APPROACHES TO THE SMALL BOWEL BIOPSY
Basel Seminars in Paediatric Pathology and Genetics

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Approaches to the Small Bowel Biopsy

Outline

• Overview of the intestinal biopsy in paediatrics – indications, normal histology, artifacts

• Histologic patterns of the small bowel biopsy in chronic diarrheal disorders of infancy
  – Preserved villous morphology
  – Villous atrophy
  – Lymphangiectasia
  – Metabolic and infiltrative disorders
# Indications of Esophagogastroduodenoscopy (EGD) in children

**Neonates and infants**
- Vomiting
- Hematemesis, melena
- Apnea
- Failure to thrive
- Chronic diarrhea
- Irritability

**Toddlers**
- Abdominal pain
- Hematemesis, melena
- Vomiting
- Dysphagia, odynophagia
- Foreign body
- Caustic ingestion
- Chronic diarrhea
- Failure to thrive
- Suspected polyp
- Chronic constipation

**Older children and teens**
- Abdominal pain
- Dyspepsia
- Hematemesis, melena
- Weight loss
- Chronic reflux
- Chronic diarrhea
- Iron deficiency anemia
- Caustic ingestion
- Suspected IBD
- Cancer surveillance and polyps

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*From Schaeppi, Mougenot, Belli, *Pediatric Gastrointestinal Disease*, 2004*
During the 20-year interval, the proportion of patients with gastrointestinal bleeding was reduced from 34% to 5%, whereas the proportion of subjects with abdominal pain increased from 23% to 43%.

The rate of complete EGD (biopsies from the esophagus, stomach and duodenum) increased from 18% in 1985 to 95% in 2005.

From Franciosi et al, JPGN, 2010
Systematic evaluation of the intestinal biopsy

- Villous architecture and villous to crypt ratio
  - Normal villous height/crypt depth = 3:1 to 4:1
- Surface epithelium and brush border
- Intraepithelial lymphocytes (IEL) or other inflammatory cells
  - normal IEL’s average 20-25/100 epithelial cells
- Presence of Paneth, goblet and endocrine cells
- Inflammatory population of lamina propria
- Presence of organisms (Giardia)
<table>
<thead>
<tr>
<th>Event</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly oriented section</td>
<td>Apparent lack of villous structures</td>
</tr>
<tr>
<td>Preparation-related changes (mainly applies to colon)</td>
<td>Clumping of inflammatory cells, epithelial degenerative changes, focal neutrophilic infiltrates, superficial hemorrhages</td>
</tr>
<tr>
<td>Insufflation of air at endoscopy</td>
<td>Air spaces in mucosa (pseudolipomatosis)</td>
</tr>
<tr>
<td>Suction trauma</td>
<td>Subepithelial blebs and dilated lymphatic spaces</td>
</tr>
<tr>
<td>Squeeze and crush artifacts</td>
<td>Crushed Brunner’s glands mistaken for pathologic condition</td>
</tr>
<tr>
<td>Inadequate sampling depth</td>
<td>Absence of submucosa</td>
</tr>
<tr>
<td>Lymphoid aggregate</td>
<td>Distorsion of villous architecture</td>
</tr>
</tbody>
</table>
Artifacts in Intestinal Biopsy samples

- Poor orientation
- Air introduced by forceps
- Squeezed glands
- Blunting over lymphoid follicle
Causes of diarrhea and malabsorption in infancy and childhood

Congenital transport and enzymatic disorders
- Glucose-galactose malabsorption
- Disaccharidase deficiency
- Lysinuric protein intolerance
- Abetalipoproteinemia
- Chylomicron retention disease
- Sodium-chloride diarrhea
- Primary bile acid malabsorption

Congenital Defects of Intestinal Epithelial Differentiation
- Microvillus inclusion disease
- Tufting enteropathy
- Enteroendocrine cell dysgenesis

Autoimmune enteropathy

Gluten-sensitive enteropathy (celiac disease)

Post-viral enteropathy and bacterial overgrowth

Bacterial infections (e.g. mycobacterium avium intracellulare)

Parasitic infections (Giardia and Cryptosporidium)

Eosinophilic enteritis

Intestinal lymphangiectasia

Congenital Immunodeficiencies

Cystic Fibrosis

Langerhans cell histiocytosis
Intestinal Biopsy Findings in Enteropathies

- **Normal villous morphology**
  - congenital chloride diarrhea
  - carbohydrate malabsorption
  - sucrose isomaltase deficiency

- **Villous atrophy +/- inflammation**
  - Celiac disease
  - Autoimmune enteropathy and IPEX
  - Microvillous inclusion disease
  - Epithelial dysplasia (“tufting”)
  - Eosinophilic gastroenteritis and dietary protein-induced enteropathy
  - Congenital immunodeficiency disorders

- **Specific or characteristic features**
  - Fat-filled enterocytes (abetalipoproteinemia, chylomicron retention)
  - Infectious agents (i.e. *Giardia*)
  - Absence of plasma cells – immunodeficiency
  - Lymphangiectasia
  - Metabolic disorders
  - Infiltrative disorders

- **Congenital immunodeficiency disorders**
Diarrheal disorders - a pattern-based approach

- Disorders with preserved or minimally abnormal villous morphology
- Severe diarrhea of infancy or early childhood with villous atrophy
- Lymphangiectasia
- Infiltrative disorders
Diarrheal disorders with preserved villous morphology

- Congenital transport and enzymatic disorders
  - Glucose-galactose malabsorption
  - COH intolerance
- Lipid transport disorders (abetalipoproteinemia)
- Some infections (Giardia)
### Molecular basis of congenital diarrhea resulting from defects of digestion, absorption and transport of nutrients

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

*Canani et al JPN 2010; 4:360*
Abetalipoproteinemia

- AR
- Deficiency of Microsomal Triglyceride Transfer Protein, 4q22
- Absence of apo-B lipoproteins
- Fat malabsorption with neurologic and visual symptoms
- Low serum cholesterol and triglycerides
- Irregular non-membrane bound vacuoles on EM (absence of fat in lacteals)

Acanthocytosis
Chylomicron Retention Disease (Anderson disease)

*Secretion Associated, Ras Related GTPase 1B (SAR1B)* gene; 5q31
Encodes protein carrier GTPase involved in transport from ER to Golgi
Neurologic manifestations less severe than abetalipoproteinemia
Key Features of Lipid Transport Disorders

- Infantile diarrhea and fat malabsorption
- Low fasting serum cholesterol and triglycerides
- Deficiencies in fat-soluble vitamins
- Neurologic and visual manifestations
- Acanthocytosis
- Lipid-filled small bowel epithelium with preserved villous architecture
- Caution: overinterpretation of epithelial fat in normal patients after ingestion of lipids
An initially mysterious case with severe CHO intolerance

- 9 month-old boy referred from OSH for early-onset diarrhea, severe CHO intolerance, adrenal and exocrine pancreatic insufficiency
- Parental consanguinity
- Normal or non-specific histological features; PAS and IHC for chromogranin, CD10, MOC 31 normal
Prohormone convertase 1/3 deficiency

- Whole exome sequencing identified homozygosity for mutations in PCSK1
- Proprotein Convertase 1/3 - endoprotease which converts prohormones to active forms

_Bandsma, J Clin Gastro 2013; 47:10_
Preserved villous morphology - Giardia

- Flagellated protozoan
- Occurs worldwide
- Easily overlooked in biopsies
- Immunocompetent and immunocompromised individuals (X-linked agammaglobulinemia, IgA deficiency)
  - Look for plasma cells
  - Immunostain for IgA
Diarrheal disorders with villous atrophy

- Congenital disorders of epithelial differentiation
  - Microvillous inclusion disease
  - Tufting enteropathy
  - Neuroendocrine dysgenesis
    - TPN dependent
    - Small bowel transplantation only cure in many cases
- Autoimmune enteropathies
  - Immunosuppression
- Celiac disease
  - Gluten withdrawal
Evolving Etiologies of Severe Protracted Diarrhea in Children in Italy


<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Enteric infection</td>
<td>18 (48%)</td>
<td>4 (12%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Food intolerance</td>
<td>8 (22%)</td>
<td>3 (10%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Autoimmune enteropathy</td>
<td>2 (5%)</td>
<td>8 (25%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Structural enterocyte defect</td>
<td>2 (5%)</td>
<td>7 (22%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eosinophilic enteropathy</td>
<td>1 (2.5%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lymphangiectasia</td>
<td>1 (2.5%)</td>
<td>1 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Motility disorders</td>
<td>2 (5%)</td>
<td>3 (9%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Munchhausen syndrome</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (15%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (7.5%)</td>
<td>5 (16%)</td>
<td>7 (11.5%)</td>
</tr>
</tbody>
</table>

Microvillus Inclusion Disease (MVID)

Severe secretory diarrhea during 1\textsuperscript{st} week of life
Villous atrophy without significant inflammation
Abnormal mucosal staining by PAS, CD10, villin
Abnormal mucosal ultrastructure
\textit{MYO5B} gene; 18q21
  - Encodes myosin Vb
  - Regulates intracellular trafficking
Intestinal transplantation only cure for \textit{most} patients
20\% -25\% of patients have low GGT cholestasis before or after Itx

PAS, case normal
Microvillous inclusion disease

Proportion of enterocytes with typical inclusions is variable
“Atypical” microvillous inclusion disease

• Some patients have an atypical presentation with later onset of symptoms, milder disease and even spontaneous cures

3 yr-old boy from UAE – symptoms began in first few months
Mutation in the gene coding for Syntaxin 3, chr 11q21 (WES)
MVID is likely genetically and clinically heterogeneous
Congenital Tufting Enteropathy (CTE)

- Diarrhea during first weeks of life
- Higher frequency in families from the Gulf states
- No diagnostic ultrastructural features (abnormal desmosomes)
- Genetically heterogeneous
  - *EpCAM* mutations (2p21)
    - Isolated GI disease
  - *SPINT 2* mutations (19q13)
    - Associated anomalies (keratitis, choanal atresia)
Congenital Tufting Enteropathy

Characteristic features evolve with time

2 months

4 months

6 months
Congenital Tufting Enteropathy – Immunostain for EpCAM

IHC for MOC 31 normal in pts with SPINT 2 mutations
Case Description:
23 day old female infant presented with a history of diarrhea since birth. Pregnancy was complicated by gestational diabetes.
Infectious/immune work-up negative
Diarrhea resolved when enteral feeds were held, but recurred with feedings.
**Hyperglycemia first presented at age 5 1/2 months requiring insulin therapy.**
Patient’s clinical condition deteriorated and she passed away at 11 months of age secondary to TPN liver disease

...initially a mystery....

Duodenal biopsy, 5 months
Chromogranin immunostain

Current case

No enteroendocrine cells per IHC
Neurogenin-3 -/- mice lack endocrine cells in pancreas and intestine, and die in the first days of life
Enteroendocrine cell dysgenesis

*NEUROG 3* mutation (10q21.3)

Congenital diarrhea and eventual type I diabetes

TPN-dependent; bowel transplantation

No immune deficiency or autoimmunity; no autoimmune ab’s

Non-specific changes on H+E

No enteroendocrine cells per IHC for chromogranin

*NEUROG 3* is a protein involved in gut and pancreatic endocrine development

Pts with autoimmune polyglandular syndrome have been described with diarrhea due to transient loss of enteroendocrine cells
Congenital disorders of Immunomodulation – autoimmune enteropathies

- Immune dysfunction, polyendocrinopathy, enteropathy, X-linked (IPEX)
- IPEX-like syndromes
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), autoimmune polyglandular syndrome type I (APS 1)
Autoimmune Enteropathy

• Most common severe enteropathy of infancy
• 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 (thyroiditis, glomerulonephritis, type I diabetes) in majority of cases
• Favorable response to immunosuppression (Tacrolimus)
• BMT attempted in some cases
Autoimmune Enteropathy

- Severe villus atrophy
- Marked inflammatory destruction of crypts
- Concomitant colitis and gastritis
- Few surface intraepithelial lymphocytes
- Marked decrease in Paneth and goblet cells
- Increased apoptosis
Gut Autoantibodies

Anti-Enterocyte Antibodies

- Linear fluorescence pattern along the apex or brush border of enterocytes
- Predominantly IgG but IgA and IgM have been described
- Not described in celiac disease, UC or CD
- Reported in symptomatic patients with AIDS
- 75kDa brush border antigen in IPEX (Kobayashi, Gastroent, 1999)
- Intestinal form of *harmonin*, from family of tight junction proteins in middle ear
- 95kDa identified in some patients – *villin* (Kobayashi, Clin Immunol; 2011)
Autoimmune enteropathy (AE) – associated 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

5 month-old boy with IPEX
Autoimmune enteropathy (AE) – associated clinical conditions

- “IPEX-like” – normal FOXP3 but mutations in
  - IL2RA, CD25, ITCH
  - STAT1, STAT5b
    (signal transducer and activator of transcription)
- Disorders of modulation of inflammation
Autoimmune-polyendocrine-candidiasis ectodermal dystrophy (APECED), Autoimmune polyglandular syndrome, type I (APLS I)

AR
AIRE (Autoimmune Regulator) gene, 21q22
Multiple endocrine manifestations
Autoimmune gastritis with B12 deficiency
Autoimmune hepatitis
Autoimmune enteropathy with loss of enteroendocrine cells

Duodenum, loss of endocrine cells, IHC for chromogranin
Autoimmune enteropathy in adults

- Protracted diarrhea, weight loss, malnutrition
- Absence of response to gluten-free diet or absence of HLA genotypes
- AEA + variety of autoantibodies
- T-cell rearrangement studies neg
- Good response to immunosuppression

Autoimmune enteropathy in adults

18 yr old female with thyroiditis and protein-losing enteropathy

36 year old male with watery diarrhea

Anti-goblet antibodies
### Differentiating features of severe diarrhea of early infancy

<table>
<thead>
<tr>
<th></th>
<th>Microvillous inclusion disease</th>
<th>Tufting enteropathy</th>
<th>Enteroendocrine cell dysgenesis</th>
<th>Autoimmune enteropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td>First 2 weeks</td>
<td>First 2 weeks</td>
<td>First 2 weeks</td>
<td>After 1 month</td>
</tr>
<tr>
<td><strong>Gene defect</strong></td>
<td>MYO5b (18q21) Syn 3 (11q21)</td>
<td>EpCAM (2p21) SynCAM (11q21)</td>
<td>NEUROG 3 (10q21.3)</td>
<td>FOXP3 (Xp11.23) in IPEX syndrome</td>
</tr>
<tr>
<td><strong>Extraintestinal disease</strong></td>
<td>Low GGT cholestasis post bowel transplantation</td>
<td>Dysmorphism; keratitis arthritis</td>
<td>Insulin-dependent diabetes</td>
<td>Polyendocrinopathy</td>
</tr>
<tr>
<td><strong>Anti-enterocyte or anti-goblet antibodies</strong></td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Villous atrophy</strong></td>
<td>yes</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
</tr>
<tr>
<td><strong>Surface epithelium</strong></td>
<td>Absent brush border</td>
<td>Tufting and desquamation</td>
<td>normal</td>
<td>Normal or atrophic</td>
</tr>
<tr>
<td><strong>Lamina propria inflammation</strong></td>
<td>minimal</td>
<td>variable</td>
<td>Minimal</td>
<td>Usually increased</td>
</tr>
</tbody>
</table>
### Criteria for Diagnosis of Celiac Disease

<table>
<thead>
<tr>
<th>Original ESPGAN criteria (1970)</th>
<th>Revised ESPGAN criteria (1990)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3 biopsies</strong></td>
<td><strong>1 biopsy</strong></td>
</tr>
<tr>
<td>• Characteristic morphologic abnormalities in small bowel of patient ingesting gluten.</td>
<td></td>
</tr>
<tr>
<td>• Improvement/normalization of biopsy findings on gluten-free diet.</td>
<td></td>
</tr>
<tr>
<td>• Deterioration of mucosal morphology following gluten challenge.</td>
<td></td>
</tr>
<tr>
<td>• Characteristic morphologic abnormalities in small bowel of patient ingesting gluten + anti-TTG, anti-endomysial (EMA) or anti-gliadin antibodies.</td>
<td></td>
</tr>
<tr>
<td>• Clinical and serologic remission while on gluten-free diet.</td>
<td></td>
</tr>
</tbody>
</table>
Celiac disease (CD)

- Major clinical presentations
  - “Classic” – malabsorption, diarrhea, wasted buttocks.
  - Vomiting, abdominal distension – especially in children < 1 year of age
  - Failure to thrive
  - Iron resistant anemia
  - Rickets
  - Short stature
  - Pubertal delay
  - Personality problems
  - Dermatitis herpetiformis
  - Dental enamel hypoplasia
  - Epilepsy with cerebellar calcifications

- Conditions associated with an increased prevalence of CD
  - Type I Diabetes mellitus
  - Down Syndrome
  - Selective IgA deficiency
  - Juvenile chronic arthritis
  - Autoimmune liver disease
  - Autoimmune thyroiditis
  - Turner Syndrome
  - Williams Syndrome
Celiac Disease

- Increased IEL’s (> 40/100 epithelial cells)
- Villus atrophy
- Crypt hyperplasia
- Enterocyte damage
- Increase in mononuclear cells, eosinophils and variable numbers of neutrophils in the lamina propria
Celiac disease – minor histological changes

3 yo girl + tTG and EMA
Celiac Disease
Histological Changes

- Great variability (essentially normal villi to severe atrophy)
- Entire bowel involved, including stomach and colon
- Damage most severe proximally, in some cases limited to the proximal duodenum (up to 25% of pediatric patients, Bonamico, 2004)
Celiac Disease

Gluten diet

Gluten-free diet
# Celiac disease – differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune enteropathy (IPEX and IPEX-like)</td>
<td>Crypt-destructive inflammatory process with loss of goblet and Paneth cells</td>
</tr>
<tr>
<td></td>
<td>Crypt apoptosis</td>
</tr>
<tr>
<td></td>
<td>No significantly increased intraepithelial lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Circulating anti-enterocyte antibodies</td>
</tr>
<tr>
<td>Non-gluten food protein intolerance</td>
<td>Often associated with increased eosinophils</td>
</tr>
<tr>
<td></td>
<td>Variable villous atrophy</td>
</tr>
<tr>
<td></td>
<td>Positive allergy testing</td>
</tr>
<tr>
<td>Kwashiokor</td>
<td>History of severe protein malnutrition</td>
</tr>
<tr>
<td></td>
<td>No increased IELs</td>
</tr>
<tr>
<td>Primary Immunodeficiency</td>
<td>Absence or paucity of plasma cells in the biopsy</td>
</tr>
<tr>
<td></td>
<td>Nodular lymphoid hyperplasia</td>
</tr>
<tr>
<td>Graft versus host disease</td>
<td>Crypt apoptosis with minimal inflammatory infiltrate</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>Usually in association with active gastritis due to <em>Helicobacter pylori</em> rather than lymphocytic gastritis</td>
</tr>
<tr>
<td></td>
<td>Changes rarely extend beyond the duodenal bulb</td>
</tr>
<tr>
<td>Viral enteritis</td>
<td>Surface epithelial degenerative and regenerative changes</td>
</tr>
<tr>
<td></td>
<td>Some infections may have increased IELs</td>
</tr>
<tr>
<td></td>
<td>Histologic changes rapidly revert as symptoms abate</td>
</tr>
</tbody>
</table>
Celiac disease – differential diagnosis

12 yo boy Kwashiorkor

17 month female collagenous enteritis

7 yo boy IgA deficiency
Duodenal Lymphocytosis with Normal Villi

<table>
<thead>
<tr>
<th></th>
<th>Kakar(^{13}) (n=43)</th>
<th>Mahadeva(^{14}) (n=14)</th>
<th>Hammer(^{16}) (n=100)</th>
<th>Shmidt(^{36}) (n=48)</th>
<th>Aziz(^{15}) (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td>9%</td>
<td>21%</td>
<td>18%</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Tropical sprue</td>
<td>1%</td>
<td>—</td>
<td>1%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>H. pylori gastritis</td>
<td>—</td>
<td>—</td>
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<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
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<td>3%</td>
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<tr>
<td>NSAIDs</td>
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<tr>
<td>IBD</td>
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<tr>
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<tr>
<td>Other</td>
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<td>9%</td>
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</table>

From Lauwers, Modern Path, 2015
Villous atrophy and negative celiac serology

Figure 1. Etiologies of seronegative villous atrophy. AIE, autoimmune enteropathy; CD4 L, CD4+ T-cell lymphoma; CS, collagenous sprue; CVID, common variable immunodeficiency; EATL, enteropathy-associated T-cell lymphoma; GM, gastric metaplasia; MRVA, medication-related villous atrophy; SIBO, small intestinal bacterial overgrowth; SN CD, seronegative celiac disease; TS, tropical sprue; US, unclassified sprue.

From DeGaetani et al, Am J Gastroenterol 2013
Intestinal lymphangiectasia

Key features:
- Protein losing enteropathy with malabsorption, hypoalbuminemia, hypogammaglobulinemia, and lymphopenia with secondary immunodeficiency
- May primarily affect gastrointestinal tract or involve multiple organs
- Secondary lymphangiectasia can result from congenital heart disease, lymphatic obstruction (e.g. malrotation), or vascular malformation
- Blunted villi with dilated lacteals

Pitfalls in diagnosis:
- Limited biopsies may not show features
- Separation and tearing artefacts may resemble the true lesion
- Occasional villi may normally contain dilated lacteals
Intestinal lymphangiectasia

1 yr-old with PLE; dilated mucosal and submucosal lymphatics

16 yr-old with metastatic carcinoma and PLE
Infiltrative disorders of the GI tract that may present with early-onset diarrhea

- Langerhans cell histiocytosis
- Myofibromatosis
- Infantile systemic hyalinosis
Langerhans cell histiocytosis

Cd1a
Myofibromatosis
Infantile systemic hyalinosis

Autosomal recessive
Painful joint contractures
Widespread deposition of glycoprotein-like substance in skin, GI tract, heart, muscle
CMG2 (Capillary morphogenesis protein gene 2) gene mutations on chr. 4q21
Approaches to the small bowel biopsy
Conclusions 1.

• Many disorders causing severe enteropathy have been delineated only in the last few decades and many rare monogenic disorders are being identified by modern genetic techniques (WES)
• Morphologic findings on H&E in many severe enteropathies may be inapparent, subtle or non-specific
• The work-up of intestinal biopsies in severe infantile enteropathies should include use of special stains (PAS), immunohistochemistry (CD10, villin, EpCAM, chromogranin) and EM; serum for indirect IF may be useful to screen for anti-enterocyte antibodies
Approaches to the small bowel biopsy
Conclusions 2.

• Celiac disease may have a variable clinical and histologic presentation
• Typical changes in celiac disease in children may be confined to the proximal duodenum
• True lymphangiectasia may be difficult to distinguish from artifact and needs good clinical-endoscopic correlation
• Infiltrative disorders may cause severe diarrhea in infancy