**Diverticular Disease**

- **Definition**: Acquired herniation of mucosa and submucosa
  - False diverticula
  - Diverticulitis – when a diverticula becomes inflamed usually due to obstruction with stool/mucous leading to bacterial overgrowth/infection

- **Clinical**
  - Western pop over 60; prevalence: 50%
  - Associated with low-fiber diet
  - Sx: Left lower quadrant pain, fever (diverticulitis), bleeding (brisk lower GI bleeding that stops spontaneously)

- **Location**: Most common in left colon; particularly sigmoid colon

- **Complications**: Perforation, peritonitis, fistula

- **Treatment**: Antibiotics (mainstay)
  - Surgical intervention if perforation, abscess formation, bleeding

---

**Pathology Of the GI Tract: Small and Large Intestines: Part 2**

- **Diverticula** (outpouching of the bowel)

---

**Image**

- **Low Power**
  - Diverticula
  - Figure 3-4A
Diverticulitis (with perforation and surrounding abscess formation) MEDIUM POWER Dense area of neutrophilic inflammation (abscess formation) and perforation

Notes
- Weakness of defect of abdominal wall that allows for a serosal-lined outpouching of peritoneum
- Most common cause of intestinal obstruction worldwide; 3rd most common in the US
- Incarceration: Loop of intestine becomes trapped within the hernia sac
- Strangulation: Bowel compressed, twisted at the mouth of hernia, compromising blood supply - infarction

Hernias

Notes
- Fibrous bridges or band-like portions of scar tissue between loops of intestine
- Abnormal adhesion of intestinal loops
- May result in obstruction

Adhesions

Notes
- Fibrous bridges or band-like portions of scar tissue between loops of intestine
- Abnormal adhesion of intestinal loops
- May result in obstruction
Intussusception

Notes
- In-folding or telescoping of one segment of bowel into the adjacent distal segment
- Infants/children: spontaneous and reversible, often idiopathic
- Adults: usually tumor is a lead point

Intussusception

Definition
- Obstruction due to rotation or twisting of a loop of bowel around its mesenteric base of attachment
- Luminal and vascular compromise (lead to infarction)
- Sigmoid colon - most common site (cecum next)

Volvulus

Definition
- Abnormal gas pattern
- Bowel twisted

Volvulus
**Ischemic Bowel Disease**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Bowel hemorrhage/necrosis secondary to hypoxic injury and/or reperfusion injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>&gt; Patients &gt; 70 years most common &lt;br&gt; - Sudden severe abdominal pain and bloody diarrhea &lt;br&gt; - More severe injury can lead to shock, sepsis, death</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Initial hypoxic injury &lt;br&gt; - Reperfusion injury (time when greatest damage occurs)</td>
</tr>
<tr>
<td>Pathology</td>
<td>Mucosal hemorrhage to transmural bowel wall necrosis</td>
</tr>
</tbody>
</table>

**Etiology: Acute arterial occlusion**
- Atherosclerosis
- Aortic aneurysm
- Hypercoagulable states
- Oral contraceptive use
- Embolization of cardiac vegetations or aortic atheromas

**Etiology: Intestinal hypoperfusion**
- Cardiac failure
- Shock, dehydration
- Vasconstrictive drugs

**Etiology: Rare causes**
- Systemic vasculitis
- Mesenteric venous thrombosis

---

**Splenic flexure (watershed area): prone to infarction**

Area commonly affected by ischemic colitis

- Superior mesenteric artery
- Inferior mesenteric artery

Diffuse mucosal hemorrhage

Dark areas represent necrosis (after formalin fixation)
Dark red secondary to hemorrhage, edema in wall. Can result in coagulative necrosis and perforation.

Ischemic injury

Mucosal necrosis (pink areas)

Hemorrhage

Notes - 5% of the population
- Dilated veins of hemorrhoidal plexus
- Predispositions: Straining at defection (~constipation), venous stasis of pregnancy, portal hypertension
- Symptoms: Rectal bleeding and pain

Hemorrhoids and Anal Varices

External Hemorrhoids
Internal vs External Hemorrhoids

**Internal**
- Above pectinate line
- Visceral innervation (not painful)
- Arterial supply: Superior rectal artery (branch of IMA)
- Venous drainage: Superior rectal vein → Inferior mesenteric vein → Portal system
- Lymphatic drainage: Internal iliac lymph nodes

**External**
- Below pectinate line
- Somatic innervation (painful; inferior rectal branch of pudendal nerve)
- Arterial supply: Inferior rectal artery (branch of internal pudendal artery)
- Venous drainage: Inferior rectal vein → Internal pudendal vein → Common iliac vein → IVC → Internal iliac vein → Portal system
- Lymphatic drainage: Superficial inguinal lymph nodes

---

Benign Intestinal Polyps Overview

- Inflammatory
- Juvenile
- Hamartomatous (Peutz Jeghers Syndrome)
- Hyperplastic

---

Inflammatory Polyps

<table>
<thead>
<tr>
<th>Notes</th>
<th>AKA: Solitary Rectal Ulcer syndrome (Rectal prolapse syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenesis</td>
<td>Impaired relaxation of the anorectal sphincter leads to sharp angle at anterior rectal shelf → abrasion/inflammation → Chronic injury and healing of the mucosa</td>
</tr>
</tbody>
</table>

May present as either as:

- Polypoid lesion
- Ulceration
Inflammatory Polyps

- Lamina propria: fibrosis and inflammation
- Glandular epithelial hyperplasia

**Definition**
- Focal malformations of mucosal epithelium and lamina propria
- Considered hamartomatous polyps
- Hamartoma definition: benign tissue arranged in a disorganized fashion; consists of normal tissue elements that would be normally located in that anatomic location

**Sporadic**
- Children younger than age 5 in the rectum
- No malignant potential

**Syndromic Association**
- Juvenile polyposis (AD, gene mutation SMAD4 (most common) or BMPR1A)
- Risk: Gastric, small and large intestinal adenocarcinoma, pancreatic adenocarcinoma

**Juvenile Polyps**

- Round, smooth polyp with erythematous cap (erosion)
- Dilated glands
- Expanded stroma with mixed inflammation

**Definition**
- Focal malformations of mucosal epithelium and lamina propria
  - Considered hamartomatous polyps
  - Hamartoma definition: benign tissue arranged in a disorganized fashion; consists of normal tissue elements that would be normally located in that anatomic location

**Sporadic**
- Children younger than age 5 in the rectum
  - No malignant potential

**Syndromic Association**
- Juvenile polyposis (AD, gene mutation SMAD4 (most common) or BMPR1A)
  - Risk: Gastric, small and large intestinal adenocarcinoma, pancreatic adenocarcinoma
Notes:

- Autosomal dominant
- Large polyp with arborizing (tree-like) projections with smooth muscle present at the mucosal surface
- Polyps themselves do NOT have malignant potential
- Germline heterozygous loss of function mutations in LKB1/STK11 gene (tumor suppressor)

Clinical:

- Hamartomatous polyposis (small intestine most common; anywhere in GI tract)
- Melanotic mucosal and cutaneous pigmentation

Increased cancer risk

Other malignancies: pancreas, breast, lung, ovary, uterus, testicles and colon

---

Hamartomatous Polyp seen in Peutz-Jeghers Syndrome

- Arborizing smooth muscle core
- Overlying mucosa maintains normal architecture

---

Hyperplastic Polyps

Notes:

- Benign non-neoplastic polyp
- Common
- Asymptomatic
- Endoscopically similar to adenomas

Pathology:

- Majority are < 0.5 mm (small); most common in left side of colon
- Proliferation of mature goblet cells
**Benign Intestinal Polyps: Summary**

<table>
<thead>
<tr>
<th>Type</th>
<th>Inflammatory</th>
<th>Juvenile (a type of hamartomatous polyp)</th>
<th>Peutz Jeghers Syndrome (hamartomatous)</th>
<th>Hyperplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Notes</strong></td>
<td>Secondary to chronic injury</td>
<td>Gynogenetic (children) or syndromic</td>
<td>Mutation/estimated or somatic mutation</td>
<td>Left side of colon</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Rectum (anterior wall)</td>
<td>Rectum</td>
<td>Small intestine (most common)</td>
<td>Left side of colon</td>
</tr>
<tr>
<td><strong>Gross</strong></td>
<td>Polypoid lesion, ulceration</td>
<td>Pedunculated smooth surfaced</td>
<td>Pedunculated, large</td>
<td>Small (&lt;0.5 mm)</td>
</tr>
<tr>
<td><strong>Microscopic</strong></td>
<td>Epithelial hyperplasia, lamina propria fibrosis</td>
<td>Hamartomatous (tissue arranged in a disorganized fashion)</td>
<td>Arborizing smooth muscle core</td>
<td>Glands with serrated surface (histologic differential a sessile serrated adenoma) - Goblet cell proliferation</td>
</tr>
</tbody>
</table>

---

**Neoplastic Polyps Overview**

<table>
<thead>
<tr>
<th>Type</th>
<th>Tubular/Tubulovillous/Villous Adenoma</th>
<th>Sessile Serrated Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Cancer</td>
<td>Size</td>
<td>Presence of high grade dysplasia</td>
</tr>
</tbody>
</table>
Notes: Neoplastic polyps that are precursors to the majority of colorectal adenocarcinoma. Majority do not progress to adenocarcinoma. Classified as tubular, tubulovillous, and villous adenomas based on histologic architecture.

Tubular, Tubulovillous, Villous Adenomas

In this example, the pedunculated adenoma shows a smooth surface. Here, the adenoma has a velvety surface.

'Tubular' adenoma (composed entirely of tubular glands)

'Villous' adenoma (composed of finger-like 'villous' projections)

Normal Adenomatous

Epithelium composed of cigar/pencil shaped, elongated dark (hyperchromatic) nuclei
Progression from Low Grade Dysplasia to Invasive Carcinoma

- Elongated cells that do not reach the surface
- Rounded atypical cells extend to the surface
- Invasive carcinoma arising on the background of high grade dysplasia

Low Grade Dysplasia  High Grade Dysplasia  Invasive carcinoma

Invasive carcinoma arising on the background of high grade dysplasia

Notes - Most common on right side colon
- Histologically lack the typical features of dysplasia

Etiology - DNA mismatch repair
- Other: Braf mutation, CpG island methylation

Sessile Serrated Adenoma

Notes - Precursors to adenocarcinoma
- Majority do not progress to adenocarcinoma
- DNA mismatch repair
- Be aware that it is not the only pathogenetic mechanism

Location - Anywhere in colon (can occur in small intestine also)
- Right side of colon (most common)

Gross - Pedunculated or sessile
- Sessile (flat)
- Size > 1 cm (larger than hyperplastic polyps)

Microscopic - Classified by architecture as tubular, tubulo-villous, or villous
- Cytologic dysplasia: Glands with elongated, hyperchromatic nuclei
- Serrated glands with a flat crypt base
- Lack cytologic dysplasia

Neoplastic Intestinal Polyps: Summary

<table>
<thead>
<tr>
<th>Tubular, Tubulo-villous, Villous Adenoma</th>
<th>Sessile Serrated Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes</td>
<td>DNA mismatch repair</td>
</tr>
<tr>
<td>Location</td>
<td>Anywhere in colon (can occur in small intestine also)</td>
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<td></td>
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Intestinal Polyps: Quiz

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Juvenile</th>
<th>Peutz Jeghers Syndrome (hamartomatous)</th>
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<td>Etiology?</td>
<td>Secondary to chronic injury</td>
<td>Hamartomatous</td>
<td>Hamartomatous (tumor suppressor)</td>
<td>Hamartomatous</td>
</tr>
<tr>
<td>Location?</td>
<td>Right side of colon (base of polyp)</td>
<td>Small intestine</td>
<td>Right side of colon</td>
<td>Right side of colon</td>
</tr>
<tr>
<td>Mutation?</td>
<td>APC gene on Ch 5q21</td>
<td>STK11 gene</td>
<td>STK11 gene</td>
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</tr>
<tr>
<td>Location (most common)?</td>
<td>Right side of colon</td>
<td>Small intestine</td>
<td>Right side of colon</td>
<td>Right side of colon</td>
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<tr>
<td>Histology of glands?</td>
<td>Cytologic dysplasia</td>
<td>Arborizing smooth muscle core</td>
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<td>Pathogenesis?</td>
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Intestinal Polyps: Answers

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</tr>
</tbody>
</table>

Familial Adenomatous Polyposis: Syndrome

Mutation -Autosomal dominant
-APC gene on Ch 5q21

Clinical -Patients with 100-thousands polyps (minimum 100 polyps)
-100% of patients develop colorectal adenocarcinoma (often before 30 years)
-Adenomas can develop anywhere in GI tract

Treatment -Prophylactic colectomy
-Colectomy prevents cancer of colon, but patients may develop adenomas at other sites (Ampulla of Vater, stomach)
Numerous polyps throughout the colon (>100 polyps)

Familial Adenomatous Polyposis

Normally, APC is a negative regulator of B-catenin. It binds B-catenin and promotes its degradation.

With APC mutation, APC cannot bind B-catenin. B-catenin accumulates and translocates to the nucleus where it promotes gene transcription (and consequently cellular proliferation).
Adenoma-carcinoma sequence
APC/B-catenin pathway

Gardner's Syndrome - Autosomal dominant
- Polyps similar to FAP
- Osteomas of the mandible, skull & long bones, epidermal cysts, desmoid tumors (soft tissue tumors), thyroid tumors and dental abnormalities

Turcots Syndrome - Intestinal adenomas
- Tumors of the CNS
- 2/3 have APC mutations and develop medulloblastomas
- 1/3 have other DNA repair mutations and develop glioblastomas

Familial Adenomatous Polyposis: Variants

Hereditary nonpolyposis colorectal cancer (HNPCC) also known as Lynch Syndrome
Microsatellites - Repetitive DNA with certain motifs being repeated that are located throughout the genome. Example: CACACA (dinucleotide microsatellite).

Notes - When mutations in microsatellites occur in coding or promoter regions, uncontrolled growth can result.

Mismatch Repair pathway of colon carcinogenesis

APC/WNT pathway - Familial Adenomatous polyposis (70%) - Sporadic colon cancer (80%)

Mismatch repair - Hereditary nonpolyposis colorectal cancer - Sessile Serrated adenomas - 10-15% of sporadic colon cancer - <10% of FAP

<table>
<thead>
<tr>
<th>APC/WNT pathway</th>
<th>Familial Adenomatous polyposis (FAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic colon cancer</td>
<td>Sessile Serrated adenomas</td>
</tr>
</tbody>
</table>

### Table 11-18 Common Patterns of Sporadic and Familial Colorectal Neoplasia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Molecular Status</th>
<th>Target Genes</th>
<th>Transmission</th>
<th>Prognostic Value</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis (70%)</td>
<td>APC/WNT inactiv.</td>
<td>APC, SMAD2, SMAD4</td>
<td>Loss of function</td>
<td>Increased risk of cancer</td>
<td>Increased risk of cancer</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (80%)</td>
<td>SMAD4 inactiv.</td>
<td>APC, SMAD2, SMAD4</td>
<td>Loss of function</td>
<td>Increased risk of cancer</td>
<td>Increased risk of cancer</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>DNA mismatch repair</td>
<td>APC, SMAD2, SMAD4</td>
<td>Loss of function</td>
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<td>Loss of function</td>
<td>Increased risk of cancer</td>
<td>Increased risk of cancer</td>
</tr>
<tr>
<td>Sporadic colon cancer (10%)</td>
<td>DNA mismatch repair</td>
<td>APC, SMAD2, SMAD4</td>
<td>Loss of function</td>
<td>Increased risk of cancer</td>
<td>Increased risk of cancer</td>
</tr>
</tbody>
</table>
Colon Adenocarcinoma Overview

Epidemiology
- 140,000 new cases/year in the U.S.
- 50,000 deaths/year in the U.S.
- Accounts for 10% of all cancer related deaths worldwide, and 15% in the US
- Peak incidence: 60-79 years (>20% before 50)

Etiological factors
- Low content of unabsorbable vegetable fiber
- High content of refined carbohydrates
- Decreased intake of protective micronutrients

Colon Adenocarcinoma Pathogenesis

Pathogenesis
Combination of molecular events is heterogeneous and includes genetic and epigenetic abnormalities.

Genetic Events
1. APC/β-catenin pathway
2. Microsatellite instability pathway

Epigenetic Events
Most common is methylation-induced gene silencing which may enhance progression along either pathway.

Colon adenocarcinoma: large irregular, exophytic mass
Colon Adenocarcinoma

- 5 year survival rate in the United States is 65%, and ranges from 40-90% depending on stage.

Colon Cancer Staging

<table>
<thead>
<tr>
<th>T1</th>
<th>Invasion into the submucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Invasion into the muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Invasion into the subserosal tissues</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion into visceral peritoneum, other organs, or perforation</td>
</tr>
</tbody>
</table>

Two most important prognostic factors

- Depth of invasion
- Presence/absence of lymph node metastasis
Invasive colon adenocarcinoma invading into the muscularis propria

Submucosa: contains lymphatics through which the tumor can metastasize

Histology: Colon Adenocarcinoma

Colon Adenocarcinoma with invasion into the muscularis propria

Lymphatic invasion
Invasion of nerves
Spread to Lymph node
Notes - Often asymptomatic for a long period of time as the lumen is wide in the right colon
Symptoms:
- Possible iron deficiency anemia due to surface ulceration and resulting blood loss

Right Sided Colon Adenocarcinoma

Notes - Left colon lumen is narrower and as a result the tumors are more common sympotmatic when compared to Right sided colon cancer
Symptoms:
- Change in bowel habits or obstruction
- Blood in stool

Left Sided Colon Adenocarcinoma

Sigmoid, rectum and Anus Adenocarcinoma
Appendicitis

| Symptoms            | - Acute  
|                    | - Nausea/vomiting with periumbilical pain that localizes to the RLQ  
| Etiology            | - Obstruction that leads to impaired blood flow and bacterial contamination  
| Pathology           | - Transmural and luminal acute inflammation  

Normal appendix  

Acute Appendicitis

- Enlarged, inflamed appendix with serosal exudate
Acute Appendicitis

Surface mucosa

Transmural inflammation (involves all layers of the appendix from mucosa to muscularis propria)

Muscularis propria

Notes - Well-differentiated neuroendocrine neoplasms
- Most common tumor of the appendix
- Usually incidentally discovered
- Most common in young adults

Pathology - Most often located in the tip of the appendix
- < 1 cm

Prognosis - Excellent (Metastasis very rare and usually with tumors >2cm)

Appendix: Carcinoid Tumor

Tumor cells (monomorphic with classic ‘salt and pepper’ chromatin)
### Mucinous Appendiceal Neoplasms

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocele</td>
<td>General term for a dilated appendix filled with mucin. May represent a mucinous cystadenoma or mucinous cystadenocarcinoma</td>
</tr>
<tr>
<td>Mucinous Cystadenoma</td>
<td>Proliferation of benign neoplastic cells with dilatation by mucinous material</td>
</tr>
<tr>
<td>Mucinous Cystadenocarcinoma</td>
<td>Neoplastic cells invade through the appendiceal wall</td>
</tr>
</tbody>
</table>

### Peritoneum

<table>
<thead>
<tr>
<th>Definition</th>
<th>Lining composed of mesothelial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral peritoneum</td>
<td>Peritoneum covering organs</td>
</tr>
<tr>
<td>Parietal peritoneum</td>
<td>Peritoneum covering the abdominal wall</td>
</tr>
</tbody>
</table>
Peritoneum

Flat lining composed of mesothelial cells

Smooth muscle

Inflammation of Peritoneum

Various etiologies
- Sterile peritonitis
  - Due to bile or pancreatic juices
- Surgical procedures
- Endometriosis
- Rupture of GI tract
  - Ruptured appendix, diverticulitis, salpingitis (fallopian tube)

Peritonitis

Pseudomyxoma peritonei

Definition
- Presence of abundant mucinous material on peritoneal surfaces
- Not a complete diagnosis in itself (it is a clinical descriptive term)

Various Etiologies
- Appendiceal mucinous neoplasms (most common)
- Other carcinomas: colorectal, pancreatic, urinary, gallbladder, stomach

Note
- If a patient has pseudomyxoma peritonei, the entire appendix needs to be histologically evaluated
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon adenocarcinoma located in which side of the colon is more commonly symptomatic?</td>
<td>Left side of colon</td>
</tr>
<tr>
<td>Iron deficiency anemia can be first sign of colon adenocarcinoma typically located where?</td>
<td>Right side of colon</td>
</tr>
<tr>
<td>What are the most common genetic pathways implicated in the pathogenesis of colon adenocarcinoma?</td>
<td>APC/beta-catenin pathway, Microsatellite instability pathway</td>
</tr>
<tr>
<td>What is the most common epigenetic event in the pathogenesis of colon adenocarcinoma?</td>
<td>Methylation induced gene silencing</td>
</tr>
<tr>
<td>What are the 2 most important prognostic factors for colon adenocarcinoma?</td>
<td>Depth of invasion, Presence of lymph node metastases</td>
</tr>
<tr>
<td>What is the etiology of acute appendicitis?</td>
<td>Obstruction of the appendix</td>
</tr>
<tr>
<td>What is the most common tumor of the appendix?</td>
<td>Well-differentiated neuroendocrine tumor (aka Carcinoid tumor)</td>
</tr>
<tr>
<td>What type of peritoneum (visceral or parietal) covers the abdominal organs?</td>
<td>Visceral</td>
</tr>
<tr>
<td>What tumors are most often implicated in causing pseudomyxoma peritonei?</td>
<td>Appendiceal mucinous neoplasms</td>
</tr>
</tbody>
</table>

**Pseudomyxoma Peritonei**

- Pools of mucin
- Tumor