageal tissue from patients with EE demonstrate thickened mucosa with basal layer hyperplasia and papillary lengthening. EE has been associated with esophageal dysmotility, and the cause of the motor disturbances is unclear, but eosinophil activation and degranulation has been postulated as a possible cause.^{162,163} Recently, esophageal ultrasonography has revealed the presence of a dysfunctional muscularis mucosa in patients with EE, providing a possible explanation for the impaired esophageal dysmotility.¹⁶⁴ Radiographic and endoscopic studies have shown many findings, including strictures, mucosal rings, ulcerations, whitish papules, and polyps.^{15,165} On endoscopy, it is common to visualize linear creases oriented longitudinally (furling).¹⁶⁰ The assessment of EE includes an extended allergy evaluation looking for food and aeroallergen sensitization either by means of skin prick tests or RASTs and the exclusion of GERD, as well as other causes of eosinophils in the esophagus. A recent study has suggested that evaluation of food protein sensitization by means of delayed skin patch testing increases the identification of food allergy compared with skin prick testing

TABLE II. Classification of eosinophil-associated gastrointestinal disorders

Eosinophil-associated esophagitis
Primary eosinophilic esophagitis
Atopic
Nonatopic
Familial
Secondary
Eosinophilic disorders
Eosinophilic gastroenteritis
Hypereosinophilic syndrome
Noneosinophilic disorders
Iatrogenic
Infection
GERD
Esophageal leiomyomatosis
Connective tissue disease (scleroderma)
Eosinophil-associated gastroenteritis
Primary (mucosa, muscularis, and serosal forms)
Atopic
Nonatopic
Familial
Secondary
Eosinophilic disorders
Hypereosinophilic syndrome
Noneosinophilic disorders
Celiac disease
Connective tissue disease (scleroderma)
Iatrogenic
Infection
Inflammatory bowel disease
Vasculitis (Churg-Strauss syndrome)
Eosinophil-associated colitis
Primary eosinophilic colitis (also allergic colitis of infancy)
Atopic
Nonatopic
Secondary
Eosinophilic disorders
Eosinophilic gastroenteritis
Hypereosinophilic syndrome
Noneosinophilic disorders
Celiac disease
Connective tissue disease (scleroderma)
Iatrogenic
Infection
Inflammatory bowel disease
Vasculitis (Churg-Strauss syndrome)

alone.³⁰ Of note, the presence of GERD does not exclude the diagnosis of EE or food allergy, demonstrating the importance of a food allergy evaluation in these patients.

Treatment for EE

A trial of specific food antigen and aeroallergen avoidance is often indicated for patients with atopic EE, and if unsatisfactory or practically difficult (when patients are sensitized to many allergens), a diet consisting of an elemental formula is advocated. Interestingly, it has been shown that an elemental diet frequently improves symptoms and reduces the number of eosinophils in the esophageal biopsy specimens in patients with primary EE (allergic or nonallergic subtypes).³¹ Patients on elemental

TABLE III. Comparison of EE and GERD

Characteristic features	EE	GERD
Clinical		
Prevalence of atopy	Very high	Normal (possibly increased)
Prevalence of food sensitization	Very high	Normal (possibly increased)
Sex preference	Male	None
Abdominal pain and vomiting	Common	Common
Food impaction	Common	Uncommon
Investigative findings		
pH probe	Typically normal	Abnormal
Endoscopic furrowing	Very common	Occasional
Histopathology		
Involvement of proximal esophagus	Yes	No
Involvement of distal esophagus	Yes	Yes
Epithelial hyperplasia	Severely increased	Increased
Eosinophil levels in mucosa	>24/hpf	0-7/hpf
Treatment		
H2-blockers	Sometimes helpful	Helpful
Proton pump inhibitors	Sometimes helpful	Helpful
Glucocorticoids	Helpful	Not helpful
Specific food antigen elimination	Sometimes helpful	Not helpful*
Elemental diet	Helpful	Not helpful*

*Unless co-occurring food allergy exists.

diets frequently require placement of a gastrostomy tube to achieve adequate caloric support. Glucocorticoids (systemic¹⁵ or topical¹⁶⁶) have also been used with satisfactory results. Systemic steroids are used for acute exacerbations, whereas topical steroids are used to provide long-term control. When using topical steroids, we recommend the use of a metered-dose inhaler without a spacer. The patient is instructed to swallow the dose to promote deposition on the esophageal mucosa. In the author's practice fluticasone dipropionate is the drug most used, with a wide range of dosages on the basis of severity and level of response. In a noncontrolled open-label study, topical fluticasone has been shown to decrease levels of eosinophils and CD8⁺ cells in the proximal and distal esophagus.¹⁶⁷ The toxicity associated with inhaled glucocorticoids (eg, adrenal suppression) is unlikely to be seen with swallowed fluticasone because this drug undergoes first-pass metabolism in the liver after gastrointestinal absorption.¹⁶⁸ However, one study reported that 2 of 13 patients treated with topical fluticasone had esophageal candidiasis.¹⁶⁷ Finally, even if GERD is not present, neutralization of gastric acidity (with proton pump inhibitors) might improve symptoms and the degree of esophageal pathology.

Prognosis for EE

It appears that EE requires prolonged treatment similar to that for allergic asthma. Although the natural history of EE has not been extensively followed, it is not uncommon for children with EE to have a parent with a long-standing history of esophageal strictures. In fact, in some cases examination of esophageal biopsy slides from such parents reveals the long-standing presence of EE. Thus it is likely that chronic EE, if left untreated, can develop into

progressive esophageal scarring and dysfunction. The risk for having Barrett's esophagitis, especially in patients with coexisting EE and GERD, has not been determined but is certainly of concern. Additionally, patients with EE are at increased risk for development of other forms of EGID, and thus routine surveillance of the entire gastrointestinal tract by endoscopy is warranted.

EOSINOPHILIC GASTRITIS AND GASTROENTERITIS

In contrast to the esophagus, the stomach and intestine have readily detectable baseline eosinophils under healthy conditions. As such, the diagnosis of eosinophilic gastritis, enteritis, and gastroenteritis is even more complex than EE. In this review, eosinophilic gastritis, enteritis, and gastroenteritis are grouped together because they are clinically similar and because there is a paucity of information available concerning their pathogenesis; however, it is likely that they are indeed distinct entities in most patients. These diseases are characterized by the selective infiltration of eosinophils in the stomach, small intestine, or both, with variable involvement of the esophagus, large intestine, or both.^{3,169,170} It is now appreciated that many disorders are accompanied by eosinophil infiltration in the stomach, such as parasitic and bacterial infections (including *Helicobacter pylori*), IBD, HES, myeloproliferative disorders, periarteritis, allergic vasculitis, scleroderma, drug injury, and drug hypersensitivity.¹⁵⁶ Similar to EE, these disorders are classified into primary and secondary subtypes. The primary subtype includes the atopic, nonatopic, and familial variants, whereas the secondary subtype is divided into 2

groups, one composed of systemic eosinophilic disorders (HES) and the other composed of noneosinophilic disorders (Table II). Primary eosinophilic enteritis, gastritis, and gastroenteritis have also been called idiopathic or allergic gastroenteropathy. The familial form has not been well characterized but is seen in about 10% of our own patients (unpublished findings).²¹ Primary eosinophilic gastroenteritis encompasses multiple disease entities subcategorized into 3 types on the basis of the level of histologic involvement: mucosal, muscularis, and serosal forms.¹³⁹ Of note, either layer of the gastrointestinal tract can be involved, so that endoscopic biopsy can be normal in patients with the muscularis subtype, serosal subtype, or both.

Cause of eosinophilic gastritis and gastroenteritis

Although these diseases are idiopathic, an allergic mechanism has been suggested in at least a subset of patients.¹⁷¹ Indeed, increased total IgE and food-specific IgE levels have been detected in the majority of patients. On the other hand, syndromes with focal erosive gastritis, enteritis, and occasionally esophagitis with prominent eosinophilia, such as the dietary (food) protein-induced enterocolitis and dietary protein enteropathy are characterized by negative skin test responses and absent specific IgE RAST results.¹⁷² A majority of patients have positive skin test responses to a variety of food antigens but do not have typical anaphylactic reactions, which is consistent with a delayed-type of food hypersensitivity syndrome. Indeed, experimental induction of delayed eosinophilic gastroenteritis (involving the esophagus, stomach, and intestine) in mice is accomplished by means of oral allergen administration (in the form of enteric coated allergen beads) to sensitized mice.⁹⁶ Notably, the mice had eosinophil-associated gastrointestinal dysfunction, including gastromegaly, delayed food transit, and weight loss, all strongly dependent on the chemokine eotaxin 1.⁵⁵ Ultrastructural analysis of intestinal tissue suggested that the eosinophils were mediating axonal necrosis, a finding that has been reported in patients with intestinal eosinophilia associated with IBD.¹⁷³ Notably, mast cells are also increased in EGIDs, and a recent murine model of oral allergen-induced diarrhea has demonstrated a critical role for mast cells in the pathogenesis of this specific cardinal feature (allergic diarrhea) of EGIDs.¹⁷⁴ In clinical studies increased secretion of IL-4 and IL-5 by peripheral blood T cells has been reported in patients with eosinophilic gastroenteritis.¹⁷¹ Furthermore, T cells derived from the lamina propria of the duodenum of patients with EGIDs preferentially secrete T_H2 cytokines (especially IL-13) when stimulated with milk proteins.¹⁷⁵ IgA deficiency has also been associated with eosinophilic gastroenteritis; it is interesting to speculate that this could be related to the associated increased rate of atopy in these patients or to an occult gastrointestinal infection in these patients.¹⁷⁶ It is important to bear in mind that eosinophilic gastroenteritis and the dietary protein-induced syndromes (enterocolitis, enteropathy, and

colitis) might represent a continuum of EGIDs with similar underlying immunopathogenic mechanisms.

Clinical and diagnostic studies for eosinophilic gastritis and gastroenteritis

In general, these disorders present with a constellation of symptoms that are related to the degree and area of the gastrointestinal tract affected. However, even patients with isolated eosinophilic enteritis (eg, duodenitis) can have a range of gastrointestinal symptoms. The mucosal form of eosinophilic gastroenteritis (most common variant) is characterized by vomiting, abdominal pain (that can even mimic acute appendicitis), diarrhea, blood loss in stools, iron-deficiency anemia, malabsorption, protein-losing enteropathy, and failure to thrive.¹⁷⁷ The muscularis form is characterized by infiltration of eosinophils predominantly in the muscularis layer, leading to thickening of the bowel wall, which might result in gastrointestinal obstructive symptoms mimicking pyloric stenosis or other causes of gastric outlet obstruction. The serosal form occurs in a minority of patients with eosinophilic gastroenteritis, and it is characterized by exudative ascites with higher peripheral eosinophil counts compared with the other forms.¹³⁶

No standards for the diagnosis of eosinophilic gastritis or gastroenteritis exist,¹⁷⁷ but a few findings support the diagnosis. For example, the presence of increased eosinophils in biopsy specimens from the gastrointestinal tract wall, the infiltration of eosinophils within intestinal crypts and gastric glands, the lack of involvement of other organs, and the exclusion of other causes of eosinophilia (eg, infections and IBD) are supportive of eosinophilic gastroenteritis. Histologic analysis of the small bowel from patients with these disorders reveals extracellular deposition of eosinophil granule constituents, and indeed, extracellular MBP and ECP are immunohistochemically detectable at increased levels.^{3,4,13,136,178} Patients with eosinophilic gastritis can have micronodules (and/or polypoid) noted on endoscopy, and these lesions often contain marked aggregates of lymphocytes and eosinophils. Food allergy and peripheral eosinophilia are not required for diagnosis. In one study 23% of patients with EGE lacked peripheral eosinophilia, but up to 50% of patients with the mucosal form had a history of food allergy or intolerance.^{136,139}

Treatment of eosinophilic gastritis and gastroenteritis

Eliminating the dietary intake of the foods implicated by skin prick testing (or RASTs) has variable effects, but complete resolution is generally achieved with amino acid-based elemental diets.¹⁷⁹ Once disease remission has been obtained by means of dietary modification, the specific food groups are slowly reintroduced (at approximately 3-week intervals for each food group) and endoscopy is performed every 3 months to identify sustained remission or disease flare up. Drugs, such as cromoglycate, montelukast, ketotifen, suplatast tosilate, mycophenolate mofetil (an inosine monophosphate

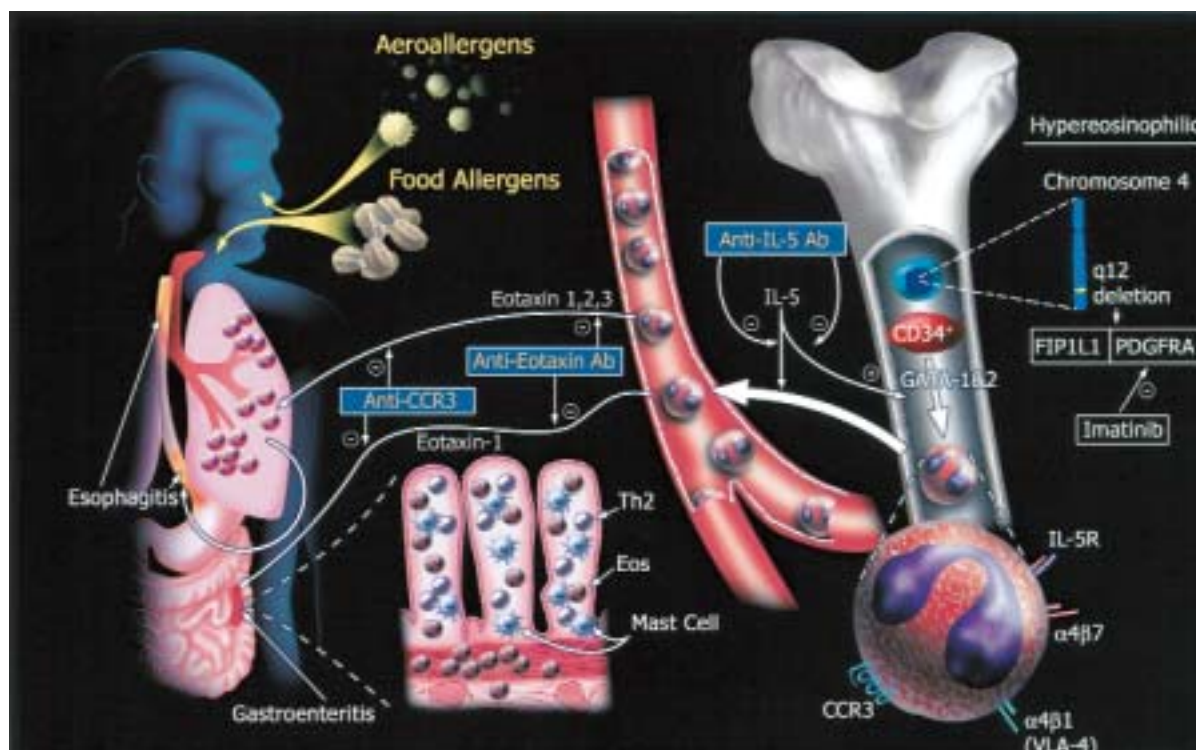


FIG 4. Summary of pathogenesis and treatment strategies for EGIDs and HES. Pathologic increases in eosinophils, accompanied by marked increases of eosinophils in the blood, occur through a variety of mechanisms, including a chromosome 4 interstitial deletion that results in the generation of a fusion gene, *FIP1L1-PDGFRα*. Clinical intervention strategies that are currently being investigated for EGIDs include allergen avoidance and therapy with anti-IL-5 and anti-eotaxin 1 humanized antibodies, CCR3 antagonists, and imatinib mesylate.

dehydrogenase inhibitor), and “alternative Chinese medicines,” have been advocated^{22,180} but are generally not successful in the author’s experience. In our institution an appropriate therapeutic approach includes a trial of food elimination if sensitization is found on the basis of food skin testing, RAST, or both. If no sensitization is found or if specific food avoidance is not feasible, elemental formulas are instituted. Anti-inflammatory drugs (systemic or topical steroids) are the main therapy in cases in which diet restriction is not feasible or has failed to improve the disease. There are several forms of topical glucocorticoids designed to deliver drugs to specific segments of the gastrointestinal tract (eg, budesonide tablets [Entocort EC] designed to deliver drug to the ileum and proximal colon). In severe cases, refractory or dependent on glucocorticoid therapy, intravenous alimentation or immunosuppressive antimetabolite therapy (azathioprine or 6-mercaptopurine) are alternatives. Finally, even if GERD is not present, neutralization of gastric acidity (with proton pump inhibitors) might improve symptoms and the degree of esophageal and gastric pathology.

Prognosis of eosinophilic gastritis and gastroenteritis

The natural history of eosinophilic gastritis, enteritis, and gastroenteritis has not been well documented; how-

ever, these diseases are often chronic waxing and waning disorders. Notably, the involved gastrointestinal segments often vary from one time to another, necessitating routine endoscopic evaluation. In patients with clear food antigen-induced disease, abnormal levels of circulating IgE and eosinophils often serve as markers for tissue involvement. Because these diseases can often be a manifestation of another primary disease process, routine surveillance of the cardiopulmonary systems is recommended. When the disease presents in infancy and specific food sensitization can be identified, there is a high likelihood of disease remission by late childhood.

EOSINOPHILIC COLITIS

Eosinophils accumulate in the colons of patients with a variety of disorders, including eosinophilic gastroenteritis, allergic colitis of infancy, infections (including pinworms and dog hookworms), drug reactions, vasculitis (eg, Churg-Strauss syndrome), and IBD.^{43-46,48,110,111,181,182} Allergic colitis in infancy (also known as dietary protein-induced proctocolitis of infancy syndrome) is the most common cause of bloody stools in the first year of life.^{183,184} Similar to other EGIDs, these disorders are classified into primary and secondary subtypes (Table II). The primary subtype includes the atopic and nonatopic variants, whereas

the secondary subtype is divided into 2 groups, one composed of systemic eosinophilic disorders (HES) and the other composed of noneosinophilic disorders.

Cause of eosinophilic colitis

In contrast to other EGIDs, eosinophilic colitis is usually a non-IgE-associated disease. Some studies point to a T lymphocyte-mediated process, but the exact immunologic mechanisms responsible for this condition have not been identified.¹⁸⁵ In a murine model of oral antigen-induced diarrhea associated with colonic inflammation, colonic T cells have been shown to transfer the disease to naive mice through a STAT6-dependent mechanism.¹⁸⁶ It has been reported that allergic colitis of infancy might be an early expression of protein-induced enteropathy or protein-induced enterocolitis syndrome.¹⁸⁰ Cow's milk and soy proteins are the foods most frequently implicated in allergic colitis of infancy, but other food proteins can also provoke the disease. Interestingly, this condition might more commonly occur in infants exclusively breast-fed and can even occur in infants fed with protein hydrolysate formulas.¹⁸⁰

Clinical and diagnostic studies for eosinophilic colitis

Similar to eosinophilic gastroenteritis, there are a variety of symptoms associated with eosinophilic colitis, depending on the degree and location of tissue involvement. Although diarrhea is a classic symptom, symptoms that can occur independent of diarrhea commonly include abdominal pain, weight loss, and anorexia. There is a bimodal age distribution given the infantile form presented at a mean age at diagnosis of approximately 60 days⁷ and the other group presenting during adolescence and early adulthood.¹⁸⁰ In infants bloody diarrhea precedes diagnosis by several weeks, and anemia caused by blood loss is not uncommon. The majority of infants affected do not have constitutional symptoms and are otherwise healthy. On endoscopic examination, patchy erythema, loss of vascularity, and lymphonodular hyperplasia are seen mostly localized to the rectum but might extend to the entire colon.^{91,112,116,180,185} Histologic examination often reveals that the overall architecture of the mucosa is well preserved, but there are focal aggregates of eosinophils in the lamina propria, crypt epithelium, and muscularis mucosa and, occasionally, the presence of multinucleated giant cells in the submucosa.¹⁸⁰ No single test is the gold standard for diagnosis, but peripheral blood eosinophilia or eosinophils in the stool are suggestive of eosinophilic colitis.

Treatment of eosinophilic colitis

Treatment of eosinophilic colitis varies, primarily depending on the disease subtype. For example, eosinophilic colitis of infancy is generally a benign disease. On withdrawal of the offending protein trigger in the diet, the gross blood in the stools usually resolves within 72 hours, but occult blood loss might persist longer.^{6,180} Treatment of eosinophilic colitis in older

individuals usually requires medical management because IgE-associated triggers are rarely identified. Drugs, such as cromoglycate, montelukast, and histamine receptor antagonists, are generally not successful in the author's experience. Anti-inflammatory drugs, including aminosaliculates and glucocorticoids (systemic or topical steroids), are commonly used and appear to be efficacious, but careful clinical trials have not been conducted. There are several forms of topical glucocorticoids designed to deliver drugs to the distal colon and rectum, but eosinophilic colitis typically also involves the proximal colon. In severe cases, refractory or dependent on systemic glucocorticoid therapy, intravenous alimentation or immunosuppressive antimetabolite therapy (azathioprine or 6-mercaptopurine) are alternatives.

Prognosis for eosinophilic colitis

When eosinophilic colitis presents in the first year of life, the prognosis is very good, with the vast majority of patients being able to tolerate the culprit food or foods by 1 to 3 years of age.¹⁸⁰ Several studies have found an association between allergic colitis and later development of IBD, but this association is controversial.¹⁸⁰ The prognosis for eosinophilic colitis when it develops later in life is more guarded than the infantile subtype. Similar to eosinophilic gastroenteritis, the natural history has not been documented, and this disease is considered to be a chronic waxing and waning disorder. Because eosinophilic colitis can often be a manifestation of other primary disease processes, routine surveillance of the cardiopulmonary systems and regular upper and lower gastrointestinal endoscopy is recommended.

SUMMARY AND CONCLUDING REMARKS

In this article we have reviewed the basic properties of eosinophils, their regulation and role in healthy states, and the pathogenesis and treatment of EGIDs (Fig 4). In brief, under baseline healthy conditions, eosinophils normally account for a small subset of circulating blood cells and primarily reside in the gastrointestinal tract and hematopoietic organs. Their production is tightly regulated by the transcription factors GATA-1, GATA-2, and c/EBP, which instruct the hematopoietic progenitor cell to differentiate into the eosinophil lineage, and the expansion and tissue distribution of the eosinophil is primarily regulated by the cytokines IL-5 and eotaxin 1. Although the beneficial function of eosinophils is not very well understood, the cell appears to be involved in the optimal development of the female reproductive organs (eg, mammary gland). In addition, evidence is emerging indicating that eosinophils contribute to the optimal innate immune response against certain parasitic infections. In a variety of medical conditions, eosinophils accumulate in numerous locations in the body and can often account for the majority of the cellular inflammatory infiltrate, as is the case in primary EGIDs and HES. EGIDs are currently being recognized more frequently, highlighted by the recent miniepidemic of EE in the pediatric population that has led

to the establishment of patient-founded support-advocacy groups, such as the American Partnership for Eosinophilic Disorders (www.APFED.org). At the author's own institution, a World Wide Web registry (www.cincinnatichildrens.org/eosinophils/) has been developed.²¹ The combined results from this registry and other studies have revealed that EGIDs have strong genetic and allergic components and share clinical and immunopathogenic features with asthma. EGIDs are associated with a variety of non-specific common gastrointestinal symptoms and laboratory findings making their diagnosis completely dependent on microscopic examination of gastrointestinal biopsy samples, generally obtained during endoscopic evaluation. A variety of clinical and experimental models have revealed that eosinophils promote potent pro-inflammatory effects mediated by their ability to release their cytotoxic secondary granule constituents and a variety of lipid mediators and cytokines. During T_H2-associated gastrointestinal inflammatory conditions, increased levels of eosinophils occur in the lamina propria in an eotaxin 1-dependent manner. Furthermore, after mucosal allergen challenge, eosinophils under the regulation of IL-5 accumulate in the esophagus, an organ normally devoid of eosinophils at baseline. Notably, eosinophil accumulation in the esophagus can be experimentally induced by aeroallergen or T_H2 cytokine (IL-13) delivery to the lung, establishing a primary link between pulmonary and esophageal eosinophilic inflammation. Preliminary investigations have shown that gastrointestinal eosinophils express the $\alpha 4\beta 7$ integrin and that this molecule is responsible, in part, for eosinophil intestinal homing. Finally, on the basis of these and other results, a variety of new therapeutic approaches are now underway for EGIDs, including treatment with humanized anti-IL-5, the tyrosine kinase inhibitor imatinib mesylate, CCR3 antagonists, and IL-4/IL-13 inhibitors. In fact, early results with a phase I/II trial of anti-IL-5 therapy (mepolizumab) for HES (including EGID) have been very encouraging.¹⁸⁷ Imatinib mesylate might not only be helpful for certain myeloproliferative forms of HES, but also for mast cell-induced problems associated with EGIDs because it inhibits c-kit, a tyrosine kinase required for normal mast cell growth and development.¹⁸⁸ Although much progress has been made concerning the gastrointestinal eosinophil and EGIDs, there is still a paucity of knowledge compared with other cell types and gastrointestinal diseases that might be even less common (eg, IBD). It is hoped that a better understanding of the pathogenesis and treatment of EGIDs will emerge by combining holistic clinical and research approaches involving experts in the fields of allergy, gastroenterology, nutrition, and pathology.

I thank the numerous colleagues who have contributed to the body of information presented in this review, including Drs Simon Hogan, Anil Mishra, Phil Putnam, Amal Assa'ad, Margaret Collins, Eric Brandt, Nives Zimmermann, Paul Foster, Jesus Guajardo, Richard Noel, Mitch Cohen, Glenn Furuta, and Ha Shem. I also thank Dr Troy Scribner for the initial draft of the cover illustration and Andrea Lippelman and Joy Rothenberg.

REFERENCES

1. Moon A, Kleinman RE. Allergic gastroenteropathy in children. *Ann Allergy Asthma Immunol* 1995;74:5-12.
2. Saavedra-Delgado AM, Metcalfe DD. Interactions between food antigens and the immune system in the pathogenesis of gastrointestinal diseases. *Ann Allergy* 1985;55:694-702.
3. Torpier G, Colombel JF, Mathieu-Chandelier C, et al. Eosinophilic gastroenteritis: ultrastructural evidence for a selective release of eosinophil major basic protein. *Clin Exp Immunol* 1988;74:404-8.
4. Keshavarzian A, Savarymurtu SH, Tai PC, Thompson M, Barter S, Spry CJ, . Activated eosinophils in familial eosinophilic gastroenteritis. *Gastroenterology* 1985;88:1041-9.
5. Sherman MP, Cox KL. Neonatal eosinophilic colitis. *J Pediatr* 1982;100:587-9.
6. Hill SM, Milla PJ. Colitis caused by food allergy in infants. *Arch Dis Child* 1990;65:132-3.
7. Odze RD, Wershil BK, Leichtner AM, Antonioli DA. Allergic colitis in infants. *J Pediatr* 1995;126:163-70.
8. Furuta GT. Eosinophils in the esophagus: acid is not the only cause. *J Pediatr Gastroenterol Nutr* 1998;26:468-71.
9. Fox VL, Nurko S, Furuta GT. Eosinophilic esophagitis: It's not just kid's stuff. *Gastrointest Endosc* 2002;56:260-70.
10. Rothenberg ME, Mishra A, Collins MH, Putnam PE. Pathogenesis and clinical features of eosinophilic esophagitis. *J Allergy Clin Immunol* 2001;108:891-4.
11. Walsh RE, Gaginella TS. The eosinophil in inflammatory bowel disease. *Scand J Gastroenterol* 1991;26:1217-24.
12. Sarin SK, Malhotra V, Sen Gupta S, Karol A, Gaur SK, Anand BS. Significance of eosinophil and mast cell counts in rectal mucosa in ulcerative colitis. A prospective controlled study. *Dig Dis Sci* 1978;32:363-7.
13. Dvorak AM. Ultrastructural evidence for release of major basic protein-containing crystalline cores of eosinophil granules in vivo: cytotoxic potential in Crohn's disease. *J Immunol* 1980;125:460-2.
14. Winter HS, Madara JL, Stafford RJ, Grand RJ, Quinlan JE, Goldman H. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. *Gastroenterology* 1982;83:818-23.
15. Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380-5.
16. Brown LF, Goldman H, Antonioli DA. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. *Am J Surg Pathol* 1984;8:899-905.
17. Rothenberg ME, Mishra A, Brandt EB, Hogan SP. Gastrointestinal eosinophils. *Immunol Rev* 2001;179:139-55.
18. Rothenberg ME, Mishra A, Brandt EB, Hogan SP. Gastrointestinal eosinophils in health and disease. *Adv Immunol* 2001;78:291-328.
19. Desreumaux P, Nutton S, Colombel JF. Activated eosinophils in inflammatory bowel disease: do they matter? *Am J Gastroenterol* 1999;94:3396-8.
20. Nishitani H, Okabayashi M, Satomi M, Shimoyama T, Dohi Y. Infiltration of peroxidase-producing eosinophils into the lamina propria of patients with ulcerative colitis. *J Gastroenterol* 1998;33:189-95.
21. Guajardo JR, Plotnick LM, Fende JM, Collins MH, Putnam PE, Rothenberg ME. Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. *J Pediatr* 2002;141:576-81.
22. Khan S, Orenstein SR. Eosinophilic gastroenteritis: epidemiology, diagnosis and management. *Paediatr Drugs* 2002;4:563-70.
23. Caldwell JH, Tennerbaum JI, Bronstein HA. Serum IgE to eosinophilic gastroenteritis. *N Engl J Med* 1975;292:1388-90.
24. Cello JP. Eosinophilic gastroenteritis: a complex disease entity. *Am J Med* 1979;67:1097-114.
25. Scudamore HH, Phillips SF, Swedlund HA, Gleich GJ. Food allergy manifested by eosinophilia, elevated immunoglobulin E level, and protein-losing enteropathy: The syndrome of allergic gastroenteropathy. *J Allergy Clin Immunol* 1982;70:129-36.
26. Furuta GT, Ackerman SJ, Wershil BK. The role of the eosinophil in gastrointestinal diseases. *Curr Opin Gastroenterol* 1995;11:541-7.
27. Iacono G, Carroccio A, Cavataio F, et al. Gastroesophageal reflux and cows milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996;97:822-7.
28. Sampson HA. Food Allergy. *JAMA* 1997;278:1888-94.
29. Walsh SV, Antonioli DA, Goldman H, et al. Allergic esophagitis in children: a clinicopathological entity. *Am J Surg Pathol* 1999;23:390-6.

30. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;109:363-8.
31. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503-12.
32. Oyaizu N, Uemura Y, Izumi H, Morii S, Nishi M, Hioki K. Eosinophilic gastroenteritis: Immunohistochemical evidence for IgE mast cell-mediated allergy. *Acta Pathol Jpn* 1985;35:759-66.
33. Bischoff SC. Mucosa allergy: role of mast cells and eosinophil granulocytes in the gut. *Baillieres Clin Gastroenterol* 1996;10:443-59.
34. Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999;103:717-28.
35. Bates B. 'Explosion' of eosinophilic esophagitis in children. *Pediatr News* 2000;34:4.
36. Weller PF. The idiopathic hypereosinophilic syndrome. *Blood* 1994;83:2759-79.
37. Assa'ad AH, Spicer RL, Nelson DP, Zimmermann N, Rothenberg ME. Hypereosinophilic syndromes. *Chem Immunol* 2000;76:208-29.
38. Roufosse F, Cogan E, Goldman M. The hypereosinophilic syndrome revisited. *Annu Rev Med* 2003;54:169-84.
39. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003;348:1201-14.
40. Kulesa H, Frampton J, Graf T. GATA-1 reprograms avian myelomonocytic cell lines into eosinophils, thromboplasts, and erythroblasts. *Genes Dev* 1995;9:1250-62.
41. Yu C, Cantor AB, Yang H, et al. Targeted deletion of a high-affinity GATA-binding site in the GATA-1 promoter leads to selective loss of the eosinophil lineage in vivo. *J Exp Med* 2002;195:1387-95.
42. Hirasawa R, Shimizu R, Takahashi S, et al. Essential and instructive roles of GATA factors in eosinophil development. *J Exp Med* 2002;195:1379-86.
43. Wardlaw AJ. Molecular basis for selective eosinophil trafficking in asthma: a multistep paradigm. *J Allergy Clin Immunol* 1999;104:917-26.
44. Rothenberg ME. Eosinophilia. *N Engl J Med* 1998;338:1592-600.
45. Dent LA, Strath M, Mellor AL, Sanderson CJ. Eosinophilia in transgenic mice expressing interleukin 5. *J Exp Med* 1990;172:1425-31.
46. Foster PS, Hogan SP, Ramsay AJ, Matthaei KI, Young IG. Interleukin 5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. *J Exp Med* 1996;183:195-201.
47. Lee NA, McGarry MP, Larson KA, Horton MA, Kristensen AB, Lee JJ. Expression of IL-5 in thymocytes/T cells leads to the development of a massive eosinophilia, extramedullary eosinophilopoiesis, and unique histopathologies. *J Immunol* 1997;158:1332-44.
48. Mishra A, Hogan SP, Lee JJ, Foster PS, Rothenberg ME. Fundamental signals regulate eosinophil homing to the gastrointestinal tract. *J Clin Invest* 1999;103:1719-27.
49. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83-90.
50. Rothenberg ME. Eotaxin. An essential mediator of eosinophil trafficking into mucosa tissues. *Am J Respir Cell Mol Biol* 1999;21:291-5.
51. Silberstein DS. Eosinophil function in health and disease. *Crit Rev Oncol Hematol* 1995;19:47-77.
52. Bochner BS, Schleimer RP. Mast cells, basophils, and eosinophils: distinct but overlapping pathways for recruitment. *Immunol Rev* 2001;179:5-15.
53. Jose PJ, Griffiths-Johnson DA, Collins PD, et al. Eotaxin: a potent eosinophil chemoattractant cytokine detected in a guinea pig model of allergic airways inflammation. *J Exp Med* 1994;179:881-7.
54. Matthews AN, Friend DS, Zimmermann N, et al. Eotaxin is required for the baseline level of tissue eosinophils. *Proc Natl Acad Sci U S A* 1998;95:6273-8.
55. Hogan SP, Mishra A, Brandt EB, et al. A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nat Immunol* 2001;2:353-60.
56. Resnick MB, Weller PF. Mechanisms of eosinophil recruitment. *Am J Respir Cell Mol Biol* 1993;8:349-55.
57. Bochner BS. Road signs guiding leukocytes along the inflammation superhighway. *J Allergy Clin Immunol* 2000;106:817-28.
58. Tachimoto H, Ebisawa M, Bochner BS. Cross-talk between integrins and chemokines that influences eosinophil adhesion and migration. *Int Arch Allergy Immunol* 2002;128:18-20.
59. Broide D, Sriramarao P. Eosinophil trafficking to sites of allergic inflammation. *Immunol Rev* 2001;179:163-72.
60. Shaw SK, Brenner MB. The beta 7 integrins in mucosal homing and retention. *Semin Immunol* 1995;7:335-42.
61. Butcher EC, Williams M, Youngman K, Rott L, Briskin M. Lymphocyte trafficking and regional immunity. *Adv Immunol* 1999;72:209-53.
62. Gurish MF, Tao H, Abonia JP, et al. Intestinal mast cell progenitors require CD49beta7 (alpha4beta7 integrin) for tissue-specific homing. *J Exp Med* 2001;194:1243-52.
63. Sandborn WJ, Targan SR. Biologic therapy of inflammatory bowel disease. *Gastroenterology* 2002;122:1592-608.
64. von Andrian UH, Engelhardt B. Alpha4 integrins as therapeutic targets in autoimmune disease. *N Engl J Med* 2003;348:68-72.
65. Kitayama J, Fuhlbrigge RC, Puri KD, Springer TA. P-selectin, L-selectin, and alpha 4 integrin have distinct roles in eosinophil tethering and arrest on vascular endothelial cells under physiological flow conditions. *J Immunol* 1997;159:3929-39.
66. Artis D, Humphreys NE, Potten CS, et al. Beta7 integrin-deficient mice: delayed leukocyte recruitment and attenuated protective immunity in the small intestine during enteric helminthic infection. *Eur J Immunol* 2000;30:1656-64.
67. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med* 2003;348:24-32.
68. Mishra A, Hogan SP, Brandt EB, et al. Enterocyte expression of the eotaxin and interleukin-5 transgenes induces compartmentalized dysregulation of eosinophil trafficking. *J Biol Chem* 2002;277:4406-12.
69. Rothenberg ME. CD44—a sticky target for asthma. *J Clin Invest* 2003;111:1460-2.
70. Floyd H, Ni J, Cornish AL, et al. Siglec-8. A novel eosinophil-specific member of the immunoglobulin superfamily. *J Biol Chem* 2000;275:861-6.
71. Kikly KK, Bochner BS, Freeman SD, et al. Identification of SAF-2, a novel siglec expressed on eosinophils, mast cells, and basophils. *J Allergy Clin Immunol* 2000;105:1093-100.
72. Rothenberg ME, Luster AD, Lilly CM, Drazen JM, Leder P. Constitutive and allergen-induced expression of eotaxin mRNA in the guinea pig lung. *J Exp Med* 1995;181:1211-6.
73. Rothenberg ME, Luster AD, Leder P. Murine eotaxin: an eosinophil chemoattractant inducible in endothelial cells and in interleukin 4-induced tumor suppression. *Proc Natl Acad Sci U S A* 1995;92:8960-4.
74. Garcia-Zepeda EA, Rothenberg ME, Ownbey RT, Celestin J, Leder P, Luster AD. Human eotaxin is a specific chemoattractant for eosinophil cells and provides a new mechanism to explain tissue eosinophilia. *Nat Med* 1996;2:449-56.
75. Ponath PD, Qin SX, Ringler DJ, et al. Cloning of the human eosinophil chemoattractant, eotaxin—expression, receptor binding, and functional properties suggest a mechanism for the selective recruitment of eosinophils. *J Clin Invest* 1996;97:604-12.
76. Luster AD, Rothenberg ME. Role of monocyte chemoattractant protein and eotaxin subfamily of chemokines in allergic inflammation. *J Leukoc Biol* 1997;62:620-33.
77. Patel VP, Kreider BL, Li Y, et al. Molecular and functional characterization of two novel human C-C chemokines as inhibitors of two distinct classes of myeloid progenitors. *J Exp Med* 1997;185:1163-72.
78. Forssmann U, Uguccioni M, Loetscher P, et al. Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes. *J Exp Med* 1997;185:2171-6.
79. Shinkai A, Yoshisue H, Koike M, et al. A novel human CC chemokine, eotaxin-3, which is expressed in IL-4-stimulated vascular endothelial cells, exhibits potent activity toward eosinophils. *J Immunol* 1999;163:1602-10.
80. Kitaura M, Suzuki N, Imai T, et al. Molecular cloning of a novel human CC chemokine (Eotaxin-3) that is a functional ligand of CC chemokine receptor 3. *J Biol Chem* 1999;274:27975-80.
81. Zimmermann N, Hogan SP, Mishra A, et al. Murine eotaxin-2: a constitutive eosinophil chemokine induced by allergen challenge and IL-4 overexpression. *J Immunol* 2000;165:5839-46.
82. Nomiya H, Osborne LR, Imai T, et al. Assignment of the human CC chemokine MPIF-2/eotaxin-2 (SCYA24) to chromosome 7q11.23. *Genomics* 1998;49:339-40.

83. Combadiere C, Ahuja SK, Murphy PM. Cloning and functional expression of a human eosinophil CC chemokine receptor. *J Biol Chem* 1995;270:16491-4.
84. Ponath PD, Qin S, Post TW, et al. Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils. *J Exp Med* 1996;183:2437-48.
85. Daugherty BL, Siciliano SJ, DeMartino JA, Malkowitz L, Sirotna A, Springer MS. Cloning, expression, and characterization of the human eosinophil eotaxin receptor. *J Exp Med* 1996;183:2349-54.
86. Bertrand CP, Ponath PD. CCR3 blockade as a new therapy for asthma. *Expert Opin Investig Drugs* 2000;9:43-52.
87. Zimmermann N, Hershey GK, Foster PS, Rothenberg ME. Chemokines in asthma: cooperative interaction between chemokines and IL-13. *J Allergy Clin Immunol* 2003;111:227-42.
88. Sallusto F, Mackay CR, Lanzavecchia A. Selective expression of the eotaxin receptor CCR3 by human T helper 2 cells. *Science* 1997;277:2005-7.
89. Uguccioni M, Mackay CR, Ochsenberger B, et al. High expression of the chemokine receptor CCR3 in human blood basophils. Role in activation by eotaxin, MCP-4, and other chemokines. *J Clin Invest* 1997;100:1137-43.
90. Gerber BO, Zanni MP, Uguccioni M, et al. Functional expression of the eotaxin receptor CCR3 in T lymphocytes co-localizing with eosinophils. *Curr Biol* 1997;7:836-43.
91. Stellato C, Brummet ME, Plitt JR, Shahabuddin S, Baroody FM, Liu MC, et al. Expression of the C-C chemokine receptor CCR3 in human airway epithelial cells. *J Immunol* 2001;166:1457-61.
92. Beaulieu S, Robbiani DF, Du X, et al. Expression of a functional eotaxin (CC chemokine ligand 11) receptor CCR3 by human dendritic cells. *J Immunol* 2002;169:2925-36.
93. Romagnani P, De Paulis A, Beltrame C, et al. Tryptase-chymase double-positive human mast cells express the eotaxin receptor CCR3 and are attracted by CCR3-binding chemokines. *Am J Pathol* 1999;155:1195-204.
94. Price KS, Friend DS, Mellor EA, De Jesus N, Watts GF, Boyce JA. CC chemokine receptor 3 mobilizes to the surface of human mast cells and potentiates immunoglobulin E-dependent generation of interleukin 13. *Am J Respir Cell Mol Biol* 2003;28:420-7.
95. Mattes J, Yang M, Mahalingam S, et al. Intrinsic defect in T cell production of interleukin (IL)-13 in the absence of both IL-5 and eotaxin precludes the development of eosinophilia and airways hyperreactivity in experimental asthma. *J Exp Med* 2002;195:1433-44.
96. Hogan SP, Mishra A, Brandt EB, Foster PS, Rothenberg ME. A critical role for eotaxin in experimental oral antigen-induced eosinophilic gastrointestinal allergy. *Proc Natl Acad Sci U S A* 2000;97:6681-6.
97. Gurish MF, Humbles A, Tao H, et al. CCR3 is required for tissue eosinophilia and larval cytotoxicity after infection with *Trichinella spiralis*. *J Immunol* 2002;168:5730-6.
98. Ma W, Bryce PJ, Humbles AA, et al. CCR3 is essential for skin eosinophilia and airway hyperresponsiveness in a murine model of allergic skin inflammation. *J Clin Invest* 2002;109:621-8.
99. Humbles AA, Lu B, Friend DS, et al. The murine CCR3 receptor regulates both the role of eosinophils and mast cells in allergen-induced airway inflammation and hyperresponsiveness. *Proc Natl Acad Sci U S A* 2002;99:1479-84.
100. Lamkhouiou B, Renzi PM, Abi-Younes S, et al. Increased expression of eotaxin in bronchoalveolar lavage and airways of asthmatics contributes to the chemotaxis of eosinophils to the site of inflammation. *J Immunol* 1997;159:4593-601.
101. Lilly CM, Nakamura H, Belostotsky OI, et al. Eotaxin expression after segmental allergen challenge in subjects with atopic asthma. *Am J Respir Crit Care Med* 2001;163:1669-75.
102. Ying S, Meng Q, Zeibecoglou K, et al. Eosinophil chemotactic chemokines (eotaxin, eotaxin-2, RANTES, monocyte chemoattractant protein-3 (MCP-3), and MCP-4), and C-C chemokine receptor 3 expression in bronchial biopsies from atopic and nonatopic (intrinsic) asthmatics. *J Immunol* 1999;163:6321-9.
103. Ying S, Robinson DS, Meng Q, et al. C-C chemokines in allergen-induced late-phase cutaneous responses in atopic subjects: association of eotaxin with early 6-hour eosinophils, and of eotaxin-2 and monocyte chemoattractant protein-4 with the later 24-hour tissue eosinophilia, and relationship to basophils and other C-C chemokines (monocyte chemoattractant protein-3 and RANTES). *J Immunol* 1999;163:3976-84.
104. Berkman N, Ohnosa S, Chung FK, Breuer R. Eotaxin-3 but not eotaxin gene expression is upregulated in asthmatics 24 hours after allergen challenge. *Am J Respir Cell Mol Biol* 2001;24:682-7.
105. Nakamura H, Luster AD, Nakamura T, et al. Variant eotaxin: its effects on the asthma phenotype. *J Allergy Clin Immunol* 2001;108:946-53.
106. Menzies-Gow A, Ying S, Sabroe I, et al. Eotaxin (CCL11) and eotaxin-2 (CCL24) induce recruitment of eosinophils, basophils, neutrophils, and macrophages as well as features of early- and late-phase allergic reactions following cutaneous injection in human atopic and nonatopic volunteers. *J Immunol* 2002;169:2712-8.
107. Sabroe I, Peck MJ, Van Keulen BJ, et al. A small molecule antagonist of chemokine receptors CCR1 and CCR3. Potent inhibition of eosinophil function and CCR3-mediated HIV-1 entry. *J Biol Chem* 2000;275:25985-92.
108. Pereira S, Taylor-Clark T, Darby Y, Powell J, Howarth P, Scadding G. Effects of anti-eotaxin monoclonal antibody CAT-213 on allergen-induced rhinitis. *J Allergy Clin Immunol* 2003;111(suppl):S268.
109. Salib R, Salagean M, Lau L, et al. The anti-inflammatory response of anti-eotaxin monoclonal antibody CAT-213 on nasal allergen-induced cell infiltration and activation. *J Allergy Clin Immunol* 2003;111(suppl):S347.
110. Kato M, Kephart GM, Talley NJ, et al. Eosinophil infiltration and degranulation in normal human tissue. *Anat Rec* 1998;252:418-25.
111. Butterworth AE. The eosinophil and its role in immunity to helminth infection. *Curr Topics Microbiol Immunol* 1977;77:127-68.
112. Butterworth AE. Cell-mediated damage to helminths. *Adv Parasitol* 1984;23:143-235.
113. Behm CA, Ovington KS. The role of eosinophils in parasitic helminth infections: insights from genetically modified mice. *Parasitol Today* 2000;16:202-9.
114. Lucey DR, Nicholson WA, Weller PF. Mature human eosinophils have the capacity to express HLA-DR. *Proc Natl Acad Sci U S A* 1989;86:1348-51.
115. Tamura N, Ishii N, Nakazawa M, et al. Requirement of CD80 and CD86 molecules for antigen presentation by eosinophils. *Scand J Immunol* 1996;44:229-38.
116. Woerly G, Roger N, Loiseau S, Dombrowicz D, Capron A, Capron M. Expression of CD28 and CD86 by human eosinophils and role in the secretion of type 1 cytokines (Interleukin 2 and interferon gamma). Inhibition by immunoglobulin A complexes. *J Exp Med* 1999;190:487-96.
117. Shi HZ, Humbles A, Gerard C, Jin Z, Weller PF. Lymph node trafficking and antigen presentation by endobronchial eosinophils. *J Clin Invest* 2000;105:945-53.
118. Pinto A, Aldinucci D, Gloghini A, et al. The role of eosinophils in the pathobiology of Hodgkin's disease. *Ann Oncol* 1997;2:89-96.
119. Pinto A, Aldinucci D, Gloghini A, et al. Human eosinophils express functional CD30 ligand and stimulate proliferation of a Hodgkin's disease cell line. *Blood* 1996;88:3299-305.
120. Throsby M, Herbelin A, Pleau JM, Dardenne M. CD11c+ eosinophils in the murine thymus: developmental regulation and recruitment upon MHC class I-restricted thymocyte deletion. *J Immunol* 2000;165:1965-75.
121. Gouon-Evans V, Rothenberg ME, Pollard JW. Postnatal mammary gland development requires macrophages and eosinophils. *Development* 2000;127:2269-82.
122. Hornung D, Dohrn K, Sotlar K, et al. Localization in tissues and secretion of eotaxin by cells from normal endometrium and endometriosis. *J Clin Endocrinol Metab* 2000;85:2604-8.
123. Salamonsen LA, Lathbury LJ. Endometrial leukocytes and menstruation. *Hum Reprod Update* 2000;6:16-27.
124. Zhang J, Lathbury LJ, Salamonsen LA. Expression of the chemokine eotaxin and its receptor, CCR3, in human endometrium. *Biol Reprod* 2000;62:404-11.
125. Gleich GJ, Frigas E, Loegering DA, Wassom DL, Steinmuller D. Cytotoxic properties of the eosinophil major basic protein. *J Immunol* 1979;123:2925-7.
126. Gleich GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol* 2000;105:651-63.
127. Slifman NR, Loegering DA, McKean DJ, Gleich GJ. Ribonuclease activity associated with human eosinophil-derived neurotoxin and eosinophil cationic protein. *J Immunol* 1986;137:2913-7.
128. Rosenberg HF, Dyer KD, Tiffany HL, Gonzalez M. Rapid evolution of a unique family of primate ribonuclease genes. *Nat Genet* 1995;10:219-23.
129. Young JD, Peterson CG, Venge P, Cohn ZA. Mechanism of membrane

- damage mediated by human eosinophil cationic protein. *Nature* 1986;321:613-6.
130. Jacoby DB, Gleich GJ, Fryer AD. Human eosinophil major basic protein is an endogenous allosteric antagonist at the inhibitory muscarinic M2 receptor. *J Clin Invest* 1993;91:1314-8.
131. Kita H. The eosinophil: a cytokine-producing cell? *J Allergy Clin Immunol* 1996;97:889-92.
132. Gharraee-Kermani M, Phan SH. The role of eosinophils in pulmonary fibrosis. *Int J Mol Med* 1998;1:43-53.
133. Phipps S, Ying S, Wangoo A, Ong YE, Levi-Schaffer F, Kay AB. The relationship between allergen-induced tissue eosinophilia and markers of repair and remodeling in human atopic skin. *J Immunol* 2002;169:4604-12.
134. Lacy P, Levi-Schaffer F, Mahmudi-Azer S, et al. Intracellular localization of interleukin-6 in eosinophils from atopic asthmatics and effects of interferon gamma. *Blood* 1998;91:2508-16.
135. Lewis RA, Austen KF, Soberman RJ. Leukotrienes and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases. *N Engl J Med* 1990;323:645-55.
136. Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990;31:54-8.
137. Tajima K, Katagiri T. Deposits of eosinophil granule proteins in eosinophilic cholecystitis and eosinophilic colitis associated with hypereosinophilic syndrome. *Dig Dis Sci* 1996;41:282-8.
138. Desreumaux P, Bloget F, Seguy D, et al. Interleukin 3, granulocyte-macrophage colony-stimulating factor, and interleukin 5 in eosinophilic gastroenteritis. *Gastroenterology* 1996;110:768-74.
139. Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. *Medicine (Baltimore)* 1970;49:299-319.
140. Walker NI, Croese J, Clouston AD, Parry M, Loukas A, Prociw P. Eosinophilic enteritis in northeastern Australia. Pathology, association with *Ancylostoma caninum*, and implications. *Am J Surg Pathol* 1995;19:328-37.
141. Al Samman M, Haque S, Long JD. Strongyloidiasis colitis: a case report and review of the literature. *J Clin Gastroenterol* 1999;28:77-80.
142. Lee JH, Rhee PL, Kim JJ, et al. The role of mucosa biopsy in the diagnosis of chronic diarrhea: value of multiple biopsies when colonoscopic finding is normal or nonspecific. *Korean J Intern Med* 1997;12:182-7.
143. Anderson RE, Hardy WR. Hypereosinophilia. *Ann Intern Med* 1968;69:1331-2.
144. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 1975;54:1-27.
145. Simon HU, Plotz SG, Dummer R, Blaser K. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med* 1999;341:1112-20.
146. Cortes J, Ault P, Koller C, et al. Efficacy of imatinib mesylate in the treatment of idiopathic hypereosinophilic syndrome. *Blood* 2003;101:4714-6.
147. Schaller JL, Burkland GA. Case report: rapid and complete control of idiopathic hypereosinophilia with imatinib mesylate. *MedGenMed [online]* 2001;3:1(6pp). Available at <http://www.Medscape.com>.
148. Ault P, Cortes J, Koller C, Kaled ES, Kantarjian H. Response of idiopathic hypereosinophilic syndrome to treatment with imatinib mesylate. *Leukoc Res* 2002;26:881-4.
149. Gleich GJ, Leiferman KM, Pardanani A, Tefferi A, Butterfield JH. Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet* 2002;359:1577-8.
150. Griffin JH, Leung J, Bruner RJ, Caligiuri MA, Briesewitz R. Discovery of a fusion kinase in EOL-1 cells and idiopathic hypereosinophilic syndrome. *Proc Natl Acad Sci U S A* 2003;100:7830-5.
151. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood* 2003;101:4660-6.
152. Klion AD, Robyn JA, Akin C, et al. Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. *Blood* 2003.
153. Yoshida T, Naganuma T, Niizawa M, Kakizaki Y, Zeniya A, Masamune O. [A case of eosinophilic gastroenteritis accompanied by perimyocarditis, which was strongly suspected]. *Nippon Shokakibyo Gakkai Zasshi* 1995;92:1183-8.
154. Hussain A, Brown PJ, Thwaites BC, Hastings AG. Eosinophilic endomyocardial disease due to high grade chest wall sarcoma. *Thorax* 1994;49:1040-1.
155. Andy JJ, Ogunowo PO, Akpan NA, Odigwe CO, Ekanem IA, Esin RA. Helminth associated hypereosinophilia and tropical endomyocardial fibrosis (EMF) in Nigeria. *Acta Trop* 1998;69:127-40.
156. Ahmad M, Soetikno RM, Ahmed A. The differential diagnosis of eosinophilic esophagitis. *J Clin Gastroenterol* 2000;30:242-4.
157. Mishra A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* 2003;125:1419-27.
158. Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954-61.
159. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002;168:2464-9.
160. Orenstein SR, Shalaby TM, Di Lorenzo C, Putnam PE, Sigurdsson L, Kocoshis SA. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000;95:1422-30.
161. Ruchelli E, Wenner W, Voytek T, Brown K, Liacouras C. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol* 1999;2:15-8.
162. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109-16.
163. Tottrup A, Fredens K, Funch-Jensen P, Aggestrup S, Dahl R. Eosinophil infiltration in primary esophageal achalasia. A possible pathogenic role. *Dig Dis Sci* 1989;34:1894-9.
164. Fox VL, Nurko S, Teitelbaum JE, Badizadegan K, Furuta GT. High-resolution EUS in children with eosinophilic esophagitis. *Gastrointest Endosc* 2003;57:30-6.
165. Fox VL. Pediatric endoscopy. *Gastrointest Endosc Clin N Am* 2000;10:175-94.
166. Faubion WA Jr, Perrault J, Burgart LJ, Zein NN, Clawson M, Freese DK. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;27:90-3.
167. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 2002;122:1216-25.
168. Grove A, Allam C, McFarlane LC, McPhate G, Jackson CM, Lipworth BJ. A comparison of the systemic bioactivity of inhaled budesonide and fluticasone propionate in normal subjects. *Br J Clin Pharmacol* 1994;38:527-32.
169. Katz AJ, Twarog FJ, Zeiger RS, Falchuk ZM. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984;74:72-8.
170. Bauer S, Schaub N, Dommann-Scherrer CC, Zimmermann DR, Simon HU, Wegmann W. Long-term outcome of idiopathic hypereosinophilic syndrome—transition to eosinophilic gastroenteritis and clonal expansion of T-cells. *Eur J Gastroenterol Hepatol* 1996;8:181-5.
171. Jaffe JS, James SP, Mullins GE, Braun-Elwert L, Lubensky I, Metcalfe DD. Evidence for an abnormal profile of interleukin-4 (IL-4), IL-5, and gamma-interferon (gamma-IFN) in peripheral blood T cells from patients with allergic eosinophilic gastroenteritis. *J Clin Immunol* 1994;14:299-309.
172. Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr* 2000;30(suppl):S58-60.
173. Dvorak AM, Onderdonk AB, McLeod RS, et al. Ultrastructural identification of exocytosis of granules from human gut eosinophils in vivo. *Int Arch Allergy Immunol* 1993;102:33-45.
174. Brandt EB, Strait RT, Hershko D, et al. Mast cells are required for experimental oral allergen-induced diarrhea. *J Clin Invest* 2003;112:1666-77.
175. Beyer K, Castro R, Bimbaum A, Benkov K, Pittman N, Sampson HA. Human milk-specific mucosal lymphocytes of the gastrointestinal tract display a TH2 cytokine profile. *J Allergy Clin Immunol* 2002;109:707-13.
176. Leung VK, Liew CT, Sung JJ. Fatal strongyloidiasis in a patient with ulcerative colitis after corticosteroid therapy. *Am J Gastroenterol* 1997;92:1383-4.
177. Kelly KJ. Eosinophilic gastroenteritis. *J Pediatr Gastroenterol Nutr* 2000;30(suppl):S28-35.

178. Talley NJ, Kephart GM, McGovern TW, Carpenter HA, Gleich GJ. Deposition of eosinophil granule major basic protein in eosinophilic gastroenteritis and celiac disease. *Gastroenterology* 1992;103:137-45.
179. Justinich C, Katz A, Gurbindo C, et al. Elemental diet improves steroid-dependent eosinophilic gastroenteritis and reverses growth failure. *J Pediatr Gastroenterol Nutr* 1996;23:81-5.
180. Guajardo JR, Rothenberg ME. Eosinophilic esophagitis, gastroenteritis, gastroenterocolitis, and colitis. In: Metcalfe DD, Sampson HA, Simon RA, eds. *Food allergy: adverse reactions to foods and additives*. 3rd ed. Malden (MA): Blackwell Publishing; 2003. p. 217-26.
181. Liu LX, Chi J, Upton MP, Ash LR. Eosinophilic colitis associated with larvae of the pinworm *Enterobius vermicularis*. *Lancet* 1995;346:410-2.
182. Khoshoo V, Schantz P, Craver R, Stern GM, Loukas A, Prociw P. Dog hookworm: a cause of eosinophilic enterocolitis in humans. *J Pediatr Gastroenterol Nutr* 1994;19:448-52.
183. Machida HM, Catto Smith AG, Gall DG, Trevenen C, Scott RB. Allergic colitis in infancy: clinical and pathologic aspects. *J Pediatr Gastroenterol Nutr* 1994;19:22-6.
184. Chang JW, Wu TC, Wang KS, Huang IF, Huang B, Yu IT. Colon mucosa pathology in infants under three months of age with diarrhea disorders. *J Pediatr Gastroenterol Nutr* 2002;35:387-90.
185. Van Sickle GJ, Powell GK, McDonald PJ, Goldblum RM. Milk- and soy protein-induced enterocolitis: evidence for lymphocyte sensitization to specific food proteins. *Gastroenterology* 1985;88:1915-21.
186. Kweon MN, Yamamoto M, Kajiki M, Takahashi I, Kiyono H. Systemically derived large intestinal CD4(+) Th2 cells play a central role in STAT6-mediated allergic diarrhea. *J Clin Invest* 2000;106:199-206.
187. Garrett JK, Jameson SC, Thompson B, et al. Anti-IL-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004;113:115-9.
188. Pardanani A, Elliott M, Reeder T, et al. Imatinib for systemic mast-cell disease. *Lancet* 2003;362:535-6.