

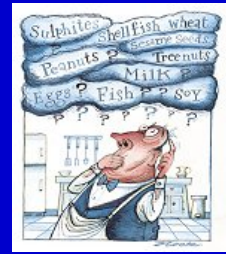
Eosinophilic Gastrointestinal Disorders (EGID)

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Overview

- Background and Definitions
- Epidemiology
- Pathophysiology
- EGIDs/EGEs
 - Definition
 - Subtypes
 - Diagnosis
 - Treatment
- Case Discussions



Definitions

- **Adverse food reaction** – any aberrant reaction after ingestion of a food or food additive
- **Food aversions** – mimic adverse food reactions, but not reproducible

TABLE 45-1 Differential Diagnosis of Adverse Reactions to Foods

Toxic reactions
Toxic reactions (food poisoning, for example, scombroid fish poisoning)
Nontoxic reactions
Intolerances
Carbohydrate malabsorption (e.g., lactase deficiency, sucrase-isomaltase deficiency)
Psychologic reactions (strongly held beliefs)
Immune
IgE mediated
Immediate (gastrointestinal, respiratory, cutaneous, ocular, cardiovascular, anaphylactic)
Immediate and late phase (atopic dermatitis, allergic gastrointestinal disorders)
Non-IgE immune mediated
Gluten-sensitive enteropathy (celiac disease, dermatitis herpetiformis)
Food protein-induced gastrointestinal illnesses
Allergic eosinophilic esophagitis and gastroenteritis
Allergic proctocolitis
Heiner's syndrome (food-induced pulmonary hemosiderosis)

Basic Gut Physiology

- Function of intestinal mucosa
 - Nutritional Uptake
 - Host Defenses
- Cells are in contact with
 - food antigens
 - Innate to foods, altered by preparation, altered by digestive enzymes
 - Swallowed Aeroallergens
 - Microorganisms
 - Normal and pathologic

Basic Gut Physiology

- Juxtaposition of active immunologic responses and large antigen load predisposes the mucosa to hypersensitivity reactions
 - May be explanation for food “intolerances”
 - i.e. symptoms despite negative allergy testing

EGID at its most basic

- Caused by an altered immune response.
 - Frequently associated with other atopic conditions
 - Not surprising, as Eos are found “infiltrating” in other atopic conditions
 - In BAL in asthmatics
 - Nasal secretions in allergic rhinitis
 - Conjunctiva in allergic conjunctivitis
 - Dermis in Atopic Dermatitis

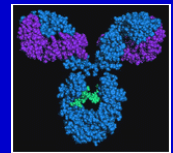
EGE at its most basic

- Eos participate in and propagate the inflammatory process
 - Need to consider parasitic disease, GER, and Celiac Disease in addition to allergy.
 - Most patients, in our experience, have an etiology identified, but this requires thorough GI and Allergy evaluation.

Historical Perspective

- Cello in 1979
 - First described the relationship between EGID (EE) and diet.
 - Noted small amounts of foods that patients were sensitive to caused severe pain
 - Proposed treatment with elemental diets
- Spergel in 2002
 - First identified cell mediated food reaction as a cause of gut eosinophilia
 - Demonstrated symptom & eosinophilia resolution with elimination of specific identified foods

IgE Mediated



- Type I - Immediate Hypersensitivity
 - Failure in oral tolerance leads to excessive food-specific IgE antibodies
 - These bind receptors on many cells (primarily basophils and mast cells)
 - Food allergens (proteins) penetrate mucosal barrier and bind with IgE antibodies
 - Cellular mediator release

Non-IgE Mediated

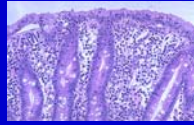
- Type II – Antibody dependent cytotoxicity
 - Specific antibody binds to a surface tissue antigen and induces complement activation
 - Complement → inflammatory mediators → tissue damage
 - Milk-induced thrombocytopenia
 - Food-induced pulmonary hemosiderosis (Heiner syndrome)



Non-IgE Mediated

- Type III – Antigen-antibody complex mediated
 - Has been implicated in food related complaints
 - Can be found in sera of normal patients
 - IgE-food antigen complexes are more commonly found in patients with food hypersensitivity
 - Little support for causing disease

Non-IgE Mediated



- Type IV – Cell-mediated hypersensitivity
 - Implicated in foods with delayed onset of symptoms
 - Likely to contribute to a number of GI disorders
 - Ingestion of sensitizing antigen linked to mucosal lesions and eosinophilia

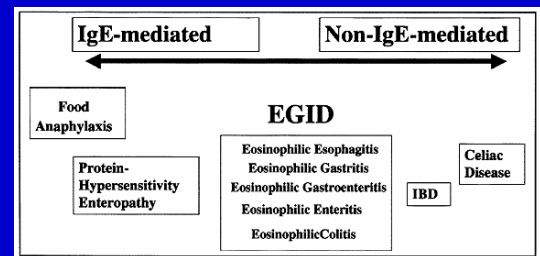
Non-IgE Mediated

- Cutaneous
 - Contact dermatitis
 - Dermatitis herpetiformis
- Gastrointestinal
 - Food protein-induced enterocolitis
 - Food protein-induced proctocolitis
 - Food protein-induced enteropathy syndromes
 - Celiac disease
- Respiratory
 - Food-induced pulmonary hemosiderosis (Heiner syndrome)

Mixed IgE and Cell Mediated

- Cutaneous
 - Atopic dermatitis
- Gastrointestinal
 - Allergic eosinophilic esophagitis
 - Allergic eosinophilic gastroenteritis
- Respiratory
 - Asthma

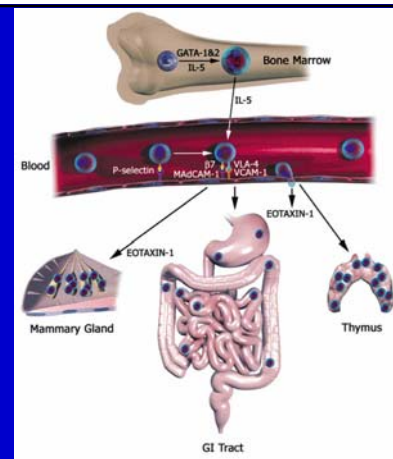
Overview



Overview

- Genetic and environmental etiologies
- ~10% have an immediate family member with an EGID
 - Likely underestimated
- 50-70% are atopic
- Only ~50% have peripheral eosinophilia
- Properties between IgE-mediated and cell-mediated

Eosinophil development and tissue localization



Classification

- Location in GI tract
 - Eosinophilic esophagitis
 - Eosinophilic gastroenteritis
 - Eosinophilic colitis
- Presenting symptoms depend on location of disease and depth of infiltration

Eosinophilic Esophagitis- Historical Perspective

- Esophageal eosinophils originally thought to be a marker for GERD
- 1995 Kelly et al* described esophageal eosinophilia unresponsive to acid blockade that responded to elimination diet
 - Symptomatic improvement within 3 weeks
 - Improvement in esophageal eosinophilia

*Gastroenterology 1995;109:1503-12

Eosinophilic Esophagitis

- Esophagus normally free of eosinophils
- Diseases with esophageal eosinophils
 - EE
 - IBD
 - EGE
 - HES
 - GERD
 - Malignancy
 - Recurrent vomiting
 - Scleroderma
 - Parasitic and fungal infections
 - Allergic vasculitis
 - Celiac

Eosinophilic Esophagitis

- Presentation
 - Vomiting / reflux symptoms
 - Epigastric or chest pain (arching)
 - Dysphagia
 - Food impaction
 - Extra-Gastrointestinal symptoms
- Typically presents in young males with GERD like symptoms, *only partially responsive to anti-reflux medications*
- Associated with both type I & IV food allergy
- Frequently have other atopic disease

Eosinophilic Esophagitis

- Incidence in pediatric population of 1 per 10,000
- Prevalence of 4.3 cases per 10,000 children in 2003

NEJM 351(9):940-41;Aug 2004.

Eosinophilic Esophagitis

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.

Eosinophilic Esophagitis

- Assessment includes
 - GI evaluation
 - Endoscopy & biopsy
 - Allergy evaluation
 - Aeroallergen (prick testing)
 - Food (prick & patch testing)
- Must exclude GERD
- Can be chronic
- If untreated can lead to stricture and esophageal dysfunction



Eosinophilic Esophagitis- A case study

- AN- 15 yr old – had meat impaction at 9 yrs of age.
- Reflux symptoms fairly mild
- Had EGD, esophagitis identified treated with high dose PPI.
- Still had occ. food impactions (severe 1x/mo)
 - Meat caught again 1/06

Case 1 (AN)

- Oculonasal symptoms during the summer
- FHx of atopy
 - Asthma in pGM
 - Allergic rhinitis in Father & pGF

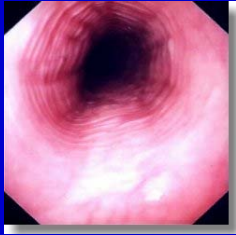
Eosinophilic Esophagitis- A case study

- Described need to have drink of liquid with every bite.
- Heartburn nightly, Tums work well
- Wakes every few days with acid brash.
- Increased heartburn with spicy foods.

Eosinophilic Esophagitis- A case study

- Suspected EE
 - Put on Prilosec 20 mg. PO BID x 6 weeks, then EGD

AN- EGD 3-06



Normal Esophagus



Eosinophilic Esophagitis- A case study

- Biopsies of small bowel and stomach normal
- Distal esophagus 52 Eos/HPF
- Proximal esophagus 180 Eos/HPF

- Started on swallowed fluticasone
- Referred to allergist.

Prick & Patch Test Results (AN)

- Prick test
 - Aeroallergens: positive
 - Grasses, cottonwood, weeds, molds
 - Foods: positive
 - Milk
- Patch test
 - Foods: negative

Treatment (AN)

- Dietary
 - Absolute avoidance of all Milk products
- Flovent 220mcg
 - Puff & swallow 2 puffs BID x 6 weeks
- Outcome
 - Resolution of symptoms

Eosinophilic Esophagitis- A case study

- Presented to ED 11/06 with food impaction after visiting Taco Bell

- Admitted to non-compliance with milk avoidance

AN – EGD 11-06



AN- second EGD 11-06



Eosinophilic Esophagitis- A case study

- Biopsies: “reactive squamous mucosa with features consistent with moderate eosinophilic esophagitis.”
- Completely eliminated dairy, symptoms again totally resolved.
- Resumed fluticasone for only 1 week.

Eosinophilic Gastroenteritis

- Originally described by Kaijser in 1937*
- Tissue eosinophilia in bowel wall
- Gastric antrum and small bowel frequently affected
- 3 categories:
 - Mucosal
 - Muscular
 - Serosal

Arch Klin Chir 1937;188:36-64.

Eosinophilic Gastroenteritis

- Affects all ages
- Slight male predominance
- Mixed IgE and non-IgE
- Increased IL-3, IL-5, and GM-CSF levels
- Increased Th2 cytokines
- 50% atopic or FHx atopy
- 75% blood eosinophilia

Symptoms of EGE

- Abdominal Pain
- Anorexia
- Ascities
- Bloating
- Blood in Stool
- Diarrhea
- Dysphagia
- Edema
- Gastric Ulcer
- Growth Failure
- Hypoalbuminemia
- Malabsorption
- Vomiting
- Weight Loss

Eosinophilic Gastroenteritis

- Mucosal
 - Most common subtype – 25-100%
 - Abd pain, N/V/D, fecal occult blood loss, anemia, protein losing enteropathy
 - DDX includes IBS, dyspepsia, pancreatitis, acute appendicitis, IBD, celiac

Eosinophilic Gastroenteritis

- Muscular
 - 13-70% of subtypes
 - Gastric outlet and intestinal obstruction
 - Colicky abdominal pain
 - Can be confused with pyloric stenosis in infants

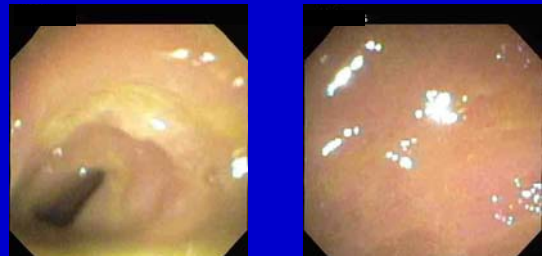
Eosinophilic Gastroenteritis

- Serosal
 - 12- 40% of cases
 - Typically presents with bloating and ascites
 - Higher peripheral eosinophilia
 - Better response to steroids

Case 2 (CG-A)

- 3 m/o male with cystic fibrosis
- Meconium ileus at 21 d/o for which he underwent small bowel resection and double barrel ileostomy
- Diet of Pregestamil & applesauce
- Creon (pancreatic enzyme)
- Re-hospitalized with fever and abdominal pain
- FHx positive for atopy
 - Asthma in mGM
 - Food allergy in mother & mGM
 - Allergic Rhinitis in mother
 - CF in pCousin

Endoscopy & Biopsy (CG-A)



Prick & Patch Testing (CG-A)

- Prick Testing
 - Foods: positive
 - Milk, Beef, Pork
 - Aeroallergens: not done
- Patch Test
 - Food: positive
 - Soy, Rye, Pea, Beef, Peanut

Prick & Patch Testing (CG-A)

- ImmunoCap Assay positive
 - Class 2 pork
- Epicutaneous Testing positive
Creon:
 - Creon-10 emulsified with HSA
 - 1:1000 negative
 - 1:100 negative
 - 1:10 positive
 - 4 controls were negative
- Immunoblot assay positive
 - Positive to pork & creon-10 (50 kD band)

Treatment (CG-A)

- Neocate
 - Some improvement
- Elemental feeds
 - Some improvement
- Intra-stoma beclomethasone
 - Some improvement
- Gastrocrom
 - Some improvement
- Oral prednisone
 - Some benefit
- Removal of pancreatic enzymes
 - Resolution of symptoms
 - Biopsy revealed dramatic reduction in eosinophils
 - Elemental diet with unoffending foods added

Eosinophilic Colitis

- AKA milk-protein colitis
- Most common cause of rectal bleeding in infancy
- Generally presents at 2 - 4 months of age

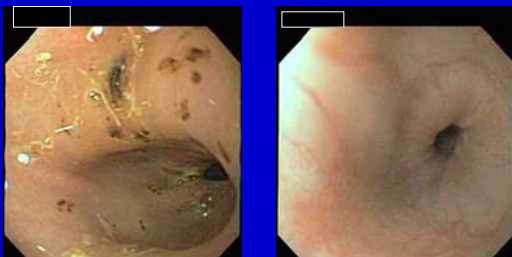
Eosinophilic Colitis

- Typical symptoms include diarrhea, rectal bleeding, and increased mucus production
- Well appearing infants, can be fussy
- Obtain stool culture and C. diff toxin
- Usually due to cow's milk, soy, corn or from dietary proteins found in breast milk

Case 3 (NS)

- 6 w/o infant girl
- 35 week gestation with neonatal course complicated by respiratory distress
- NICU for 5 days, septic w/u negative
- Breast fed with formula supplement
- Bloody stools, abdominal cramping & arching at 4 w/o.
- Formula supplement switched to Nutramigen then Alimentum w/o change
- Mom removed corn, milk, peanut and soy from her diet w/o change
- FHx positive for atopy
 - Food allergy & Allergic Rhinitis in Father

Colonoscopy & Biopsy



Allergy Evaluation (NS)

- Prick testing
 - Food negative
 - Aeroallergens not done
- Patch Testing
 - Food positive
 - Egg, Pork, Peanut

Treatment (NS)

- Dietary
 - Offending foods removed from Mom's diet
 - Egg, Pork, Peanut
 - Breast feeding continued
 - Complete resolution of symptoms within 1 week

Historical Description

Milk-sensitive eosinophilic gastroenteritis in a 10-day-old boy

Abstract Eosinophilic gastroenteropathy in children is a rare, idiopathic disease characterized by eosinophilic infiltration of the gastrointestinal tract. We describe a 10-day-old boy with a specific clinical manifestations (inconsolable crying). Treatment with a semi-elemental diet was successful, suggesting a milk-sensitive enteropathy, although he had been exclusively breast fed.

British Journal of Pediatrics, January 1990

Diagnosis of EGID

- Guided by a good history
- Family and personal history of atopy
- Good dietary history
- Total IgE and peripheral eosinophil count may be helpful
- Specific IgE testing (prick test preferred) and patch testing
- Biopsy
- Elimination diets alone are rarely helpful

Diagnostic Criteria

- Has been proposed, but no consistent lab value or radiographic finding is pathognomonic.
- Diagnosis requires
 - GI Symptoms
 - Eosinophilic Infiltrate of GI tract

Cell Counts From Biopsy

- No standard cell counts exist
- No generally agreed upon pathologic number of Eos in mucosa
 - Eos, however, do not typically occur in groups in the submucosa, muscularis, or serosa

Cell Counts From Biopsy

- EE abnormal-
 - Have used 24 Eos/HPF, now 17.
 - Count not significantly less in lower esophagus
 - Cells deeper than mucosa or in abscesses
- EGE abnormal
 - 24 Eos/HPF in Duodenum
 - 30 Eos/HPF in Cecum
 - Eos that do not decrease in number distally in colon

Cell Counts

- Autopsy study
 - Found essentially no Eos in fundus or antrum of stomach
 - Therefore, presence thought to be pathologic
 - Found up to 30 Eos/HPF in TI and Cecum, not different than Pts with chronic abdominal pain
 - Therefore, counts not thought to be useful in lower GI tract

Lowichik A, Weinberg AG- Mod Pathol 1996; 9-110-4

Specific IgE Testing

- Most published studies focus on eosinophilic esophagitis or the mucosal form of eosinophilic gastroenteritis
- Screen with a standard panel of foods plus targeted testing based on history

The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis*

- Purpose was to identify potential food antigens in eosinophilic esophagitis

*JACI 2002;109:363-8.

Methods

- 26 patients (22 male/4 female)
- Mean age 7 years (range 2-14 years)
- Biopsy confirmed diagnosis of EE
- Underwent skin prick testing and patch testing
- Patients instructed to eliminate positive foods
- Causative foods also implicated by elimination and reintroduction

TABLE II. Skin prick and patch testing

Food	No. of patients*		
	Skin prick tests	Patch tests	Implicated food†
Milk	9 (36%)	6 (24%)	13
Egg	9 (36%)	6 (24%)	12
Soy	2 (8%)	6 (24%)	5
Wheat	3 (12%)	9 (36%)	5
Beef	3 (12%)	6 (24%)	5
Rye	3 (12%)	7 (28%)	5
Peanut	4 (16%)	0 (0%)	3
Chicken	2 (8%)	5 (21%)	3
Corn	2 (8%)	6 (24%)	3
Peas	4 (16%)	2 (8%)	2
Potato	3 (12%)	4 (16%)	2
Rice	2 (8%)	2 (8%)	2

*Numbers of patients found to have positive skin prick test and patch test results to specific foods.

†Foods implicated on dietary challenges.

Results

- Demographics
 - 21/26 had atopic history
 - 14/16 positive to aeroallergens
 - 11 had > 1 atopic disease

Results

- 19 patients with positive prick tests
 - Average 2.7 foods per patient
- 21 patients with positive patch tests
 - Average 2.7 foods per patient
 - 8 control patients negative on patch testing
- Average 3.6 causative foods (combined) identified per patient

Results

- 24 of 26 available for f//u
 - 2 patients lost to f/u
 - 24 with partial or complete resolution
- 6 patients had partial improvement of symptoms
 - 5 were not avoiding positive foods
- 18 were asymptomatic at f/u
- Repeat biopsies done in 24 patients
 - 13 normal
 - 11 significant improvement
 - 55 eos/HPF → 8.4 eos/HPF

Food Patch Test Technique

- Perform on uninvolved skin, usually the back
- 12 mm aluminum cups
 - Finn chambers on Scanpor adhesive tape



Technique

- Spergel's method
 - 1 g dry food with 1 mL saline
 - Soy, milk, egg white, wheat, oats, barley, rye, rice flour, corn meal, potato
 - Single ingredient baby food fruits, vegetables, and meats undiluted
- We use a standard panel of 19 antigens plus any others elicited by history

Technique

- 48-hour occlusion time
- 72-hour reading time



Interpretation

- Spergel's grading scale
 - 1+ positive with erythema, infiltration, and papules, no vesicles
 - 2+ positive with erythema, infiltration, papules, and vesicles
 - 3+ positive with bullous, spreading and ulcerative
- * Trace positive with erythema and induration, no papules or vesicles

Experimental Testing

- Possible to do COLAP
 - Colonoscopic Allergen Provocation
 - Wheal and Flare reaction correlating to mast cell and Eos activation
- Detection of inflammatory mediators in intestinal lavage fluid or stool samples
- Use of Anti-Gliadin IgG as a marker

Treatment: Dietary

- Specific food avoidance
 - Effective for most (approximately 85%)
- Strict elemental diets
 - Reversal of symptoms in ~ 10 days
 - Histological improvement in 4 weeks
- Food reintroduction after 1 year avoidance
 - Single food at a time
 - We recommend a 2 week interval
- Diet Therapy Consult

Treatment: Medications

- Cromolyn
 - Gastrocrom 5 – 10 ml QID
- Montelukast
 - DBPC crossover / n=46 / 6 – 18 y/o / EGE *
 - 62% vs 32%
 - 84% vs 45%
- Corticosteroids
 - EE
 - Flovent 2 puffs BID for 6 weeks
 - EGE
 - Prednisone at 1 mg/kg/day then tapered
 - Beclomethasone (formulated) 1 – 3 mg TID
 - Budesonide (with splenda) 1 respule TID
- Consider other immunosuppressive agents (6-MP, Imuran)

*Friesen CA, et al. J Pediatr Gastroenterol Nutr. 2004 Mar;38(3):343-351

Conclusions

- Eosinophilic disorders of the GI tract becoming increasingly recognized
- The body of literature addressing the etiology and role of food allergy is growing
- Biopsy is the key to confirming the diagnosis
- Allergy testing, both prick and patch guide specific food elimination diets
- Corticosteroids are effective, but relapse is common if the offending food is not removed
- Case reports of other medications that may be beneficial

