ENTEROPATHIES OF INFANCY

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Speaker Disclosure

In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.

Pathophysiology of diarrhea

- **Inadequate absorption of water, due to**:
  - Congenital transport defect
  - Lumenal fermentation of unabsorbed solute
  - Diffuse mucosal injury
- **Acute**
  - Usually infectious, + stool cult, rarely biopsied
- **Chronic**
  - > 2-3 weeks, often associated with FTT
  - may require biopsy, nutritional support, etc.
  - Congenital diarrheas
    - Osmotic - unabsorbed solute
      - disorder of digestion or transport
      - remits with removal of solute or NPO
    - Secretory - diffuse mucosal disease or injury
      - does not remit when NPO

Causes of chronic diarrhea and malabsorption in infancy and childhood

- Congenital transport and enzymatic deficiencies
- Severe (Primary) Enteropathies of Infancy
- Allergic enteropathies
- Metabolic disorders (GSD I, Wolman's, MPS)
- Motility disorders (Hirschsprung disease)
- Infections (bacterial overgrowth, Giardia, HIV)
- Anatomical Disorders (malrotation, short gut, lymphangiectasia)
- Tumors (direct infiltration, secretion of VIP)
- Pancreatic disorders
- Endocrine disorders – hyper/hypothyroidism

Outline of topics covered in this lecture

- Congenital Transport and Enzymatic Deficiencies
- Primary Enteropathies
- Autoimmune Enteropathy
- Allergic/eosinophilic Enteritides

TABLE 1. EVOLVING ETIOLOGIES OF SEVERE PROTRACTED DIARRHEA IN CHILDREN IN ITALY

ETIOLOGY	1977-1993 (*N=38*) *n(%)*	1993-1996 (*N=32*) *n(%)*	1997-2001 (*N=61*) *n(%)*
Enteric infection	18 (48)	4 (12)	2 (3)
Food intolerance	8 (22)	3 (10)	10 (17)
Autoimmune enteropathy	2 (5)	8 (25)	7 (12)
Structural enterocyte defects	2 (5)	7 (22)	16 (26)
Celiac disease	1 (2.5)	0 (0)	0 (0)
Eosinophilic enteropathy	1 (2.5)	1 (3)	0 (0)
Lymphangiectasia	1 (2.5)	1 (3)	2 (3)
Motility disorders	2 (5)	3 (9)	16 (26)
Munchausen syndrome by proxy	0 (0)	0 (0)	1 (15)
Unknown	3 (7.5)	5 (16)	7 (11.5)

From: Guarino A and DeMarco G. Persistent Diarrhea, chapter 10, in Pediatric Gastrointestinal Disease, 4th edition (2004)

Molecular basis of disorders of digestion, absorption and transport

Disease	Gene	Location	Function
Disaccharidase Deficiency			
Congenital lactase deficiency	LCT	2q21	Lactase-phlorizin hydrolase activity
Sucrase-isomaltase deficiency	EC 3.2.1.48	3q25-q26	Isomaltase-sucrase
Maltase-glucoamylase deficiency	MGAM	7q34	Maltase-glucoamylase activity
Ion and Nutrient Transport Defects			
Glucose-galactose malabsorption	SGLT1	22q13.1	Na+/glucose contransporter
Fructose malabsorption	GLUT5	1p36	Fructose transporter
Fanconi-Bickel syndrome	GLUT2	3q26	Basolateral glucose transporter
Cystic fibrosis	CFTR	7q31.2	cAMP-dependent CL- channel
Acrodermatitis enteropathica	SLC39A4	8q24.3	Zn^{2+} transporter
Congenital chloride diarrhea	DRA	7q22-q31.1	CL-/base exchanger
Congenital sodium diarrhea	SPINT2*	19q13.1	Serine-protease inhibitor
Lysinuric protein intolerance	SLC7A7	14q11	Hydrolyzes endo-/exopeptidases Amino acid basolateral transport
Congenital bile acid diarrhea	ABAT	13q3	Ileal Na+/bile salt transporter
Pancreatic Insufficiency			
Enterokinase deficiency	PRSS7	21q21	Proenterokinase
Trypsinogen deficiency	PRSS1	7q35	Trypsinogen synthesis
Pancreatic lipase deficiency	PNLIP	10q26.1	Hydrolyzes triglycerides to fatty acids
Lipid Trafficking			
Abetalipoproteinemia	MTP	4q22	Transfer lipids to apolipoprotein
Hypobetalipoproteinema	APOB	2p24	Apolipoprotein that forms chylomicrons
Chylomicron retention disease	SAR1B	5q31.1	Intracellular chylomicron trafficking

Canani, R.B., et al., *Congenital Diarrheal Disorders:* Journal of Pediatric Gastroenterology & Nutrition, 2010. **50**(4, April 2010).

Primary epithelial defects – gene, location and function

Disease	Gene	Chromosome	Function
Microvillous Inclusion	*MYO5B*	18q21	Distribution of endosomes
Tufting enteropathy	*EpCAM*	2p21	Cell adhesion
Syndromic diarrhea (THE)	*TTC37*	5q14	Thespin; function unknown
Enteroendocrine deficiency	*Neurog 3*	10q21	Enteroendocrine development
IPEX	FOXP3	Xp11.23-q13.3	Scurfin – Treg development
IPEX-like	unknown		
Autoimmune polyglandular syndrome	*AIRE*	21q22	Autoimmune regulator

Intestinal Biopsy Findings in Enteropathies

- **Normal villous morphology**
  - congenital chloride diarrhea
  - carbohydrate malabsorption
  - sucrose isomaltase deficiency
- **Villous atrophy +/- inflammation**
  - Autoimmune enteropathy and IPEX
  - Microvillous inclusion disease
  - Epithelial dysplasia ("tufting")
  - Gluten-sensitive enteropathy
  - Eosinophilic gastroenteritis and dietary protein-induced enteropathy
  - Congenital immunodeficiency disorders
- **Specific or characteristic features**
  - Fat-filled enterocytes (abetalipoproteinemia, chylomicron retention)
  - Infectious agents
  - Absence of plasma cells – immunodeficiency
  - Lymphangiectasia
  - Metabolic storage disorders

Congenital Transport and Enzymatic Deficiencies

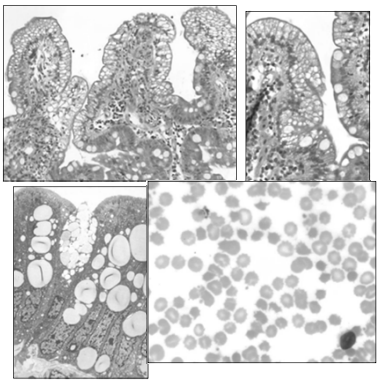
- Normal or slightly abnormal biopsy
  - Carbohydrates
  - Aminoacids
  - Electrolytes and trace metals
  - Vitamins
- Abnormal biopsy
  - Lipids

Lipids

1. Abeta/hypobetalipoproteinemia
2. Chylomicron retention disease

- Fat malabsorption
- Low levels of serum lipids
- Failure to thrive
- Neurologic and visual problems

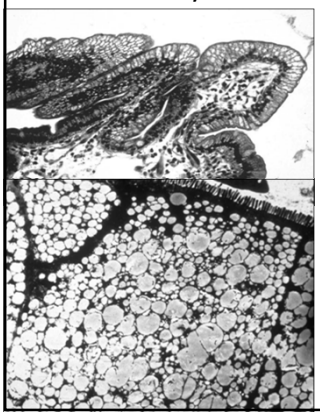
Abetalipoproteinemia



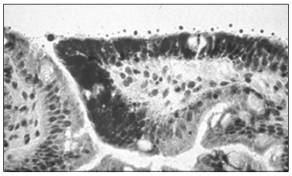
AR
Deficiency of MTTP (Microsomal Triglyceride Transfer Protein)
Chr 4q22
Irregular vacuoles
Non-membrane bound
Absence of apo-B lipoproteins

Acanthocytosis

Chylomicron Retention Disease



AR
SAR1B, chr 5q31
(Sar1-ADP-ribosylation)
Codes for GTPase
Chylomicron trafficking



Primary enteropathies of infancy

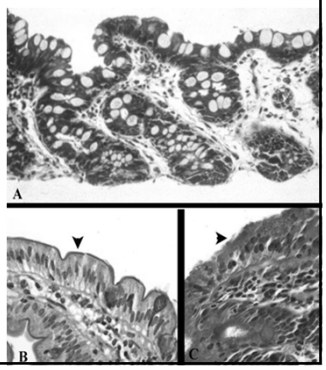
Epithelial defects
- Microvillous inclusion disease
- Tufting enteropathy
- Enteroendocrine cell deficiency

Autoimmune enteropathies

Others

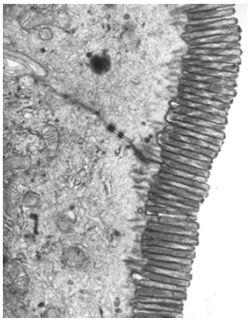
Microvillus Inclusion Disease (MVID), Microvillous Atrophy (MVA)

- Described in 1978 by Davidson et al
- Severe secretory diarrhea during 1st week of life
- Absence of infectious/enzymatic etiology
- Villous atrophy without significant inflammation
- Abnormal mucosal staining by PAS, CD10
- Abnormal mucosal ultrastructure
- *MYO5B* gene; 18q21
  - Encodes myosin Vb, regulates distribution of endosomes

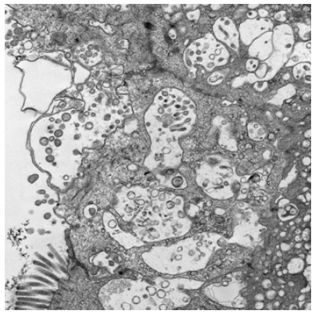


PAS stain

Microvillous inclusion disease

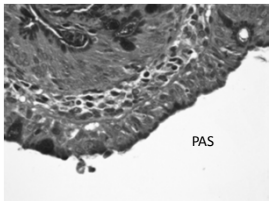


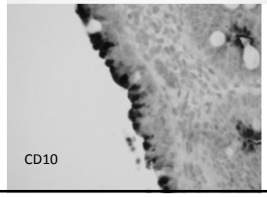
normal

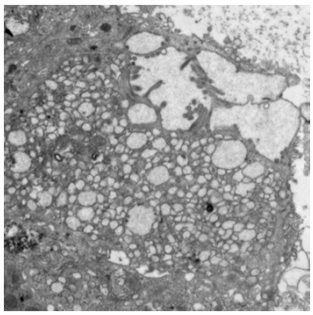


Microvillous Inclusion Disease

Microvillous inclusion disease



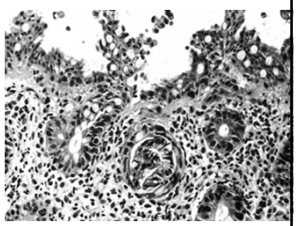




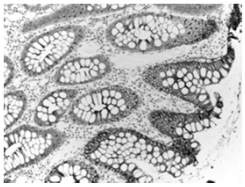
18 day-old boy

"Tufting" Enteropathy

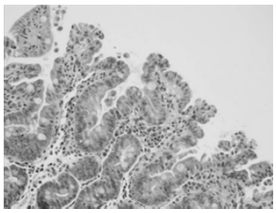
- Severe diarrhea 1st week
- Dysmorphic features in some infants
  - Choanal atresia
  - Esophageal/rectal atresia
- –+/- "tufting" in colon
- AR
- *EpCAM* gene mutations (chr 2p21)
- TPN dependent
- Clusters of cases described in families from Malta and from the Gulf states

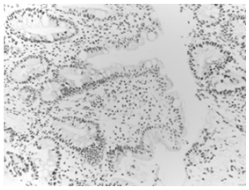


Tufting enteropathy



EpCAm MOC 31 + control

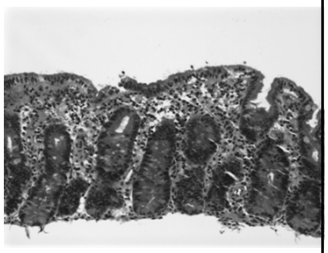




EpCAm MOC 31 - case

Enteroendocrine cell dysgenesis – Neurogenin-3 mutation

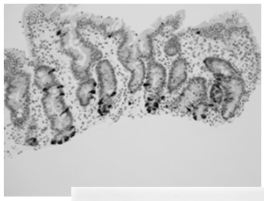
- NEUROG 3 is a protein involved in gut and pancreatic endocrine development
- Pts with Neurogenin 3 mutations present with congenital diarrhea and eventually develop type I diabetes
- TPN-dependent; bowel transplantation



Duodenal biopsy, 5 months

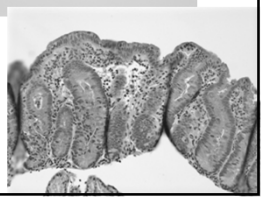
Enteroendocrine cell dysgenesis – Neurogenin-3 mutation

- No enteroendocrine cells per IHC for chromogranin
- Neurogenin-3 -/- mice lack endocrine cells in pancreas and intestine, death from diabetes in the first days of life



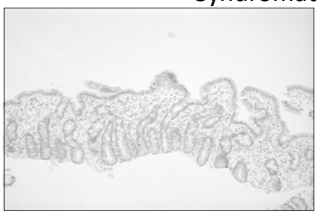
control

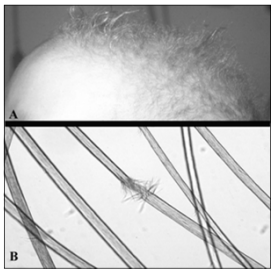
Immunostaining for chromogranin



case

Enteropathy with dysmorphic features "Syndromatic diarrhea"





Chronic diarrhea in first year of life
Facial dysmorphism
Trichorrhexis nodosa
Immunodeficiency
Poor prognosis
Similar patients described as tricho-hepato-enteric syndrome
Gene *TTC37* (5q14) - Thespin

Autoimmune Enteropathy

- Most common severe enteropathy of childhood
- Rarely observed in adults, but may account for some cases of refractory celiac disease
- Heterogenous entity
- Severe early-onset diarrhea, male preponderance
- Concomitant colitis and gastritis present in majority
- Circulating gut-autoantibodies
- Autoimmune phenomena in majority of cases
- Favorable response to immunosuppression (Tacrolimus)
- BMT attempted in some cases

Autoimmune enteropathy - extra-intestinal manifestations

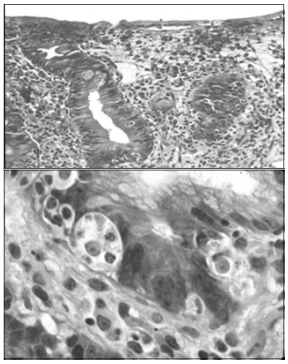
- Insulin-dependent DM
- Nephrotic syndrome, membranous GN with granular IgG deposits or interstitial nephritis
- Thyroid insufficiency
- Acute or chronic hepatitis
- Coombs –positive hemolytic anemia and thrombocytopenia
- Diffuse pulmonary interstitial infiltrates
- Autoantibodies: ASMA, AMA, ANA, anti-parietal cell antibodies

Autoimmune enteropathy (AE) –clinical conditions

- IPEX Immunodysregulation / polyendocrinopathy / enteropathy / X-linked.
  - Mutation in *FOXP3* gene, Xp11.23-q13.3
  - FOXP3 codes for a protein called Scurfin which is predominately expressed in CD4+/CD25+ regulator T-cells
- 50% of patients with clinical features of IPEX have normal *FOXP3* gene – "IPEX-like"
  - A few cases reported with specific CD 25 deficiency

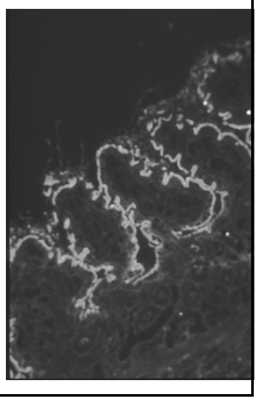
Autoimmune Enteropathy

- Severe villous atrophy
- Marked inflammatory destruction of crypts
- Increased apoptosis
- Loss of Paneth and goblet cells
- Concomitant colitis and gastritis
- Few surface intraepithelial lymphocytes



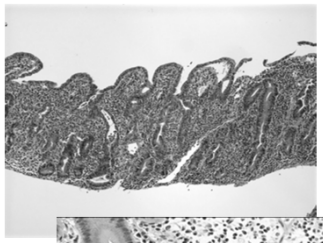
Gut Autoantibodies
Anti-Enterocyte Antibodies

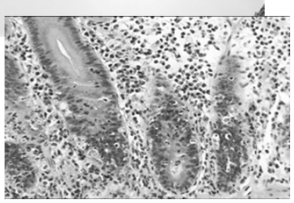
- Linear fluorescence pattern along the apex or brush border of enterocytes
- Also anti-goblet abs
- Predominantly IgG but IgA and IgM have been described



Autoimmune enteropathy in adults

- Protracted diarrhea, weight loss, malnutrition
- Absence of response to gluten-free diet and/or absence of typical celiac antibodies and/or characteristic HLA immunotype
- AEA + variety of autoantibodies
- T-cell rearrangement studies neg
- Good response to immunosuppression

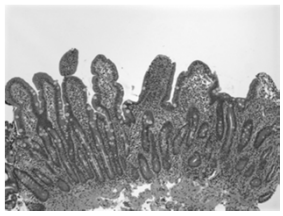




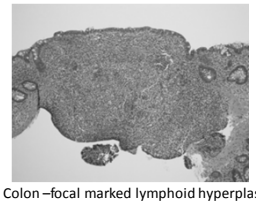
Autoimmune enteropathy - differential diagnosis

- Celiac disease
- Enteritis in congenital immunodeficiencies
- Food allergy
- IBD
- GVHD
- Collagenous or lymphocytic enterocolitis
- Autoimmune polyglandular syndrome

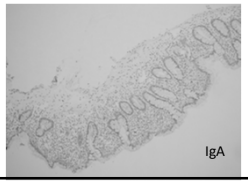
IgA deficiency - 6 yr-old boy with chronic diarrhea and FTT



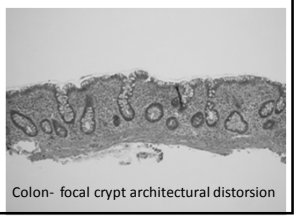
Duodenum – celiac-like



Colon –focal marked lymphoid hyperplasia

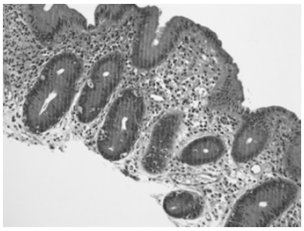


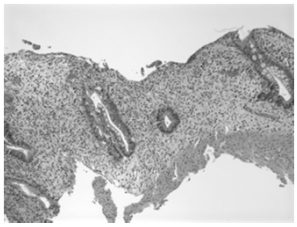
IgA



Colon- focal crypt architectural distorsion

Common Variable Immunodeficiency





Increased basal crypt apoptotic activity, or extensive loss of goblet and Paneth cells GVHD-like or IPEX-like histology

Crohn's-like enteritis, especially in younger age

Differentiating features of severe diarrhea of early infancy

	Microvillus inclusion disease	Tufting enteropathy	Enteroendocrine cell dysgenesis	Syndromic (THE)	Autoimmune enteropathy
Presentation	First 2 weeks	First 2 weeks	First 2 weeks	First months	After 1 month
Gene defect	MYO5b (18q21)	EpCAM (2p21)	NEUROG 3 (10q21.3)	TTC37 (5q14)	FOXP3 (Xp11.23) in IPEX syndrome
Extraintestinal disease	Low GGT cholestasis post bowel transplantation	Dysmorphism keratitis arthritis	Insulin-dependent diabetes	Dysmorphism Trichorrhexis nodosa	Polyendocrinopathy
Anti-enterocyte antibodies	no	no	no	no	yes
Villous atrophy	yes	variable	variable	variable	variable
Surface epithelium	Absent brush border	Tufting and desquamation	Normal	Normal	Normal or atrophic
Inflammation	Minimal	Variable	Variable	Minimal	Increased

Food Allergy

The New Epidemic

- Food hypersensitivity reactions affect up to 8% of children under 3 years of age and approximately 2.5% of the general population
- 3x increase in the prevalence of food allergies over the past 20 years
  - Changes in environment
  - Changes in the processing of foods
  - Alteration of immunologic recognition
  - Use of antibiotics
- *Food intolerance* (non-allergic food hypersensitivities) are adverse responses caused by metabolic or enzymatic disorder (lactose)

Immunopathology of Food Allergic Disorders

- IgE mediated (Immediate hypersensitivity)
  - Oral allergy
  - Urticaria
  - Anaphylaxis
- Cell mediated (delayed onset/chronic)
  - Dietary protein enteropathy/enterocolitis
  - Dietary protein-induced proctocolitis
  - Gluten-sensitive enteropathy
- Mixed IgE and Cell mediated (delayed onset/chronic)
  - Atopic dermatitis
  - Eosinophilic gastrointestinal disease

From Sicherer, S. H. Annu Rev Med 2009. 60:261-77

Eosinophilic Gastroenteropathies

The New Epidemic

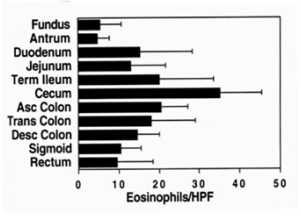
Spectrum of disease or unique diseases

Colon — Esophagus

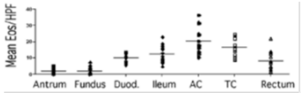
Allergic proctocolitis — Eosinophilic esophagitis

Eosinophilic gastroenteritis

"Normal" Number of Eosinophils



Lowichik and Weinberg *Mod Pathol 1995;9:110-4*



DeBrosse et al. *Pediatr Dev Pathol.* 2006;9:210-8

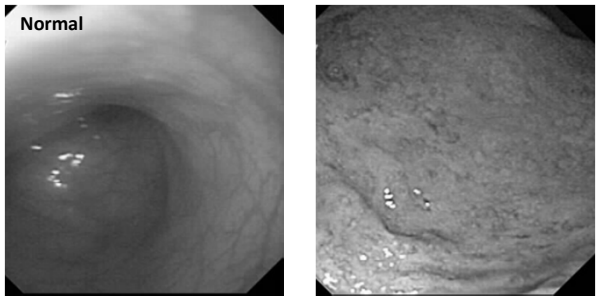
Allergic proctocolitis: key features

- Usually presents by 6 months of life
- Blood streaked, loose stools +/- diarrhea in otherwise well-appearing infants
- Some may present with constipation, mimicking HD
- Usually occurs in breast-fed (50-60%) or cow/soy milk formula-fed infants
- Diagnosis is via clinical history; food prick skin tests negative
- Treatment via protein elimination; resolution of symptoms in 48–72 h
- Tolerance to allergen usually occurs by 1 yr of life

Adapted from Maloney, J. Pediatr Allergy Immunol 2007:18:360-367

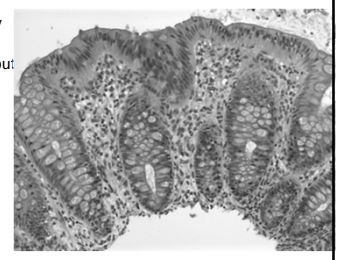
Endoscopy

Colon



Allergic Proctocolitis

Eosinophilic infiltrate, frequently patchy and rather variable in severity.
Neutrophilic cryptitis can also be seen but usually not to the extent seen in infectious colitis.
Chronic mucosal changes are not seen.

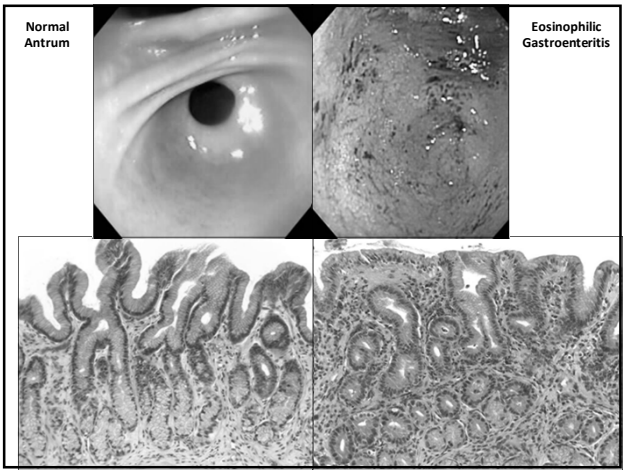


Occasional cases may cause constipation, mimicking Hirschsprung disease clinically and radiographically

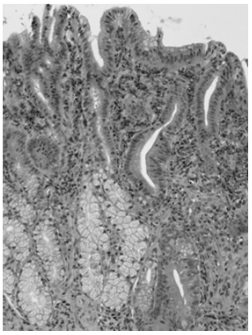
Allergic Eosinophilic Gastroenteritis in children: Key features

- Usually occurs from infancy through adolescence
- Chronic symptoms of poor appetite, poor weight gain or weight loss, emesis, diarrhea, occult blood in stool
- Endoscopy and biopsy helpful in diagnosis with usually marked eosinophilic infiltration of mucosa and submucosa
- > 90% of cases have involvement of gastric antrum
- Approximately, 50% are atopic; 50% have peripheral blood eosinophilia
- Resolution of symptoms with removal of causal food within 6 wk
- Most common foods: cow's milk, egg, soy, cereals, fish
- Excellent response to amino-acid-based formula
- Responsive to steroids
- Typically prolonged; natural history not well understood

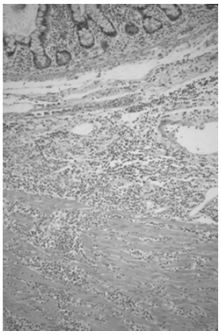
Adapted from Maloney, J. Pediatr Allergy Immunol 2007:18:360-367



Allergic Eosinophilic Gastroenteritis



Mucosal type



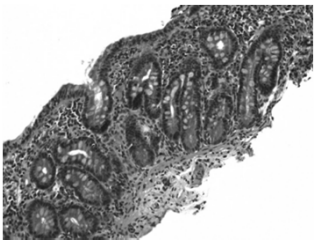
Mural type

Eosinophilia in the GI Tract

- Allergy ≠ Eosinophilia
- Eosinophilia ≠ Allergy

Dietary protein-induced enteropathy/enterocolitis

- Dietary protein-induced enteropathy/enterocolitis
  - Infancy to school age
  - Cow's milk, soy, wheat, rice, chicken and fish
  - Malabsorption and osmotic diarrhea
  - Biopsy : flat villi, +/- increased eosinophils; diff dx: celiac disease

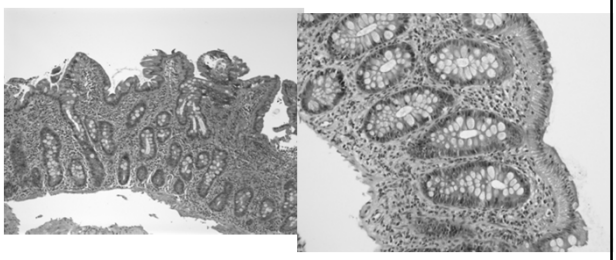


2 month-old with malabsorption; improved on elemental formula

Eosinophilic Gastroenteritis – Differential Diagnosis

- Infections, particularly parasitic
  - Stool ova and parasite study may be diagnostic
- Drug reactions
  - Check drug history – Azathioprine, NSAIDS, tacrolimus
- Crohn's disease
  - May primarily show eosinophilic abscesses
  - Typically more of a focal lesion
- Some primary immunodeficiencies
- Connective tissue disorders
  - Consider lupus, polyarteritis, and Wegeners.
  - Are fibrinoid changes present in vessels?
- Inflammatory fibroid polyps
  - Check configuration of lesion on endoscopy
- Hypereosinophilic syndrome.
  - Are tumorous lesions present, particularly in soft tissue?
- Post-transplant eosinophilic gastroenteritis
  - Check transplant history, immunomodulatory drugs

Post-Liver Transplant Eosinophilic Gastroenteritis



2yr-old girl 18 months post-OLT with weight loss, food refusal, peripheral eosinophilia