Food Allergy Track 4
Non-IgE-Dependent Food Sensitization

Eosinophilic GI Diseases: Shining a light on Eosinophils Beyond the Esophagus

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Collins MH. Immunol Allergy Clin N Am 2009;29:109-117

Disclosures

- APFED: Medical Advisory Panel member
- DBV Technologies: Consultant, member of Data Safety Monitoring Board for the study entitled:

  "A DBPC Randomized Trial to Study the Viaskin Milk Efficacy and Safety for Treating IgE-mediated Cow's Milk Allergy in Children"

Learning Objectives

- List some of the common features of EGIDs other than eosinophilic esophagitis (EoE).
- Discuss the prevalence of EGIDs other than EoE.
- Review the clinical presentations of the different EGIDs.

Eosinophils in GI Diseases

Eosinophils are associated with a healthy intestine and increase during disease states.

- Parasites
- Food allergies
- GERD
- Drug reactions
- Inflammatory Bowel Diseases
- Connective tissue disease
- Graft versus host disease
- Post transplant eosinophilic enteritis
- EGIDs

Features of EGIDs Other Than EoE

- Rarer than EoE
- No consensus on disease definition
  - Normal numbers of eosinophils in other areas of the GI tract?
- Case reports or small case series
- Significant number of patients are atopic
- Familial involvement noted in some cases
- Natural history not well documented
  - Chronic waxing and waning course
- Difficult to treat

Proposed Conceptual Definition of EGIDs

EGIDs represents a group of chronic, immune/antigen-mediated gastrointestinal diseases characterized clinically by symptoms related to gastrointestinal dysfunction depending upon the segment(s) and layer(s) involved and histologically by eosinophil-predominant inflammation.

Modeled after conceptual definition of EoE proposed in Liacouras CA, et al. J Allergy Clin Immunol 2011;128:3-20

Primary Eosinophilic Gastrointestinal Diseases (EGIDs)

- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Eosinophilic enteritis
- Eosinophilic colitis

“Normal” number of eosinophils in GI tract

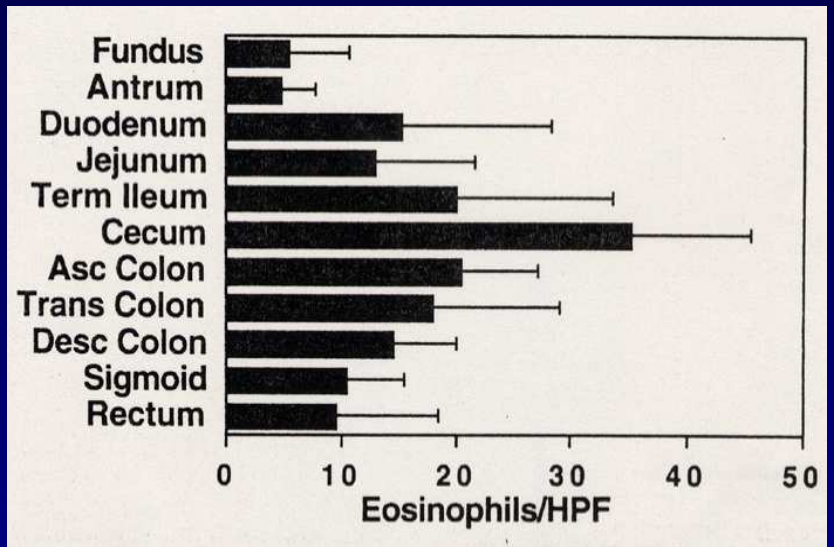

Figure 1. Mean mucosal eosinophil count/HPF and standard deviation for 11 medical examiner autopsy cases (mean age 5.6 yrs) according to anatomic site. The number of cases examined varied slightly between sites, as occasional sites were too autolyzed to count (n = 8, cecum; n = 9, duodenum; n = 10, jejunum, terminal ileum, ascending colon, descending colon; n = 11, gastric fundus and antrum, transverse colon, sigmoid colon, rectum). Mean and median eosinophil counts were similar.

Lowichik A, Weinberg AG. Mod Path 1996;9:110
Debrosse CW et al. Pediatr Dev Path 2006;9:210

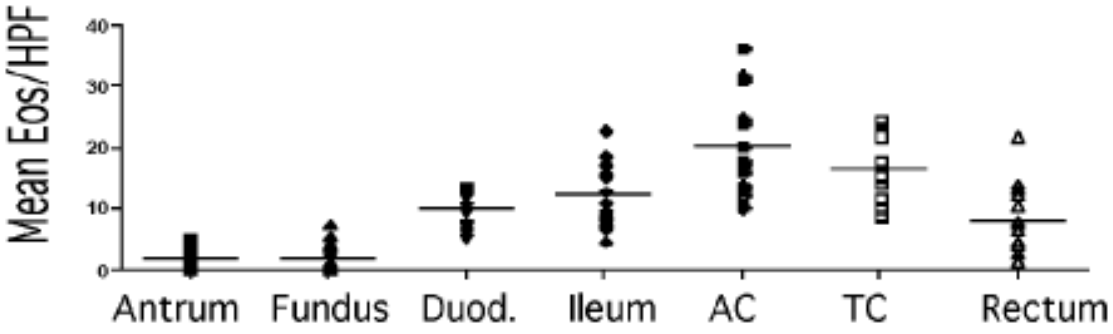

Figure 1. Eosinophil levels in gastrointestinal segments. The mean number of eosinophils in the lamina propria of individual patients is shown. The solid black line represents the mean eosinophil level in the lamina propria for all patients. Each point on the graph represents the mean number of eosinophils/high-power field (hpf) for a patient in our study.

Evaluation of Biopsies for EGIDs

- Eosinophil quantification (comparison with normal values at each medical center)
- Location of the eosinophils in abnormal regions such as intraepithelial, superficial mucosal and intestinal crypt regions
- Presence of extracellular eosinophilic staining constituents
- Associated pathologic abnormalities, i.e. epithelial hyperplasia
- Absence of pathological findings associated with other disorders (neutrophilia, vasculitis)

Variation in Prevalence, Diagnostic Criteria, and Initial Management Options for Eosinophilic Gastrointestinal Diseases in the United States

Spergel JM ET, et al. JPGN 2011;52:300-306

- Electronic survey of members of:
  - American College of Gastroenterology
  - American Academy of Allergy, Asthma and Immunology
  - North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition
- Question regarding:
  - Number and proportion of patients with EG, EGE and EC
  - Methods used to diagnose and treat these conditions

Variation in Prevalence, Diagnostic Criteria, and Initial Management Options for Eosinophilic Gastrointestinal Diseases in the United States

Spergel JM ET, et al. JPGN 2011;52:300-306

Results: 1,836/10,874 (17%) response rate

Estimated prevalence for EGIDs:

	EoE	EGE - EC
	Ave/ # pts/yr	Ave/ # pts/yr
Pediatric GI	20.2 (12.4 – 27.3)	8.9 (3.2 – 13.8)
Adult GI	10.7 (4.7 – 15.7)	5.9 (0.7 – 10.1)
Estimate of US Patients	158,705 (72,332 – 231,224)	85,281 (12,040 – 145,677)
Prevalence/100,000	52.2 (23.8 – 76.1)	28.1 (4.0 – 48.0)

Variation in Prevalence, Diagnostic Criteria, and Initial Management Options for Eosinophilic Gastrointestinal Diseases in the United States

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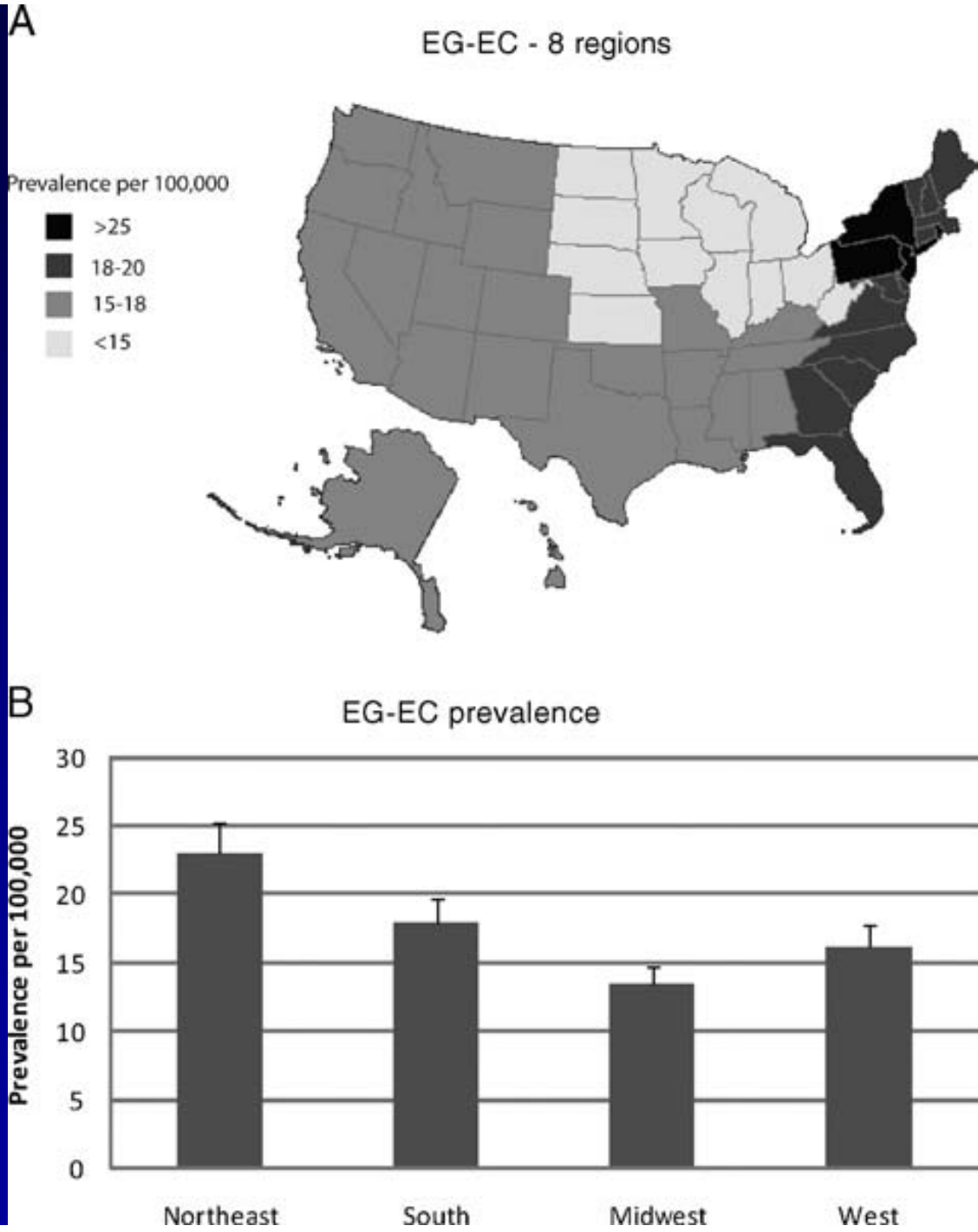
JPGN 2011;52:300-306



Distribution of EG-EC in the United States. Prevalence based on physician response corrected for the number of physicians per state and state population. States divided into 9 regions (A) or 4 regions (B) based on previous studies.

Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates from a National Administrative Database

Jensen ET, et al. JPGN

- IMS Health LifeLink, PharMetrics Plus Claims Database
- National commercially-insured population with medical and pharmaceutical claims for >76 million lives
- Population examined: aged 0-64 years, continuously enrolled from 7/1/2009-6/30/2011
- Identified EG, EGE, EG by ≥1 instance of ICD 9 codes 535.70, 558.41 and 558.42
- Calculated prevalence of codes in the database and standardized the estimates to the US population by age and sex

Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates from a National Administrative Database

Jensen ET, et al. JPGN 2015

Standardized estimated prevalences per 100,000:

- Eosinophilic gastritis: 6.3
  - More prevalent in older age groups
  - Co-existing allergies 38.5%
- Eosinophilic gastroenteritis: 8.4
  - More prevalent among children < 5 years old
  - Co-existing allergies 45.6%
- Eosinophilic colitis: 3.3
  - Co-existing allergic conditions: 41.8%

Eosinophilic Gastritis

- Symptoms- abdominal pain, vomiting, hematemesis
- Can be associated with protein losing enteropathy and eosinophils elsewhere in GI tract

Ko HM, et al. Am J Gastroenterol 2014;109:1277-85

Biopsy Evaluation for EGIDs:Gastritis

Collins MH. Gastroenterol Clin N Am 43 (2014) 257-268

- ≥30 eosinophils/hpf in 5 hpf
- Altered eosinophil behavior: lamina propria sheets, eosinophilic glandulitis, eosinophilic gland abscesses
- Epithelial changes: reduced mucin, increased nuclear/cytoplasmic ratio, increased epithelial mitotic activity
- Altered distribution: 1 or more eos/hpf in surface epithelium, excess eosinophils in muscularis mucosa or submucosa

Eosinophilic Gastritis in Children: Clinicopathological Correlation, Disease Course, and Response to Therapy

Am J Gastroenterol 2014;109:1277-85

Huaibin M. Ko, MD[1], Raffaella A. Morotti, MD[2], Oksana Yershov, MS[3] and Mirna Chehade, MD, MPH[3]

- Reviewed pathology database for EG in children (<18 yrs) seen from 2005-2011

- 36 children (20 female) (31 Caucasian)
  - Median age 7.2 yrs (0.2-15.2 yrs)
  - 5 had solid organ transplant

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Table 2. Presenting clinical features of patients with HEG, including those with eosinophilia limited to the stomach (EG) and those HEG with concurrent eosinophilia at other gastrointestinal sites

	Total no. of patients (%)	EG (*n*=14)[a]	HEG + esophageal eosinophilia (*n*=10)[a]	HEG + duodenal eosinophilia (*n*=4)[a]	HEG + esophageal and duodenal eosinophilia (*n*=2)[a]
Main symptom (n=28)[b]					
Abdominal pain	12 (43)	6/13	3/10	2/3	1/2
Vomiting	10 (36)	4/13	6/10		
Anemia/melena	3 (11)	2/13		1/3	
Food aversions/failure to thrive	2 (7)		1/10		1/2
Edema/ascites	1 (4)	1/13			
Atopic history					
Asthma (*n*=24)	10 (45)	2/10	6/9	1/3	1/2
Allergic rhinitis (*n*=23)	9 (43)	2/9	4/9	3/3	0/2
Atopic dermatitis (*n*=23)	5 (22)	1/9	3/9	1/3	0/2
Food allergies (*n*=23)	10 (43)	1/9	6/9	1/3	2/2
Food sensitizations (*n*=21)	18 (86)	6/8	8/8	3/3	1/2
Protein-losing enteropathy (*n*=27)	6 (22)	3/12	1/10	2/3	0/2

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Table 4. Clinical and histological response to various therapies in all patients with HEG, and in the subset with HEG alone

Type of therapy received	Clinical response (No. of responders/No. available for review)	Histological response (No. of responders/No. available for review)
Dietary therapy		
Amino acid-based formula with 1–12 foods	6/6 (2/2)[a]	4/5 (1/1)
Seven-food empiric dietary restriction therapy	5/6 (3/3)	5/6 (3/3)
Empiric avoidance of 1–3 foods	3/5 (1/2)	2/3 (1/2)
Pharmacological therapy		
Proton pump inhibitor	1/2 (0/1)	1/1 (—)
Cromolyn sodium	1/2 (0/1)	0/1 (0/1)
Pyloromyotomy	1/1	—

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Table 5. History of sensitization to common food allergens in patients with HEG, defined by positive skin prick test and/or serum food-specific IgE level

	Positive skin prick test/serum food-specific IgE (No. of patients/No. of tested)
Milk	13/18
Wheat	10/16
Egg	13/19
Soy	7/15
Peanut	12/15
Tree nuts	9/11
Fish	5/11
Shellfish	2/6
Beef	7/10
Lamb	2/6
Serum total IgE (units/ml; *n*=11 patients), median (range)	151 (30–5,000)

Eosinophilic Gastritis in Children: Clinicopathological Correlation, Disease Course, and Response to Therapy

Am J Gastroenterol 2014;109:1277-85

Huaibin M. Ko, MD[1], Raffaella A. Morotti, MD[2], Oksana Yershov, MS[3] and Mirna Chehade, MD, MPH[3]

"Standard allergy testing is not predictive of the food triggers in this disease, pointing toward a cell-mediated rather than an IgE-mediated mechanism. An empiric dietary restriction therapy consisting of removal of common food triggers established for EoE or a very restricted elemental diet is warranted in this population."

Eosinophilic Gastritis in Children: Clinicopathological Correlation, Disease Course, and Response to Therapy

Am J Gastroenterol 2014;109:1277-85

Huaibin M. Ko, MD[1], Raffaella A. Morotti, MD[2], Oksana Yershov, MS[3] and Mirna Chehade, MD, MPH[3]

WHAT IS CURRENT KNOWLEDGE

- ✓ Eosinophilic gastritis is rare in children.
- ✓ The clinical and endoscopic features of eosinophilic gastritis have not been well characterized.
- ✓ Eosinophilic gastritis in children is steroid-responsive.
- ✓ The role of food antigens in triggering eosinophilic gastritis is poorly understood.

WHAT IS NEW HERE

- ✓ Children with eosinophilic gastritis have very variable symptoms.
- ✓ Endoscopic appearance is variable and can be normal, highlighting the importance of tissue diagnosis.
- ✓ Eosinophilic gastritis can be patchy; biopsies from both antral and fundic mucosae are needed.
- ✓ Peripheral eosinophilia is not a reliable marker for disease activity.
- ✓ Severe gastric eosinophilia can be at times associated with a protein-losing enteropathy even without duodenal eosinophilia.
- ✓ Eosinophilic gastritis is highly amenable to dietary restriction therapy in children.

Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, T_H2 immunity, and a unique gastric transcriptome

Julie M. Caldwell, PhD,[a] Margaret H. Collins, MD,[b] Emily M. Stucke, BA,[a] Philip E. Putnam, MD,[c] James P. Franciosi, MD, MS, MSCE,[c]* Jonathan P. Kushner, MD,[d] J. Pablo Abonia, MD,[a] and Marc E. Rothenberg, MD, PhD[a] *Cincinnati, Ohio*

JACI 2014;134:1114-24

Methods:

- 15 subjects with EG and 15 controls
- Analyzed:
  - Histologic features of gastric biopsies
  - Blood eosinophil counts
  - Genome-wide transcript profiles

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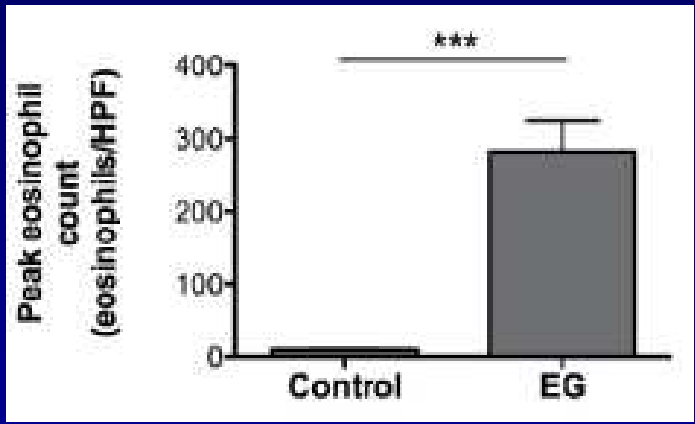
JACI 2014;134:1114-24

Results:

- Peak gastric antrum eosinophil count
  - EG: 283 ± 164 eos/x 400 hpf
  - Controls: 11 ± 9 eos/x400hpf



- 87% of EG patients had coexistent eosinophilic inflammation in multiple GI segments
  - Esophagus was most common secondary site

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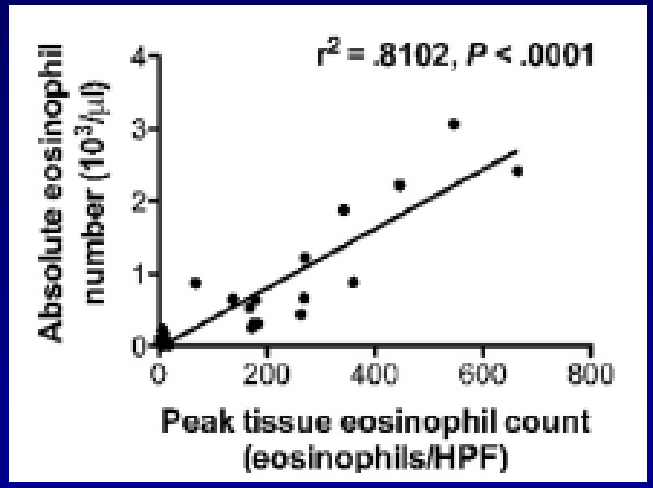
JACI 2014;134:1114-24

Results:

- Peripheral blood eosinophil counts
  - EG: 1.09 $\pm$ 0.88 x 10^3/mL
  - Controls: 0.09 $\pm$ 0.08 x 10^3/μL
- Increased MIB-1^+, CD117+ (mast cells), FOXP3+ (regulatory or activated T cells, or both) in EG pts



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JACI 2014;134:1114-24

Results:

- Transcript profiling
  - Changes in 8% of the genome in gastric tissue from EG patients
  - Only 7% of EG transcriptome overlapped with the EoE transcriptome
  - Observed increased IL4, IL5, IL13, IL17, CCL26 and mast cell transcripts and decreased IL33 transcripts

Eosinophilic Gastroenteritis

Epidemiology

- Affects all ethnicities, all ages, both genders
- Most often diagnosed between 3rd & 5th decade of life
- May be second peak in 1st decade of life
- Chronic disease with few remissions after the first year
- Personal or family history of atopy present in 70%
- Familial involvement ~ 10%

Gastrointestinal Eosinophilic Diseases Classification Scheme: Gastroenteritis

Primary (mucosa, muscularis, 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)

Rothenberg ME. JACI 2004;113:11-28

EGE: Differential Diagnosis

- Infection
  - Parasites: helminths, hookworns, pinworms, Giardia lamblia, Anasakis, Trichinella spiralis, Ascaris, Trichuris, Schistosomiasis, Toxocara cana, Strongyloides sterocoralis
  - Other: H pylori, CMV
- Medications: interferon, gemfibrozil, enalapril, co-trimoxazole
- Connective tissue disease & Vasculitis
  - Scleroderma, dermatomyositis, lupus, Churg-Strauss syndrome, polyarteritis nodosa
- Inflammatory fibroid polyps
  - Benign localized polyps with variable eosinophilic infiltrate, found in stomach and small intestine
- Hypereosinophilic syndrome
- Inflammatory bowel disease
- Transplantation (tacrolimus)

Biopsy Evaluation for EGIDs:Enteritis

Collins MH. Gastroenterol Clin N Am 43 (2014) 257-268

- > Twice normal number of eos/hpf in lamina propria
  - > 52 eos/hpf in duodenum
  - > 56 eos/hpf in ileum
- Altered eosinophil behavior: lamina propria sheets, eosinophilic cryptitis or eosinophilic crypt abscesses
- Epithelial changes: reduced mucin, increased nuclear/cytoplasmic ratio, increased epithelial mitotic activity

Biopsy Evaluation for EGIDs:Enteritis

Collins MH. Gastroenterol Clin N Am 43 (2014) 257-268

- Altered eosinophil distribution
  - Surface epithelium: > 2 eos/hpf in duodenum, > 4 eos/hpf in ileum
  - Crypt epithelium:> 6 eos/hpf in duodenum, > 4 eos/hpf in ileum
  - Excess eos in muscularis mucosa or submucosa
  - Concentration of eos in the subepthelial superficial lamina propria instead of deep lamina propria
  - Acute inflammatory cells are not present

Eosinophilic Gastroenteritis

Clinical Features: Organ

- Gastric dominant
  - Nausea, vomiting, early satiety
- Duodenal dominant
  - Malabsorption, PLE
- Other
  - Crampy abdominal pain, bloating

Eosinophilic Gastroenteritis

Clinical features: Layer

Klein Classification (mucosal, submucosal, serosal)

- Mucosal (25-100%):
  - Abdominal pain, nausea, vomiting, diarrhea, occult GI bleeding, anemia, wt loss, protein-losing enteropathy
  - Often confused with: IBS, dyspepsia, pancreatitis, acute appendicitis, IBD
  - Intestinal blood & protein loss is unique presentation of children with allergic EGE
  - Often associated with atopy and elevated IgE levels

Eosinophilic Gastroenteritis

Clinical Presentations: Layer

Muscular (13-70%)

- Presents with gastric outlet or intestinal obstruction
- Colicky abdominal pain
- Strictures are rare, but most often involve the jejunum

Serosal (12-40%)

- Classically adults presenting with ascites
- Significant bloating
- Higher levels of peripheral eosinophilia
- Respond to steroids

Eosinophilic Gastroenteritis

Chang JY, et al. Clin Gastroenterol Hep 2010;8:669-675

- Retrospective review of 59 patients with EGE referred from 1987-2007
  - 52 mucosal, 3 muscularis, 4 subserosal
- Compared to 11 controls with GI symptoms and eosinophilia

Eosinophilic Gastroenteritis

Chang JY, et al. Clin Gastroenterol Hep 2010;8:669-675

Clinical and Laboratory Features of EGE and Other

Variable	Mucosal n = 52	Muscular n = 3	Serosa n = 4	Other n = 11
Age at Dx (yrs)	48	45	29	37
Yrs sxs	3.4	2.8	7.0	4.6
Fm Hx of atopy%	27	0	0	0
Hx of atopy%	63	67	50	73
Food int/all%	19	33	0	18
Median Eos	0.9 (.3-1.9)	3.3 (.4-3.8)	1.3 (.9-2.0)	1.7 (.7-2.3)
IgE level	622	27	86	690

Eosinophilic Gastroenteritis

Chang JY, et al. Clin Gastroenterol Hep 2010;8:669-675

Distribution of Self-Reported Allergies (%)

Type	EGE (59)	GI sx + eos (11)
Drug allergy	36	45
Asthma	24	9
Rhinitis	21	9
Food intolerance/allergy	21	27
Hay fever	7	0
Nasal polyps	5	0
Eczema	2	0

Eosinophilic Gastroenteritis

Chang JY, et al. Clin Gastroenterol Hep 2010;8:669-675

Foods Identified by PST or ImmunoCAP (%)

Type	EGE (n = 22)
None	50
Vegetables	36
Grains	32
Nuts	27
Fruit	27
Dairy	23
Meat	23
Legumes	23
Seafood	23
Poultry	18
Spices	9

Eosinophilic Gastroenteritis

Chang JY, et al. Clin Gastroenterol Hep 2010;8:669-675

"Although a variety of types of food allergy were identified, it is notable that 50% of all subjects had negative food allergy testing."

Eosinophilic Gastroenteritis

Chang JY, et al. Clin Gastroenterol Hep 2010;8:669-675

"Our findings, in conjunction with the low sensitivity and high rates of false positive results of commonly available allergy tests may argue for great caution when contemplating the use of these tests for suspected EGE patients."

Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis

Craig Reed [a], John T. Woosley [b], Evan S. Dellon [c,d,*]

Digestive and Liver Disease 2015;47:197-201

Methods:

- Reviewed pathology reports of patients with endoscopy with biopsy from 1/1/2000 – 6/20/13

- Diagnosed with EGE if
  - ≥20 eos/hpf on either gastric or duodenal biopsy
  - GI symptoms
  - No known secondary cause of eosinophilia

Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis

Craig Reed [a], John T. Woosley [b], Evan S. Dellon [c,d,*]

Digestive and Liver Disease 2015;47:197-201

Results:

- 44 patients diagnosed with EGE
- Most common symptoms
  - Vomiting (71%)
  - Abdominal pain (62%)
- Other areas of GI tract also involved
  - Esophagus - 12 pts (30%)
  - Colon - 11 pts (28%)

Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis

Craig Reed [a], John T. Woosley [b], Evan S. Dellon [c,d,*]

Digestive and Liver Disease 2015;47:197-201

Results:

- Treatment
  - Steroids - 36 pts (80%)
- Resolution:
  - Symptoms - 27 pts (60%),
  - Endoscopic - 27 pts (51%)
- Mean of 5 endoscopies per case per year

Eosinophilic Colitis

Okpara N, Aswad B, Baffy G. World J Gastroenterol 2009;15:2975-2979

Gastrointestinal Eosinophilic Diseases Classification Scheme: Colitis

Primary eosinophilic colitis (allergic colitis of infancy)

- Atopic
- Nonatopic
- Familial

Secondary

- Eosinophilic disorders
  - Eosinophilic gastroenteritis
  - Hypereosinophilic syndrome
- Noneosinophilic disorders
  - Celiac disease
  - Connective tissue disease (scleroderma)
  - Iatrogenic
  - Infection
  - Inflammatory bowel disease
  - Vasculitis (Churg-Strauss syndrome)

Rothenberg ME, et al JACI 108:891-94, 2001

Biopsy Evaluation for EGIDs: Colitis

Collins MH. Gastroenterol Clin N Am 43 (2014) 257-268

- > Twice normal number of eos/hpf in lamina propria
  - > 100 eos/hpf in right colon
  - > 84 eos/hpf in transverse and descending colon
  - > 64 eos/hpf in rectosigmoid colon
- Altered eos behavior: lamina propria sheets, eosinophilic cryptitis or eosinophilic crypt abscesses
- Epithelial changes: reduced mucin, increased nuclear/cytoplasmic ratio, increased epithelial mitotic activity

Biopsy Evaluation for EGIDs: Colitis

Collins MH. Gastroenterol Clin N Am 43 (2014) 257-268

- Altered eosinophil distribution
  - Surface epithelium: > 3 eos/hpf in right,>4 eos/hpf in transverse/descend, >2 eos/hpf rectosigmoid
  - Crypt epithelium:> 11 eos/hpf in right, > 4 eos/hpf in trans/descend, > 9 in rectosigmoid colon
  - Excess eos in muscularis mucosa or submucosa
  - Concentration of eos in the subepthelial superficial lamina propria instead of deep lamina propria
  - Acute inflammatory cells are not present

Eosinophilic Colitis

Bimodal distribution

- Infancy
  - Often due to food allergy (commonly milk and/or soy)
  - Often responds to elimination diet
  - Excellent prognosis
- Adolescents and young adults
  - No gender prevalence
  - Rarely related to food allergy
  - Often requires steroid treatment
  - Relapse not uncommon

Diagnostic Evaluation for EGIDs

General

- Upper and lower GI endoscopy with biopsies
- Histologic evaluation of multiple biopsy specimens
- CBC with differential, total IgE, ESR, CRP
- Prick skin tests to foods and environmental allergens and IgE (ImmunoCAP FEIA) to foods
- Evaluation for infection (travel history, stool and colonic aspirate analysis)
- Autoantibody evaluation: tissue transglutaminase for celiac disease, antineutrophil cytoplasmic antibodies for vasculitides and IBD, *Saccharomyces cerevisiae* IgG and IgA antibodies for IBD

Diagnostic Evaluation for EGIDs

In association with hypereosinophila

- ECG & Echocardiogram
- Pulmonary function testing
- CT of chest, abdomen and pelvis
- Evaluation and biopsy of other potentially involved tissue
- Bone marrow analysis (cytogenetics and special staining)
- Serum tryptase
- Vitamin B12
- Genetic analysis for FIP1L1-PDGFRA fusion
- T & B cell receptor rearrangement studies

Treatment for EGIDs

- Steroids (systemic/topical)
- Diet
- Aminosalicylic acids
- Immunosuppressives
- Mast cell inhibitors: cromolyn, ketotifen
- Leukotriene receptor antagonists
- Biologics: anti-IL5
- Anti-IgE
- Surgery: sometimes necessary for obstructive presentations