Pathology Of the GI Tract: Small and Large Intestines: Part 1

Small Bowel: Anatomy

Tennis Court = Absorbive area of the Small Intestine
Mucosa: Villi, lamina propria and muscularis mucosae

Paneth cells

Antimicrobial proteins such as defensins
Duodenum: **Brunner’s glands** (located in the submucosa)

Ileum: Cross section

**Peyer’s patches** (lymphoid aggregates that can be located in lamina propria or submucosa)

Large Intestine Anatomy

- 5 feet
Normal colonic mucosa

Lamina Propria

Goblet cells: numerous compared to small intestine

Muscularis Mucosae

Submucosa

**Present in both small and large intestine**

Meissner’s and Auerbach’s Plexus

General Organization of the Gastrointestinal Tract

GANGLION CELLS

Meissner’s Plexus

Auerbach’s Plexus

NERVES

Meissner’s Plexus

Auerbach’s Plexus

Submucosa

Ganglion cells

Muscularis propria
Congenital Anomalies

1. Gastroschisis / Omphalocele
2. Intussusception / Volvulus
3. Necrotizing Enterocolitis
4. Meckel’s Diverticulum
5. Congenital Aganglionic Megacolon aka Hirschsprung’s Disease

Gastroschisis

- Small (generally < 5 cm) defect involving all layers of the abdominal wall
- Leading to evisceration of bowel loops and other structures
- Distinguished from an omphalocele by the absence of a sac covering the eviscerated contents

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Omphalocele

- Abdominal wall defect characterized by incomplete closure of the abdominal musculature and viscera herniate into a membranous sac (formed by amnion and peritoneum)
Meckel Diverticulum

Definition:
- Failed involution of the vitelline duct (duct that connects the lumen of developing gut to the yolk sac) leading to a blind outpouching
- True diverticulum
- 2 types of ectopic tissue can be present (gastric and pancreatic)
- If present, gastric tissue can secrete acid leading to peptic ulceration

Clinical
- Major complications (pain with inflammation; hemorrhage with ulcer)

Disease of 2's
- 2% of population (mostly asymptomatic)
- 2:1 Male:Female ratio
- 2 inches in length
- 2 feet from ileocecal valve
- 2 years of age (most often symptomatic by age 2)

Question
- What is the difference between a true diverticulum (as seen in Meckel’s diverticulum) versus a false diverticulum (as seen in diverticulosis)?

Answer
- True diverticulum: involves all 3 layers of intestinal wall
  - Mucosa, submucosa, and muscularis propria
- False diverticulum: only the mucosa/submucosa outpouch
**Hirschsprung Disease (Congenital Aganglionic Megacolon)**

| Definition: | Premature arrest or death of neural crest cells migrating from cecum to rectum<br>RET proto-oncogene mutation: Present in majority of familial cases and 15% of sporadic cases |
| Clinical: | M:F 1:5000 live births<br>Rectum always involved<br>Symptoms: Failure to pass meconium, obstruction/constipation<br>Pass Fluid/electrolyte disturbances, enterocolitis, perforation, peritonitis<br>Congenital Megacolon: Proximal segment dilatation that can rupture |
| Associations: | Down Syndrome (10%)<br>Serious neurologic abnormalities (5%) |
| Histopathology: | Complete lack of ganglion cells in both Meissner’s and Myenteric (aka Auerbach’s) plexuses |

**Histology Images:**
- A: Dilated proximal segment with normal neural plexus<br>Dilated aganglionic segment with narrowing
- Normal<br>Hirschsprung’s

**Normal:**
- Ganglion cells<br>Submucosa

**Hirschsprung’s:**
- No Ganglion cells present
Surgery: Resect Aganglionic Colon

Before Surgery: The diseased section is the part of the intestine that doesn't work.

Step 1: The doctor removes the diseased section.

Step 2: The healthy section is attached to the rectum or anus.

Nectrotizing Enterocolitis

Definition: Acute necrotizing inflammation of small and/or large intestines

Clinical:
- Premature infants
- MCC, intestinal perforation in neonates
- Bloody stools, circulatory collapse, abdominal distention
- Associated with high prematurity mortality

Etiology:
- Pathogenesis uncertain (associated with prematurity, enteral feeding, infection)

Gross examination:
- Typically involves terminal ileum, cecum, and right colon
- Congested to gangrenous intestine
Case

- Infant born at term. No significant passage of meconium is noted. Three days after birth, the infant vomits all feedings. On exam, abdomen is distended and bowel sounds are reduced. A x-ray shows marked colonic dilatation above a narrow segment of the sigmoid region. A biopsy shows an absence of ganglion cells in the muscle wall and submucosa. Which of the following is most likely to produce these changes?

A. Trisomy 21  
B. Volvulus  
C. Hirschsprung disease  
D. Intussusception  
E. Colonic atresia

Malabsorption Overview – Full Lecture by Dr. Palmer

**Etiologies**

- Celiac Disease
- Pancreatic insufficiency
- Disaccharidase Deficiency
- Abetalipoproteinemia

**Symptoms**

- Chronic diarrhea, weight loss, abdominal pain

**Nutritional deficiencies**

- Pyridoxine, folate, vit b12 (anemia)
- Vitamin K (bleeding)
- Calcium, Magnesium, Vitamin D (osteopenia and tetany)
- Vitamin A and Vitamin D (peripheral neuropathy)

Celiac Disease

**Definition**

- Immune-mediated enteropathy triggered by the ingestion of gluten-containing foods (wheat, rye, barley) in genetically predisposed individuals

**Gluten**

- Major storage protein of wheat and similar grains
- The alcohol soluble fraction (gliadin) largely responsible for disease

**Clinical**

- Most common 30-50 years
- Symptoms: Diarrhea, bloating, fatigue, anemia (often asymptomatic)

**HLA**

- HLA-DQ2 or HLA-DQ8 (class II MHC)

**Other important associations**

- Dermatitis Herpetiformis (skin blistering disease)
- Other autoimmune diseases: DM type 1, Sjogren, thyroiditis

**Pathogenesis:**

<table>
<thead>
<tr>
<th>Complex</th>
<th>Gliadin</th>
<th>IL-15 expression by epithelial cells</th>
<th>Proliferation of CD8+ T-lymphocytes kill enterocytes</th>
<th>Epithelial damage may contribute to gliadin entry into cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the cell: Gliadin deamidated by tissue transglutaminase</td>
<td>Presented to CD4+ T-cells</td>
<td>Antibody production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overview – Full Lecture by Dr. Palmer**

**Etiologies**

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- Vitamin A and Vitamin D (peripheral neuropathy)
Pathogenesis

Histopathology
- Increased intraepithelial lymphocytes
- Blunting of villi

Testing
- IgA antibodies to tissue transglutaminase (most sensitive; *In patients with IgA deficiency, IgG anti-tissue transglutaminase may be present
- IgA anti-endomysial (specific, but less sensitive)
- Anti-gliadin antibodies
- Absence of HLA-DQ2 and DQ8 useful for negative predictive value, but not helpful in confirming diagnosis

Risks
- Enteropathy associated T-cell lymphoma
- Small intestinal adenocarcinoma

Treatment
- Gluten free diet

Celiac Disease

Celiac Disease: Endoscopy

Normal Endoscopy

Celiac endoscopic photo

Atrophic mucosa

Plattned folds
Villous blunting / atrophy

Increased intraepithelial lymphocytes

Immunohistochemical stain for CD8 lymphocytes (brown) show a marked increase in intra-epithelial lymphocytes
Tropical Sprue

Epidemiology
- Tropical
- Estimated 150 million children worldwide

Etiology
- Possible infectious etiology suggested

Clinical
- Chronic bouts of diarrhea
  - In children, nutritional deficiencies can lead to poor physical development and uncorrectable cognitive deficits

Note
- Tends to involve distal small bowel. This may explain malabsorption of vitamin B12 and folate that can lead to megaloblastic anemia.

Histology
- Similar to celiac sprue

Pseudomembranous Colitis (aka Antibiotic associated Colitis)

Clinical
- Symptoms: Abdominal pain, fever, watery diarrhea
  - MAC follows a course of broad spectrum antibiotics (almost any antibiotic can be responsible, third generation cephalosporins implicated most often)
  - Predisposing factor: Immunosuppression

Pathogenesis
- Disruption of normal colonic microbiota by antibiotics leads to Clostridium difficile overgrowth
- Toxins (Toxins A and B) released by C. difficile cause ribosylation of small GTPases (such as Rho) leading to cytoskeleton disruption, tight junction barrier loss, cytokine release, and apoptosis.

Testing
- Detection of C. difficile toxin (not culture)

Pathology
- Colonic mucosa covered by a yellow/green false (pseudo-) membrane (composed of mucus and neutrophils)

Pseudomembranous Colitis
Pseudomembrane (mucous and neutrophils)

Neutrophils: "volcanic eruption" from crypts

Clinical - Rare multisystem chronic disease
- Gram + rod shaped actinomycete: Tropheryma whipplei
- Triad: Diarrhea, weight loss, arthralgia
- Extra-intestinal: Arthritis, lymphadenopathy, neurologic, cardiac, pulmonary disease

Pathogenesis - Macrophages (filled with organisms) accumulate in lamina propria of small intestine and lymph nodes → lymphatic obstruction
- Malabsorptive diarrhea due to impaired lymphatic transport

Histopathology - Distended foamy macrophages filled with organisms (PAS+, diastase resistant material represents lysosomes filled with bacteria)

Whipple disease
Whipple Disease: Electron Microscopy

Foamy macrophages (comprise the large pale staining areas)

PAS+, diastase resistant organisms

Whipple disease

Foamy macrophages (comprise the large pale staining areas)
PAS+, diastase resistant organisms

Inflammatory Bowel Disease

- Crohn’s Disease
- Ulcerative Colitis
Inflammatory Bowel Disease: Crohn's Disease and Ulcerative Colitis

Pathogenesis

- Complex pathogenesis that is incompletely understood.
- Factors include: Alterations in host interactions with intestinal microbiota, altered composition of the gut microbiome, intestinal epithelial dysfunction, and aberrant mucosal immune responses.

### Crohn's Disease

**Location**
- Upper GI tract involvement (Segmental Disease / "Skip lesions")

**Symptoms**
- +/- Bloody Diarrhea

**Gross morphology**
- Variable rectal involvement

**Microscopic**
- Architectural Distortion
- Crypt abscesses / Cryptitis
- Transmural lymphoid aggregates
- Granulomas

**Complications**
- Fissures, sinuses, fistulous tracts
- Colon Adenocarcinoma

**Extra-intestinal manifestations**
- Pyoderma gangrenosum
- Erythema nodosum

### Ulcerative Colitis

**Location**
- Colon involved only
- Diffuse, continuous disease

**Symptoms**
- Bloody diarrhea

**Gross morphology**
- Rectum involved

**Microscopic**
- Architectural Distortion
- Crypt abscesses / Cryptitis
- No granulomas

**Complications**
- No fissures
- Toxic Megacolon
- Colon Adenocarcinoma

**Extra-intestinal manifestations**
- Primary sclerosing cholangitis (p-ANCA)
**Ulcerative Colitis**

- Distal Rectum
- Ascending Colon

**Pseudopolyp (seen in Ulcerative Colitis)**

**Crypt Architectural Distortion**
Crypt abscess (colonic gland filled with neutrophils)

Cryptitis (neutrophils within epithelium of a colonic gland)

*No granulomas seen in Ulcerative Colitis (granulomas are composed of macrophages forming a nodule)*

Ulcerative Colitis

Cryptitis (high power)

Neutrophil within the epithelium of a colonic gland

Crypt Abscess (high power)

Collection of neutrophils (abscess) in lumen of colonic gland
Crohn’s disease

Mucosa showing longitudinal deep ulcers. The mucosa shows a ‘cobblestone’ appearance.

Note the segmental (patchy) nature of the disease process (in contrast to the diffuse continuous involvement seen in Ulcerative Colitis).

Crohn’s Disease: Cut section of colon

Transmural inflammation (involving all layers of the bowel; corresponds to fistula grossly)

Non-caseating granuloma

Crypt abscess with cryptitis

Low power

High power

High power
**Crohn's: creeping fat**

Normal location of fat along the mesenteric area. In this area, the serosa adjacent to the mesentery does not show creeping fat.

*Creeping fat*: the mesenteric fat is seen extending around the serosal surface. The exact pathogenesis of this phenomenon is unclear. Some hypothesize that it may be a reaction to inflammation or that it may serve a protective role in the background of mucosal injury.

- Transmural inflammation
- Diffuse/continuous disease
- Rectum always involved
- Fissures and fistulas
- Can occur in any portion of GI tract
- Creeping fat
- Granulomas
- Cancer
- Pseudopolyp
- Primary Sclerosing Cholangitis

**Quiz:**

Crohn's disease, Ulcerative Colitis, or both?

- Transmural inflammation: Crohn's
- Diffuse/continuous disease: Ulcerative Colitis
- Rectum always involved: Crohn's
- Fissures and fistulas: Crohn's
- Can occur in any portion of GI tract: Crohn's
- Creeping fat: Crohn's
- Granulomas: Crohn's
- Cancer: Both (more common in Ulcerative Colitis)
- Pseudopolyp: Ulcerative Colitis
- Primary Sclerosing Cholangitis: Both (more common in Ulcerative Colitis)
Question - USMLE

- What is frequency of the basal electric rhythm of the duodenum and ileum respectively?
  - A. Duodenum? 12 waves/minute or 8-9 waves/minute?
  - B. Ileum? 12 waves/minute or 8-9 waves/minute?

Answer

- A. Duodenum: 12 waves/minute
- B. Ileum: 8-9 waves/minute
Question - USMLE

- Where is Iron absorbed in the small bowel?
- Where is vitamin B12 absorbed in the small bowel?
- Why is intrinsic factor important?

Answer

- Where is Iron absorbed in the small bowel?
  - Answer: Duodenum (Iron is absorbed as Fe2+)
- Where is vitamin B12 absorbed in small bowel?
  - Answer: Ileum
- Why is intrinsic factor important?
  - Intrinsic factor is needed for B12 absorption