<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathology</th>
<th>Clinical</th>
<th>Diagnostics/TXT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td><strong>Erythema</strong> -/+ complications = ulcers or strictures &lt;br&gt;-epithelial inflammation and necrosis &lt;br&gt;-epithelial edema = <strong>spongiosis</strong> &lt;br&gt;-epithelial basal zone hyperplasia</td>
<td>• <strong>Sx:</strong> Substernal chest pain (specific not sensitive), Regurgitation, belching or dysphagia; Sometimes silent &lt;br&gt;<strong>Atypical presentation:</strong> hoarseness, asthma, chronic cough, sinusitis, bronchitis, bronchiectasis, erosion of dental enamel &lt;br&gt;<strong>Complications:</strong> Stricture (dysphagia – for solids only), erosive esophagitis, laryngeal cancer, ulceration (odynophagia or GI bleeding)</td>
<td>• Empiric txt &lt;br&gt;• Endoscopy – good for looking for complications &lt;br&gt;• Barium swallow not useful – good for dysphagia &lt;br&gt;• Manometry &lt;br&gt;• BS or EGD for alarm symptoms &lt;br&gt;• 24 hour pH probe <strong>best test</strong> for GERD &lt;br&gt;• TXT: stop all vices &lt;br&gt;• bed up 6 inches &lt;br&gt;• Antacids and H2 blockers &lt;br&gt;• Proton pump inhibitors – heals esophagitis &lt;br&gt;• Surgery = Nissen &lt;br&gt;<strong>ALARM SYMPTOMS:</strong> weight-loss, dysphagia, anemia, early satiety, bleeding</td>
</tr>
<tr>
<td>CMV Esophagitis</td>
<td>-<strong>gross:</strong> superficial ulcers &lt;br&gt;-infects endothelial cells and fibroblasts &lt;br&gt;-Replicated viral material collects in infected cells: nuclear and cyto-megaly and nuclear inclusions</td>
<td>• <strong>dysphagia,</strong> <strong>odynophagia</strong> &lt;br&gt;• Viral infection that leads to large shallow ulcers</td>
<td>• Seen in immuno-compromised – HIV population &lt;br&gt;• <strong>See punched out ulcers of esophagus</strong> &lt;br&gt;• TXT: ganciclovir, cidofovir, foscarnet</td>
</tr>
<tr>
<td>Herpetic Esophagitis</td>
<td>-<strong>gross – superficial ulcers and plaques</strong> &lt;br&gt;-infects epithelial cells &lt;br&gt;-replicated viral material collects in nucleus; nuclear inclusions look like ground glass; pushes chromatin to edge = margination; some cells are multi-nucleated with nuclear molding</td>
<td>• <strong>dysphagia,</strong> <strong>odynophagia</strong> &lt;br&gt;• Punctate small ulcerations in esophagus &lt;br&gt;• Viral infection → leads to ulceration</td>
<td>• Seen in immuno-compromised persons – HIV population</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>Slide: 5</td>
<td>-white plaques with hyperemic borders -same as general pathology of esophagitis - Budding yeast and pseudohyphae readily visible on PAS-stained section -Pseudomembranes composed of: pseudohyphae, inflam. cells (PMN), squames, necrotic debris -Mucosal lesions</td>
<td>• dysphagia, odynophagia • Most common in esophagus • Most frequent fungal infection of GI tract</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Pill Esophagitis</td>
<td>Slide: 6</td>
<td>-localized inflammations, +/- ulcerations -Characteristic round ulcer in the shape of a pill</td>
<td>• Odynophagia • Ingested pill that lodges in esophagus, usually in LES region (secondary to esophageal dysmotility or cardiac enlargement) • Allergic drug reaction</td>
</tr>
<tr>
<td>Corrosive esophagitis</td>
<td></td>
<td>-Alkali $\rightarrow$ liquefactive necrosis with inflammation and saponification; thrombosis adds ischemic necrosis -Acids $\rightarrow$ coagulative necrosis $\rightarrow$ protective eschar -Circumferential burn $\rightarrow$ Chronic stricture</td>
<td>• Ingestion of strong alkaline agents (lye) or strong acids (sulfuric or HCl – cleaning products) • Alkaline solutions worse than $&gt;$ acids $&gt;$ alkaline solids • Adults: suicide; Children: accidental ingestion</td>
</tr>
<tr>
<td>Barrett’s Esophagus Slide: 7, 8</td>
<td>-<strong>Metaplastic change of mucosa from squamous to specialized columnar with goblet cells</strong> -Can have <strong>Barrett dysplasia</strong> – high N/C ratio, pleomorphic, hyperchromatic, prominent nucleoli, increase in mitotic figures</td>
<td>-Premalignant condition for adenoCA of esophagus – higher risk if BE is dysplastic • Risk of cancer is low • Less symptomatic than GERD • Disease of white males over 40</td>
<td>-<strong>No treatment</strong> for regression • Periodic EDG for adenocarcinoma screening</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Squamous Cell CA of esophagus Slide: 10</td>
<td>-Can occur in any region of esophagus - same patterns as adeno -nests/cords of atypical squamous epithelial cells in desmoplastic stroma</td>
<td><strong>Dysphagia</strong> • Sometimes weight loss = mets • Associated with smoking, drinking and lower SES, toxic ingestions • Fisulas w/trachea can form</td>
<td>-<strong>Endoscopy</strong> • EUS – to detect invasion • Barium Swallow • Resection of tumor • Rad and chemotherapeutic; laser therapy • Poor prognosis</td>
</tr>
<tr>
<td>Adeno CA of esophagus Slide: 11</td>
<td>-distal esophagus -patterns = fungating, ulcerating, infiltrating -invasive atypical glands</td>
<td><strong>Dysphagia</strong> • Sometimes weight loss = mets; sometimes presents with GI bleeding, SOB, chest pain • In Caucasians with reflux • Rate increasing</td>
<td>-<strong>Endoscopy</strong> • EUS • Barium Swallow – to rule out motility disorder • Resection of tumor • Rad and chemotherapeutic • Stents to open esophagus • Poor prognosis</td>
</tr>
<tr>
<td>Benign esophageal tumors</td>
<td>Gross: See Slide 12</td>
<td>Usually occur in the submucosa • Leiomyoma • Lipoma</td>
<td><strong>Endoscopic ultrasound</strong> to see in which layer tumor is located</td>
</tr>
</tbody>
</table>
| Acute Gastritis Slide: 13 | -acute inflammation of mucosa (PMNs) +/- necrosis (erosion) → punctate erosions w/hemorrhages -+/- hemorrhage -petechial hemorrhage -superficial mucosal erosions with a thin layer of exuded serum and necrotic debris and sparse infiltrate of neutrophils in the underlying lamina propria | -**Etiology:** drugs (NSAIDS, chemo), complication of other disease, stress (trauma, burns, etc) • Direct injury to gastric mucosa and/or interference with normal protective mechanisms • Common cause of GI bleeds | -**H pylori** also associated with acute gastritis → antibiotics
### Chronic Gastritis

**Slide: 14**

- **Gross** – see thin wall
  - gastric gland and mucosal atrophy; intestinal metaplasia
  - mucosa with few short glands and chronic inflammation
- In autoimmune form see gastrin cell hyperplasia
- Protease from *H. pylori* → chronic indirect epithelial damage and inflammation; ammonia and exotoxins lead to direct epithelial damage

- **Etiology:** *H. pylori*; autoimmune (+/- pernicious anemia)
  - risk factors: SES, siblings infected
- Chronic inflammatory cells → epithelial cell necrosis → gland atrophy → intestinal metaplasia (+/- dysplasia → +/- cancer)
- In autoimmune – autoAB to parietal cells and/or intrinsic factor

- **Urease testing, breath testing, histology**
- **Antibiotics**

### Peptic Ulcer Disease

**Slide: 15**

- **Chronic cell injury from** *H. pylori* → necrosis → peptic ulcer disease
- **Gross** – punched out cookie-cutter appearance
- **Seen in** proximal duodenum and lesser curvature and antrum of stomach
- **When healed** see starfish pattern
- **See 4 characteristic zones:**
  1. Fibropurulent exudate
  2. Necrotic tissue
  3. Granulation tissue
  4. Fibrotic tissue
- Erosion in the mucosal surface, penetrating through the muscularis or deeper

- **Abdominal pain:** burning, epigastric, post-prandial and nocturnal, relieved with food or medication
- Chronic ulcers in GI tract regions exposed to pepsin-acid luminal contents
  - **Etiology:** *H pylori, NSAIDS*, increased gastric acid
  - **Complications:** Hemorrhage, Perforation, Obstruction
  - H pylori → urease, inflammatory response, increased gastrin secretion

- **H Pylori Diagnosis:** Histology, C13 UBT, C14 UBT, Serology, Rapid Urease = CLO, Culture
- With Eradication of h pylori get low recurrence of ulcers
- Ulcer Diagnosis: Endoscopy, Radiography
- Text: medical therapy, endoscopy for acute bleeding, surgery for refractory bleeding and complications
- Antibiotics, Acid inhibitors, reduce NSAID use, Smoking cessation

### Zollinger-Ellison Syndrome

**Slide: 16**

- **Parietal Cell hyperplasia**
- **Non-Beta Islet cell tumors of the pancreas**

- Often from pancreatic gastrinoma causing increased HCl secretion → severe peptic ulceration
- Sporadic vs. MEN-1 gene
- **Sx:** GERD, PUD, diarrhea

- **DX:** Basal Acid Output levels, Fasting gastrin levels; Secretin stimulation test
- To find gastrinoma: CT, Endoscopic ultrasound, Nuclear scan
- TXT: proton pump inhibitors, surgery, chemo (not too effective)
<table>
<thead>
<tr>
<th><strong>Gastric Lymphomas</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Slide: 17</td>
</tr>
<tr>
<td>- Chronic cell injury from <em>H. pylori</em> → chronic inflammation → gastric lymphomas</td>
</tr>
<tr>
<td>- Small malignant lymphocytes infiltrate mucosa and destroy gastric glands (lymphoid-epitheliod lesion)</td>
</tr>
<tr>
<td>- SX: dyspepsia, nausea, satiety</td>
</tr>
<tr>
<td>- B-cell non-Hodgkin’s lymphoma that involves stomach</td>
</tr>
<tr>
<td>- MALToma and <em>H. pylori</em> (stomach does not usually have MALT tissue) → antigen driven B-cell proliferation</td>
</tr>
<tr>
<td>- Ig monoclonality</td>
</tr>
<tr>
<td>- Some regress with <em>H. pylori</em> eradication</td>
</tr>
<tr>
<td>- Indolent growth → good 5 yr survival with removal **</td>
</tr>
<tr>
<td>- Concept = antibiotics for cancer</td>
</tr>
<tr>
<td>- Diagnosis = EGD</td>
</tr>
<tr>
<td>- May digress to high-grade lymphoma → poorer survival</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>GI Stromal tumor (GIST)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Slide: 18</td>
</tr>
<tr>
<td>- Presumed to arise from pluripotent mesenchymal cell → undergoes differentiation similar to interstitial cells of Cajal (spindle cell that acts as pacemaker for peristalsis) based on immunophenotype</td>
</tr>
<tr>
<td>- Overexpress Kit protein b/c of c-kit mutation (a TK) → increase of mitotic and anti-apoptotic events</td>
</tr>
<tr>
<td>- Can occur anywhere; are well circumscribed; cut surface appears tan with patchy areas of necrosis and hemorrhage</td>
</tr>
<tr>
<td>- Spindle or epitheloid cell patterns</td>
</tr>
<tr>
<td>- Mesenchymal neoplasms of GI tract that are not clearly benign</td>
</tr>
<tr>
<td>- Tumor recurrence common even when completely excised</td>
</tr>
<tr>
<td>- Even small on can have mets</td>
</tr>
<tr>
<td>- Many GISTs respond, at least partially, to Gleevec (STI-571) an inhibitor of kit-associated tyrosine kinase.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gastric adenocarcinoma</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Slide 19, 20</td>
</tr>
<tr>
<td>- Gross – heaped up margins, irregular sides, shaggy base</td>
</tr>
<tr>
<td>- Pre-existing disease → intestinal metaplasia → dysplasia → cancer</td>
</tr>
<tr>
<td>- Early (only in mucosa or submucosa) v. advanced (spread into muscularis propria or serosa)</td>
</tr>
<tr>
<td>- <strong>Intestinal type:</strong> with intestinal metaplasia → intestinal glands +/- mucin growth in expanding front</td>
</tr>
<tr>
<td>- <strong>Diffuse type:</strong> arise from gastric mucous</td>
</tr>
<tr>
<td>- Insidious: dyspepsia, nausea, satiety; Advanced: emesis, bleeding, mass.</td>
</tr>
<tr>
<td>- Etiology: diet, genetics, pre-existing dx: <em>H. pylori</em>, chronic atrophic gastritis, pernicious anemia</td>
</tr>
<tr>
<td>- Lesser curvature and antro-pyloric regions more common sites</td>
</tr>
<tr>
<td>- 2 nd leading cause of cancer worldwide.</td>
</tr>
<tr>
<td>- Diagnosis: endoscopy</td>
</tr>
<tr>
<td>- Staging: CT, EUS, surgery</td>
</tr>
<tr>
<td>- Once cancer is present in muscularis, survival rates go way down</td>
</tr>
<tr>
<td>- Survival Factors: tumor depth; mid-body &gt; distal &gt; proximal; intestinal &gt; diffuse; well &gt; poorly differentiated</td>
</tr>
<tr>
<td>- TXT: Surgery for cure and palliation; possibly screening EGD or <em>H. pylori</em></td>
</tr>
</tbody>
</table>
| **Colorectal Carcinoma** | cells, poorly discohesive (signet ring cells) +/- desmoplasia; Growth: infiltrative spread of single cells, cell clusters or sheets; Mucicarimine stain of signet cells | • Interaction between genetics (IL-1B), diet and infection -- Bug interacts with promoter region to cause chronic inflammation | eradication and diet interventions  
• Diet: nitrates vs. anti-oxidants |
|---|---|---|---|
| **Achalasia** | -Circumferential (napkin ring) tumor  
- Fibromuscular hyperplasia → kinking bowel wall  
- Endometriosis, carcinoid | • Can present with pain, distension, nausea vomiting or if colonic – constipation, obstipation | Abdominal films, CT, Endoscopy, surgery |
| **Diffuse Esophageal Spasm** | - Repetitive, simultaneous abnormally long contractions of esophagus in response to swallows  
Both achalasia and DES are due to degeneration of Auerbach’s plexus | • Progressive dysphagia for both solids and liquids  
• Failure of hypertensive LES to relax  
• Aperistalsis of eso  
• Often present with weight loss  
• Secondary development of bacterial toxins in static food → cancer risk factor | EGD to rule out mechanical obstruction  
• BS shows dilated esophagus with debris – Bird’s beak  
• Esophageal manometry  
• TXT: calcium channel blockers (relax SM), pneumatic dilation of LES, surgical myotomy, Botox |
| **IBD with Fulminant Colitis (Toxic Megacolon)** | - Histo – edematous and hemorrhagic, inflammation extends beyond mucosa, unlike typical superficial inflammation of ulcerative colitis  
- All layers of bowel are hemorrhagic and/or necrotic appearing; the pale eosinophilia, loss of nuclei, and fragmentation of muscle fibers in the muscularis | • Sx of obstruction  
• Perforation is common  
• Gross-large bowel become paper thin, with a fibrinous, fibrinopurulent exudates  
• 10% of people with UC develop this | Emergency partial colectomy |
<table>
<thead>
<tr>
<th>Hirschsprung Disease</th>
<th>Slide: 24</th>
<th>- Thick inspissated meconium plugs bowel lumen - Cone or funnel shaped bowel is common - See spindly Schwann cells but no ganglionic cells - Muscle hypertrophy in proximal segments</th>
<th>• Congenital absence of ganglion cells in part of colon – defective migration of neural crest cells → get persistent contraction • Intestinal obstruction with vomiting, distension and constipation</th>
<th>• Diagnosis: Biopsy, 2 cm above rectum, need access to intermuscular section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral Myopathy</td>
<td>Slide: 25</td>
<td>- Degeneration, atrophy, and fibrous replacement of muscle wall - Familial disease often associated with inclusions or vacuoles within smooth muscle cytoplasm</td>
<td>• Disorder of smooth muscle of bowel wall leading to pseudo-obstruction, bowel dilatation, and muscle wall atrophy - Familial or acquired</td>
<td>•</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Slide: 26</td>
<td>- Most patients have GI involvement and half are symptomatic - Smooth muscle atrophy and gut wall fibrosis, <em>more marked in circular</em> rather than longitudinal fibers - Abnormal collagen deposition throughout the body - Esophagitis often results in stricture formation</td>
<td>• GERD or esophagitis • Esophageal dysfunction: reflux, stricture or abnormal motility • Intestinal malabsorption → stasis and bacterial growth • Can also affect stomach and small intestine → stasis and bacterial overgrowth or nausea and vomiting; Colonic effects – constipation and diarrhea</td>
<td>• Treat symptoms • Decreased motility and decreased resting LES pressure</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Slide: 27</td>
<td>- Edema due to reduced lymphatic return, which worsens causing venous drainage impairment → arterial inflow inhibited → infarction - Mucosa most sensitive to ischemia – furthest from arterial supply</td>
<td>• Current jelly stool – sloughed mucosa • Idiopathic – affects toddlers and infants at ileocolic junction (prominent Peyer’s patch) • Enteroenteral – elderly – tumor</td>
<td>• Surgery • Untreated can get gangrene and perforation of leading edge</td>
</tr>
</tbody>
</table>
| Volvulus Slide: 28 | - bowel massively dilated, wall thinned with acute congestion and sometimes ischemia with hemorrhagic infarction - dusky purple brown color | • Twisting around vascular pedicle → obstruction and vascular occlusion  
• Volvulus neonatorum  
• Cecal Volvulus  
• Sigmoid volvulus | • Can untwist it with scope but need surgery to prevent recurrence  
• Neonatorum → gangrene  
• Cecal → congenital  
• Sigmoid → fiber |
|----|----|----|----|
| Herpes Simplex | - center and base may show necrotic debris and granulation tissue; basophilic "ground glass" intranuclear inclusions and multinucleated epithelial cells | • small shallow ulcers with whitish necrotic debris and an erythematous border  
• Can cause diarrhea | • Diarrhea-related diagnosed with sigmoidoscopy → small vesicles or diffuse ulcers  
• TXT: Acyclovir, Valacyclovir or Famcyclovir |
| Kaposi’s Sarcoma Slide: 29 | - Gross: reddish, purple patches  
- Micro: spindle cell proliferation forming blood-filled, slit-like vascular spaces – spindle cells may have only moderate atypia: mitotic figures and hyaline inclusions | • skin, oral cavity, GI tract, pulmonary  
• Can develop on mucosal surfaces in disseminated disease | • tissue biopsy  
• local therapy, chemotherapy, HAART, emerging therapies |
| CMV GI Infections | - Advanced lesions have shallow or deep ulcers and can give rise to bleeding or perforation  
- Cytomegaly, large eosinophilic intranuclear inclusion bodies and smaller eosinophilic cytoplasmic inclusions  
- Preferentially grows in endothelial cells and fibroblast cells, but will grow in many cell types  
- Infection of endothelial lined vessels → inflammation and occlusion → necrosis → ulceration | • 3 infection patterns: primary, re-infection and superinfection  
• Esophagus: shallow, painful mucosal ulcers  
• Colon: mucosal ulcers, watery diarrhea, and in severe infections, deep ulcers with profuse bloody diarrhea | • Diagnosis made on biopsy with CMV inclusion cells – owl’s eye halo  
• sometimes requiring colectomy  
• Gancyclovir and Foscarnet |
| Condlyoma Acuminatum Slide 30 | - Gross: cauliflower-like growth  
- Micro: papillomatous thickening of squamous epithelium with koilocytosis; infection with HPV 16, 18 is associated with anal intraepithelial neoplasia and squamous cell carcinoma | • Sexually-transmitted HPV infections producing warty growth on perianal skin and within anal canal | • |
<table>
<thead>
<tr>
<th>Slides</th>
<th>Conditions</th>
<th>Imaging Findings</th>
<th>Pathologic Findings</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 31     | GI MAI infections | - gross – thickened mucosal folds  
- lamina propria expanded by a sheet-like infiltrate of macrophages with abundant pale or granular blue-gray cytoplasm; small bowel villi may be broadened and flattened massive infiltrates  
- resembles Whipple’s | • GI infection – usually generalized and can involve liver spleen and other sites  
• May co-exist with other GI infections (CMV and crypto)  
• acid-fast stain – identifies mycobacteria  
• Different from Whipple’s in that it lacks lipid droplets  
• more rare with modern drug therapy | |
| 32     | Histoplasmosis | - Gross – may have no findings; ulcers, polyps, etc seen in severe disease  
- Lymphohistiocytic infiltrate in lamina propria with macrophage cytoplasm filled by multiple small, ovoid yeasts  
- Yeasts are PAS and silver-stain positive  
- Acute disseminated histoplasmosis typically involves small bowel  
- Seen in Ohio and Mississippi river valleys – a soil saprophyte – usually inhaled | • In endemic areas can be an AIDS defining illness | |
| 33     | Amebiasis | - Gross – mucosa is friable, erythematous, and granular; may be small ulcers, cecum commonly involved  
- classic flask-shaped ulcers extend through the muscularis mucosae and undermine the mucosa  
- May cause acute colitis, chronic colitis, or an asymptomatic carrier state; blood-borne dissemination may result in amebic abscesses in liver or other organs | • More common and serious in immunosuppressed | |
| 34     | Strongyloidiasis | - Complete disruption of small bowel mucosal patterns, ulcerations, and paralytic ileus have been observed  
- Dissemination with pulmonary involvement  
- Bacterial and fungal infections often occur  
- filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes  
- Hyperinfection seen in immunocompromised | • Detection of larvae in stool – need 7 samples  
• Lugol iodine stain; nutrient agar plate culture  
• Duodenal aspirate very sensitive  
• Duodenal or jejunal biopsy | |
| 35     | Lymphangiectasia | Primary: mucosal lymphatics are widely distended and leak into GI tract  
- Gross – multiple tiny white flecks (chylous lymph in dilated mucosal lymphatics)  
- Lacteals greatly dilated  
- Diarrhea  
- Primary vs. Secondary – retroperitoneal LN obstruction  
- hypoalbuminemia and lymphopenia | |
| Whipple’s Disease | Slide 36 | - Rare systemic infection  
- Organs infiltrated with histiocytes (contain phagocytized bacteria)  
- Small bowel contains many macrophages with pale PAS+ cytoplasm expanding LP and widening villi; clear spaces = lipid droplets | - Malabsorption syndrome can occur  
- Identified by PCR as Tropheryma whipplei, a gram positive actinomycete |
| Giardiasis | Slide 37 | - Protozoan parasite  
- Trophozoites form physical barrier to absorption  
- Damage to microvillus brush border leads to mucosal enzyme deficiency  
- Curved or sickle shaped structures that look like falling leaves | - Chronic diarrhea and malabsorption  
- Most common cause of epidemic water borne diarrhea – cysts are highly infective  
- Stool samples and duodenal aspirates  
- Enzyme immuno-assay looking for Giardia specific antigen – more sensitive and specific  
- Metronidazole |
| Cryptosporidiosis | Slide 38 | - Round, 2 to 4 micrometer, PAS-positive organisms in microvillus brush border of the mucosa of the stomach, small bowel, large bowel, or biliary tract; line both surface and crypts  
- Severe can cause villus atrophy and neutrophil influx  
- Host response = lymphocytes in lamina propria and mild epithelial damage | - Protozoa  
- Immuno-suppressed develop watery chronic diarrhea  
- Increased shedding of infected cells leads to their replacement by less mature epithelial cells having poorly developed surface enzymes, worsening malabsorption  |
| Carcinoid Syndrome | Slide 39 | - Secrete 5-hydroxy-tryptamine (5HT) and its breakdown product  
- Release of serotonin and other tumor-derived vasoactive compounds from liver metastases directly into the systemic circulation via the hepatic vein | - Syndrome consists of: episodic cutaneous flushing of the face and neck, sweating, diarrhea, wheezing, hypotension and, right-sided valvular heart disease  
- Elevated levels of the serotonin metabolite 5-HIAA in a 24-hour urine |
| Laxative Abuse | Slide 40 | - Melanosis coli describes an accumulation of a brown granular pigment within histiocytes in the lamina propria of the colorectum; lipofuscin | - Diarrhea  
- Melanosis coli is a marker for antraquinone laxative abuse |
<table>
<thead>
<tr>
<th>Slide 41</th>
<th>Abetalipoproteinemia</th>
<th>-villi with marked foamy vacuolation of the cytoplasm of enterocytes covering the upper two-thirds of the villus -RBCs with five to ten irregular, blunt, finger-like projections</th>
<th>• accompanied by acanthocytosis • Inability to transfer preformed triglyceride from enterocytes to lymphatics in the lamina propria • retinopathy and central nervous system disease • causes osmotic diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slide 42</td>
<td>Celiac Disease</td>
<td>-Changes are most severe in the distal duodenum and upper jejunum, decreases distally and may be minimal in the distal ileum -transglutamase (tTG) in lumen which crosslink with gliadan; anti-endomysial antibody leads to epithelial damage -gross: flat mucosa with loss of ridges and convolutions -normal villi are thin, with a length of at 3 times the depth of the crypts -Cubocolumnar epithelium and numerous intra-epithelial lymphocytes, microvilli fusion</td>
<td>• Inflammatory disease of small bowel caused by intolerance to gliadin • Malabsorption, with steatorrhea, weight loss and bloating • Diagnosis – small bowel with villus atrophy • Clinical improvement on gluten free diet • Serologic tests: Anti-gliadan; Anti-endomysial • Increased risk of lymphoma and carcinoma (adenoma of he small bowel)</td>
</tr>
<tr>
<td>Slide 43</td>
<td>Hyperplastic Polyps</td>
<td>-Gross: small sessile, slightly pale -Crypts in upper half of polyp have a characteristic serrated or convoluted appearance with decreased numbers of goblet cells</td>
<td>• Most common polyp of distal colon and rectum • Prevalence increases with age • Benign and less than 3 mm • Do not need to be removed – no malignant potential – Do not increase risk of more proximal cancer</td>
</tr>
<tr>
<td>Slide 44</td>
<td>Juvenile Polyps</td>
<td>-Small spherical polyp with thin stalk -cystic crypts filled with mucin and PMNs surrounded by an edematous inflamed lamina propria; mucosal surface often ulcerated and replaced by granulation tissue</td>
<td>• Probably Hamartomas – usually occur between ages 4-14 (&gt;10 seen w/ Chromosome 10 abnormality) • Usually solitary, but can be multiple sporadic or familial • Peutz-Jeghers syndrome: mucocutaneous hyper-pigmentation (autosomal dominant chromosome 19)</td>
</tr>
</tbody>
</table>
| Adematous Polyps | - circumscribed monoclonal disturbance in growth and differentiation manifest as architectural and cytologic dysplasia
- may be flat, sessile, or pedunculated; tend to be either paler or darker than the surrounding mucosa
- Tubular (most common), villous or tubulovillous
- pleomorphic, Hyperchromatic nuclei; loss of mucin | • Precursors for adenomas of small bowel and colon
• Size, multiplicity and microscopic appearance are significant markers | • Post-polypoidectomy bleeding is a common occurrence – rarely segmental colectomy required to control bleeding |
|---|---|---|---|
| Ampullary Carcinoma | - May be polypoid, ulcerating or infiltrating
- Severely atypical glands within a desmoplastic stroma with invasion of adjacent structures | • Tumor may originate from: epithelium of duodenal mucosa, common bile duct, pancreatic duct, or head of pancreas
• Can lead to bile duct obstruction → jaundice and pancreatitis | • By the time it presents it’s usually bad news |
| Malignant Polyp | - back to back glands infiltrating submucosa and mucosa | • Appears benign to endoscopist but is later found to be malignant | • Excise and examine lymph vessels/nodes for spread |
| Adenomatous Polyposis Syndrome | - See great difference in size and shape of glands, hyperchromicity | • Patients have 100s to 1000s of polyps, which will progress to colorectal cancer if untreated | • Colectomy
• Chance of getting cancer is 100% |
| Colorectal Cancer | - Tumors of rt. colon usually fungating or polypoid; left colon usually annular
- mucin secretion varies; may have signet ring formation
- Tumor cells have oval or rounded nuclei, clumped chromatin and nuclear pleomorphism; nucleoli may be large or irregular | • Mass, bleeding or obstruction
• Prognosis related to degree of differentiation (grade) and extent of bowel penetration and nodal involvement (stage)
• 2nd leading cause of cancer death; M>F; > 50
• 90% sporadic – not familial | • Presence of obstruction worsens prognosis
• Mucinous carcinoma tends to present at later stage
• Protective Measures: screening, calcium, selenium and folic acid, aspirin, NSAIDs
• Fecal Occult blood testing
• Screening endoscopy
• Sequellae of IBD |
<table>
<thead>
<tr>
<th>Carcinoid Tumor</th>
<th>-Most carcinoids are sessile, umbilicated nodules or polyps; larger tumors that may thicken and kink the bowel wall and have surface ulceration. Neuroendocrine tumor composed of small, strikingly uniform cells growing in nests, trabeculae, cords, tubules, or sheets. -Tumor cells have a columnar or polygonal shape, nuclei are rounded to oval, uniform in shape and size.</th>
<th>• Usually asymptomatic, in ileum; can have vague abdominal pain. • Carcinoid Syndrome (only 10%): A set of clinical findings caused by release of tumor secretory products (primarily serotonin) from liver metastases - diarrhea, episodic flushing, bronchospasm, cyanosis, telangiectasia, fibrotic plaques on tricuspid and pulmonic valves. • Diagnosis: neuroendocrine cells stain for synaptophysin. • 90% of people with carcinoid syndrome have metastatic disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma</td>
<td>-Fascicles of smooth muscle radiating in many directions. -Originates from either muscularis mucosae or muscularis propria.</td>
<td>• Benign: can present with acute or chronic blood loss, bowel obstruction, or a palpable mass. • May present with bleeding when it outgrows its blood supply.</td>
</tr>
<tr>
<td>Intestinal Lymphoma</td>
<td>-B-cell: MALToma or Burkitt’s. -T-cell- associated with celiac disease. -Infiltrates of large atypical lymphoid cells; stain uniformly for CD 20+.</td>
<td>• GI tract is predominant site of extranodal non-HLNs; predisposing factors: immuno-deficiency, celiac disease, IBD. • Primary vs. systemic nodal infection.</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>-Stromal tumor -submucosal</td>
<td>• Vascular and may present w/bleeding.</td>
</tr>
<tr>
<td>Anal SCC</td>
<td>-Gross: typically ulcerated with raised borders. -About half are basaloid (cloacogenic) and about half are keratinizing squamous carcinomas.</td>
<td>• Link with HPV infection – like cervical cancer – transition epithlia. • LN depend on above or below dentate line.</td>
</tr>
</tbody>
</table>
| **Esophageal Varices** | - Gross: varices collapse after death  
- Dilated veins | • Generally asymptomatic until bleeding occurs  
(especially bleeding in distal 5.0 cm) | • TXT: Rubber bands down your throat.  
Tasty.  
TIPS  
Balloon pressure  
Sclerocent to scar down veins  
Beta-blockers decrease pressure in varix |
| **Ischemic Colitis** | - Watershed areas most affected (splenic flexure, rectosigmoid)  
- Early acute ischemia → extreme congestion and hemorrhage of the mucosa and submucosa → infarction and ulceration → with progression muscularis propria becomes infarcted and may perforate  
- Subacute ischemia → areas of ulceration exude a protein-rich fluid → pseudo-membrane formation  
- Chronic ischemia → fusiform strictures | • Colon is predisposed b/c of lower blood supply  
• Causes: vascular obstruction, drugs, low-flow states, physical obstruction  
• Risk of perforation with necrosis of muscularis propria |
| **Hemorrhoid** | - Gross: dilated venous plexuses  
- Dilated vascular spaces, often with thrombosis and recanalization | • Uncommon with high fiber diets; common in western countries  
• Can present with bright red bleeding or prolapse of polypoid mass |
| **Angiodysplasia** | - Degenerative lesion of previously healthy blood vessels; commonly in the cecum and proximal ascending colon  
- Telangiectasias  
- Ectatic vessels collapse after resection and may be difficult to identify; most are < 5 mm in diameter  
- Irregularly shaped clusters of ectatic small arteries, small veins, and capillary connections | • Typically nonpalpable and small, frequently noted incidentally during colonoscopy  
• 2nd leading cause of lower GI bleeding in patients >60; diverticulosis #1 |

- **Differential includes hemangiomas**
**Drug Induced GI Bleeding**

Slide 55

- Mucosal ulceration with fibrinous exudate, brown deposit on ulcerated surface

- **NSAIDs**
- Iron Sulfate tablets
- Anti-depressants – interfere with uptake of platelet serotonin

- NG aspirate

**Diverticular Disease**

Slide 56

- Protrusions of the mucosa through the muscle wall; occur mainly at points of weakness where muscle wall is penetrated by blood vessels
- May contain hard calcified feces
- Flask-shaped outpouching of mucosa and submucosa through loose connective tissue tunnel in the muscularis propria; diverticulitis characterized by mucosal ulceration, granulation tissue, and variable inflammation; fistulas can form

- 70% never experience symptoms
- Can range from mild abdominal discomfort with fevers, to sepsis, perforation with abdominal rebound tenderness and death
- Complications: Hemorrhage, fistula, Intestinal obstruction, perforation, abscess
- More common in Western countries; incidence increases with age
- Almost all occur in the left colon
- Stool with less bulk harder to propel → high pressure → diverticulae

- Diagnosis: colonoscopy
- Bleeding Scan: can detect bleeding with rate of loss as low as 0.5 ml per minute
- Angiography: more accurate but requires higher rate of blood loss
- Most cases limited to Sigmoid Colon
- Diverticulitis work-up: abdominal Xray, abdominal CT, colonoscopy should not be performed in the acute setting (could lead to perforation)

**Mallory-Weiss tear**

Slide 57

- Tear at GE junction
- Bleeding results when tear involves the underlying esophageal venous or arterial plexus

- Tear occurs after a bout of retching or vomiting; common in alcoholics with portal hypertension

**Amyloidosis**

Slide 58

- Gross: no abnormalities usually present
- Amyloid is an amorphous, homogeneous pink-staining substance, often having an artifactual cracked appearance
- Congo-red staining
- Fibrils can be in vessels - extra-vascular deposition can be found in muscle tissue

- Most cases of GI amyloidosis are asymptomatic, but GI manifestations can include bleeding, gastroparesis, constipation, bacterial overgrowth, malabsorption, and intestinal pseudo-obstruction

- Diagnosis: take a sample of perianal fatpad and stain with congo red.
- Hepatomegaly with or w/o splenomegaly is also common in some forms
<table>
<thead>
<tr>
<th>IBD</th>
<th>Crohn’s Disease</th>
<th>Slide 59</th>
</tr>
</thead>
</table>
| - Crypts irregularly distributed  
- Lower crypt density  
- Crypts of variable diameter and branching  
- Crypts non-parallel with variable diameter, branched, and crypt base may not reach muscularis mucosae  
- In lamina propria densely cellular infiltrate of lymphocytes, eosinophils, and plasma cells  
- Crypt epithelium infiltrated by neutrophils  
- Usually inflammatory diarrhea | - Most disease found in ileum and cecum and colon  
- Small intestine ulcerated with strictures and fissuring  
- Fissures can form cobblestoning pattern; ulcers have serpiginous appearance  
- Small-bowel hose-pipe strictures  
- Almost always discontinuous ulceration  
- Transmural thickening  
- Serosal tubercles = granulomas  
- Fat wrapping  
- Lymphoid aggregates = Crohn’s rosary  
- Hyperplasia of nerve fibers  
- Granuloma is not always seen but always see deeper inflammation | - Includes Crohn’s Disease and Ulcerative colitis  
- Patients with IBD have an ~20-fold increased risk of developing colon cancer over the general population  
- Compared with sporadic colorectal cancer (CRC), the patient population is younger, there is more difficulty in recognizing tumor endoscopically, and tumors are more often multiple  
- Crohn’s disease has greater genetic etiology than UC |
| - Diagnosis: see below  
- Can often be difficult to distinguish the two diseases  
- Environmental influences: Altered flora (antibiotics, diet); altered barrier functions (stress, NSAIDs, smoking, acute infections)  
- Can lead to increased risk of cancer anywhere in body  
- After 10 years of disease need screening colonoscopy | - Pain, tenderness, weight loss, non-bloody diarrhea, low-grade fever; common – palpable mass, post-prandial abdominal pain  
- Enlarged regional lymph nodes  
- Complications: small bowel obstruction, ulceration → hemorrhage and iron deficiency; perforation; fissures and fistulations → intra-abdominal abscesses; small bowel malabsorption; bile duct lesions  
- Association of Crohn’s with dysplasia and adenocarcinoma  
- Arthritis and dermatological lesions and eye issues | - Radiology: string sign in small bowel stricture  
- Susceptibility is determined by genes encoding immune responses and barrier function  
- Onset/reactivation is triggered by environmental stimuli  
- Nearly 80% require surgery within 20 years of onset  
- High numbers of recurrence after surgery |
### Ulcerative Colitis

**Slide 60**

- Begins in rectum and spreads proximally
- Serosa not involved
- Gross: granular, velvety, hyperemic surface oozing blood with loss of mucosal folds
- Junction between normal and inflamed is usually well defined
- Inflammation is continuous
- Inflammatory polyps are common with ulcerations undermining inflamed mucosa, making this mucosa appear elevated relative to the adjacent ulceration
- Diffuse inflammatory infiltrate in crypts and lamina propria with involvement of superficial submucosa
- Only superficial submucosa is involved
- Ulcerations are not sharp like in CD
- Pseudopolyps
- Cryptitis and crypt abscess

### Microscopic Colitis

**Slide 61**

- Lymphocytic and collagenous colitis
- Presence of subepithelial collagen band in collagenous form
- Mucosal inflammation with chronic inflammatory cells
- The absence of a thickened subepithelial collagen layer (>10 mm in CC) distinguishes LC from CC

### Ileal Pouch-Anal Anastomosis

- Always involves rectum; may involve part or rest of colon
- Almost always involves rectal bleeding
- Abdominal pain before bowel movements
- Rare ileal involvement
- Crypt abscesses more common than CD

### Drug Therapies

- Diagnosis: colonic biopsy that shows inflammatory change
- Intraepithelial lymphocytic infiltrate, with greater than 20 lymphocytes per 100 epithelial cells required for the diagnosis of LC
| IBS | - No gross or microscopic changes are seen. | • Abdominal pain (w/ looser stools, with more frequent BMs, relieved by BM); abdominal distension; mucous; incomplete evacuation  
• Other related psychological symptoms  
• More intense response to intestinal stimuli → increased motility in small and large bowel  
• Sensation and motility abnormalities; visceral hypersensitivity, larger areas of referred pain  
• > developing world; F>M | • CBC (rule out blood loss, anemia)  
• Sed rate  
• Stool Testing (occult blood, O&P, Leukocytes, culture)  
• Endoscopy  
• RED FLAGS: abnormal PE, fever, occult blood, weight loss, older patients, nocturnal awakening, Fam Hx of CA, IBD, abnormal blood tests, chemistries  
• TXT: diet modifications, fiber, treat the diarrhea or constipation, Anti-depressants (Tricyclics can cause constipation; SSRIs can cause diarrhea); Psychological txts. |
|---|---|---|
| Appendicitis | - Luminal obstruction from fecalith, lymphoid hyperplasia, or other cause; infection involves flora of luminal origin  
- Dilatation and congestion of the small vessels on the serosal surface with hyperemia  
- Distal lumen dilated, filled with purulent material; outside becomes swollen and hemorrhagic with dull shaggy serosa – fibrinopurulent serosal exudates; intra-luminal pressure > venous pressure → local necrosis and transmural inflammation  
- Microscopically: edema and congestion of wall, infiltration by PMNs, with perforation → gangrenous necrosis | • Peri-umbilical pain, anorexia, nausea, vomiting +/- fever  
• Pain localizes to lower R quadrant  
• Peritonitis → rebound pain, guarding  
• Complications: Abscess, phlegmon and rupture  
• Highest incidence 20-40; M=F except 15-25 | • CT Scan  
• Ultrasonography  
• Misdiagnosed 15-20%; better to go in with suspicion than wait it out |
<table>
<thead>
<tr>
<th><strong>Pseudomembranous Colitis</strong></th>
<th><strong>Diarrhea with or without pseudomembranes with crampy abdominal pain, small amounts of blood</strong></th>
<th><strong>Diagnosis:</strong> Cytotoxin test (high sp and sn); Toxin enzyme immunoassay (less cost but lower sn) → first-line and economical <strong>Lower endoscopy with show characteristic pseudomembranous plaques</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>-A gram-positive, anaerobic, spore-forming bacillus responsible for the development of antibiotic-associated diarrhea and colitis. Discrete raised indurated creamy-yellow plaques, firmly attached to the underlying mucosa and separated from each other by congested mucosa. Basal portion of each crypt is usually viable, while the superficial two-thirds is dilated and filled with degenerating epithelial cells, mucus, fibrin and acute inflammatory cells. Organism produces a potent enterotoxin, toxin A and a cytotoxin, toxin B (way more toxic).</td>
<td>More severe cases: fever, chills, abdominal distension. Toxic Megacolon develops in &lt; 3%. One of the most common nosocomial infections. Rarely progresses to ischemic colitis. Strongly associated with the use of Clindamycin. Can follow infection of another enteric organism.</td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial Colitis</strong></td>
<td><strong>Diarrhea, fever, nausea, vomiting, abrupt onset</strong></td>
<td><strong>Stool Culture</strong></td>
</tr>
<tr>
<td>-Bacteria colonize the bowel or invade mucosa and produce toxins (enterotoxins → secretion vs. cytotoxins → damage or kill cells) or factors that resist host defenses. Gross: erythema that can mimic IBD, shallow aphthous ulcers. Micro: see edema and neutrophil infiltration; crypt architecture maintained; changes in upper third of crypt; Crypt abscesses.</td>
<td>Antibiotic-induced diarrhea with colitis is a form of infectious colitis related to selective bacterial overgrowth. Preformed toxin causes illness ~ 6 hours after ingestion. Direct tissue invasion ~ 1-2 days. Cyto-entero toxins ~ 8-72 hrs.</td>
<td><strong>CBC</strong> <strong>C diff toxin</strong> <strong>Serum electrolytes to manage dehydration</strong> <strong>Sigmoidoscopy</strong> <strong>Not UC b/c crypt architecture maintained</strong></td>
</tr>
<tr>
<td><strong>E. Coli Serotype O157:H7</strong></td>
<td><strong>Seasonal pattern; contaminated food; Stay away from state fair petting zoos</strong></td>
<td></td>
</tr>
<tr>
<td>-Gross: can see extensive ulceration, edema, erythema and hemorrhage; most severe on right side; pseudomembranes may form. Micro: spectrum of</td>
<td>Symptoms range from asymptomatic to mild diarrhea.</td>
<td></td>
</tr>
</tbody>
</table>
## Changes in Colonoscopic Biopsies

Changes in colonoscopic biopsies include normal areas, neutrophil infiltrates and edema resembling any infectious colitis, changes similar to ischemia, and pseudomembranous colitis similar to that seen with *Clostridium difficile*.

<table>
<thead>
<tr>
<th>Hemolytic colitis or Uremic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colon:</strong> Hemorrhagic colitis</td>
</tr>
<tr>
<td><strong>Kidney:</strong> Hemolytic Uremic Syndrome</td>
</tr>
<tr>
<td><strong>Disseminated:</strong> TTP</td>
</tr>
</tbody>
</table>

### Shigellosis

Shigellosis - Invade epithelial cells and produce a potent cytotoxin, *(Shiga toxin)*

- *Shigella dysenteriae* type 1: a virulent bacterium causing severe dysentery with considerable mortality
- *Shigella flexneri*: less virulent, may cause diarrhea or dysentery

<table>
<thead>
<tr>
<th>Transmitted Fecal-Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Shigella sonnei</em>: usually a self-limited watery diarrhea with fever lasting 48 to 72 hours</td>
</tr>
</tbody>
</table>

### Acute Pancreatitis

**Mild Acute:** enlarged and swollen with foci of fat necrosis; form calcium soaps (yellow/waxy) -- saponification; mild interstitial acute inflammation; vascular wall necrosis; edematous vs. necrotic

**Severe Acute:** large confluent areas of chalky-white fat necrosis (can be surrounded by PMNs), hemorrhage, can look like hematoma, accumulation of pancreatic fluid; large amts of calcium can be trapped as salts → hypocalcemia; fat necrosis at distant sites

<table>
<thead>
<tr>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cullen’s sign → umbilical ecchymosis and flank indicate severe disease</td>
</tr>
<tr>
<td>Etiology: gallstones or alcohol, most common</td>
</tr>
<tr>
<td>Duct is obstructed → hypertension → Trypsinogen activates trypsin and leads to tissue destruction</td>
</tr>
<tr>
<td>Edematous: most common, no tissue destruction, abdominal pain, nausea and vomiting, self-limited</td>
</tr>
<tr>
<td>Necrotizing Pancreatitis: gallstones most common cause → inflammatory response; multiple organ failure, severe abdominal pain, nausea,</td>
</tr>
</tbody>
</table>

Know the anatomy of the pancreas – partially retroperitoneal

<table>
<thead>
<tr>
<th>Diagnosis of Edematous Pancreatitis: history and PE; Confirmed by hyper-amylasemia or hyperlipasemia; LFT – bilirubin, Alkaline Phosphatase, GGT; ultrasound looks for gallstones; common electrolyte disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>TXT: IV fluids and pain control; if gallstone induced can take out gallbladder during hospitalization</td>
</tr>
<tr>
<td>Necrotizing Pancreatitis: Lab findings ---- increased amylase, lipase, creatinine and BUN; Leukocytosis and thrombocytosis, increased LFTs, Hypoxia and hypocalcemia; Ultrasound = gallstones; CT =</td>
</tr>
<tr>
<td>Chronic Pancreatitis</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Acute complications:</td>
</tr>
<tr>
<td>Systemic complication:</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis:**
- **Lab:** Non-specific poor nutritional status → low albumin and transthyretin, dehydrated
- **Radiographs:** Pancreatic calcification; **CT:** Pancreatic head enlargement, dilated duct, atrophy; **ERCP:** Obstruction of duct for larger ducts; **Endoscopic ultrasound**
- **TXT:** Pain control, pancreatic enzyme replacement, decreased gastrin secretion; **Endoscopic:** Pancreatic duct stent, stone retrieval, pancreatic duct sphincterotomy, shock wave lithotripsy; **Surgical:** duct necrosis; ERCP = diagnostic and therapeutic

**TXT:** Pain control, IV fluids, nutrition, therapeutic ERCP, surgery for infected necrosis

**Hypovolemia major cause of death – 3rd spacing – punkin head**

**Infected necrosis accounts for 30-70% of deaths in acute necrotizing pancreatitis and 80% in acute pancreatitis**

**CT test of choice when it doesn’t resolve in a few days**

---

**Slide 66**

**-Continuing inflammation with irreversible morphological changes; obstruction of pancreatic duct can cause chronic pancreatitis distal to obstruction**

- **Hypersecretion of protein with out the bicarb → precipitate to pancreatic plugs → calcification → stenosis**

- **Associated with CF – CFTR responsible for secreting bicarb**

- **Gross:** Enlarged, indurated with nodular scarring, loss of lubarulations, calculi firm and gritty

- **Micro:** Inflammation and fibrosis, variable from one lobule to another, plugs are eosinophilic; islets of langerhans can proliferate and resemble neoplasm

- **Pain** and/or permanent impairment of function; unremitting epigastric pain, nausea and vomiting, steatorrhea, chronically ill and disabled; jaundice from biliary

- **Etiology:** Alcohol (70%), nutrition, hereditary, idiopathic

- **Can have acute exacerbations**

- **Loss of endocrine and exocrine functions can result in malabsorption and diabetes**

- **Complications:**
  - Pseudocyst
  - Splenic vein thrombosis and gastric varices
  - Superior mesenteric or

**Interlobular or**
<table>
<thead>
<tr>
<th>Pancreatic Pseudocyst</th>
<th>Perilobular fibrosis is more prominent than intralobular fibrosis surrounding distorted glands within densely sclerotic stroma; interlobular luets surrounded by fibrosis are dilated</th>
<th>Portal vein thrombosis, Biliary obstruction, Duodenal, gastric or colonic obstruction, Pancreatic ascites and pleural effusion, Pancreatic cancer</th>
<th>Drainage, pancreatic resection</th>
</tr>
</thead>
</table>
| Pancreatic Ductal Adeno-Carcinoma | - A collection of turbid fluid enclosed by a wall of fibrous tissue or granulation tissue - Arises as a complication of pancreatitis when necrotic tissue becomes walled off, entrapped material → osmotic pressure draws water in; also increases in intraductal pressure can cause rupture leading to formation of pseudocyst - Gross: unilocular, round or oval, Once drained has muddy material on shaggy inside - Micro: inner layer of fibrin rich exudates, outside layer of dense collagen, no epithelial lining | - Local expansion may compress adjacent structures with complications such as portal vein thrombosis, jaundice due to obstruction of the common bile duct, hydroureronephrosis, and lower extremity edema due to compression of the inferior vena cava - Most serious complications are hemorrhage, rupture, and infection | Drainage  
If small go away on their own |
| | - Gross: most located in head of pancreas, producing hard mass; most associated with obstruction of pancreatic or bile duct - Micro: most are moderately to well differentiated but behave like high grade neoplasms; Well differentiated: composed of glands of various size and shapes, lined by columnar to cuboidal cells; Moderately differentiated adeno-carcinomas have predominantly medium- | - Presentation: painless jaundice, preuritis, early satiety  
- Risk Factors: chronic pancreatitis, booze, tobacco, coffee, fatty diet  
- Complications: weight-loss, pain radiating to back, Courvoisier sign (painless dilation of the gallbladder); Trousseau sign (migratory phlebothrombosis, due to hypercoagulable state) | Diagnosis: H & P, CA 19-9 may be helpful, Ultrasound, CT, Magnetic resonance imaging, ERCP Endoscopic ultrasound, Biopsy often not necessary  
TXT: Whipple; palliative for unresectable disease (biliary stent placement, relief of abdominal obstruction); Chemo (5-FU, gemcitibime); RT  
Outcome: 20% 5-year survival  
Almost always |
### Endocrine Neoplasms of Pancreas
**Slide 69**

- **Gross:** solitary, well-circumscribed, yellow-tan color
- **Histo:** Incomplete fibrous capsule; Solid, trabecular, or island-like patterns of uniform cells with oval nuclei and inconspicuous nucleoli, mitotic figures infrequent

- Beta cell tumors → hypoglycemia
- Pancreatic gastrinoma → ZES
- Alpha cell → secretes glucagons
- Delta tumor → somatostatin

- Skin = well known site of mets (Sister Mary Joseph sign)

- Metastatic by the time we find it

### Hereditary Hemochromatosis
**Slide 70**

- Iron circulates in non-transferrin bound form which readily enters cells by a non-saturable process
- Excess iron damages cell organelle membranes leading to functional defects of mitochondria, lysosomes, microsomes with release of hydrolytic enzymes into cytosol
- Periportal fibrosis due to activated hepatic stellate cells making collagen
- More iron becomes deposited as hemosiderin
- **Gross:** hepatomegaly, liver dark red brown
- **Histo:** iron accumulation periportally and in heart and other tissues, spotty necrosis

- No symptoms early in disease
- SX: Bronze diabetes, cirrhosis, fatigue, hepatomalgy, athropathy, etc
- Autosomal recessive; **C282Y** most common
- Excessive iron absorption in the duodenum; transferritin becomes fully saturated
- Women not as symptomatic b/c of menses
- Worsens alcoholic liver disease
- Must distinguish from secondary causes of iron accumulation
- Irreversible myocardial dysfunction
- Deposition in pituitary cells → endocrine dysfunction → hypogonadism

- Most common way to diagnose is elevated serum iron levels on PE
- Screening: Transferrin saturation - usually 90% (increases in iron deficiency), must be >50% for women and >60% for men to be diagnostic of hemochromatosis
- Ferritin for tissue storage of iron → increases in iron overload
- Definitive Diagnosis: hepatic iron index → biopsy; molecular DNA probe for both mutations
- Disease is treatable!
  - Therapeutic Phlebotomy
    - Screen Diabetics
    - Phlebotomy failures get desferoxamine – chelates iron, poor SE profile
### Wilson’s Disease

**Slide 71**

- Copper accumulation in mitochondria in the tissues: liver, brain, cornea and kidneys
- Early nonspecific features: steatosis, lipofuscin deposition, intranuclear glycogen inclusions, focal necrosis
- Mallory bodies and steatosis

**SX:**
- acute or fulminant hepatitis or chronic hepatitis with cholestasis; cirrhosis; behavioral problems in childhood; neurological manifestations; Kayser-Fleischer rings; hypercalciuria
- AR disease of copper metabolism → copper overload in liver; M>F; Chrom 13
- Copper excretion ¼ normal in WD
- Occurs predominantly in young adults and children

**Diagnosis:**
- Low ceruloplasmin, not pathogenic or specific, low total serum copper, increased free serum copper.
- Increased copper in 24 hour urine
- Sterlieb criteria: KF rings, neurological symptoms, low serum ceruloplasmin
- Low alkaline phosphatase in setting of high total bilirubin, hemolytic anemia
- TXT: copper chelation (D-pencillamine, Trientine, Zinc, liver transplant is cure)

### A1AT deficiency

**Slide 72**

- α1-AT synthesized by the liver is folded abnormally → accumulates insoluble aggregate in the ER of the hepatocyte
- Eosinophilic PAS-D positive cytoplasmic globules in periportal hepatocytes; bluish dots
- Non-specific inflammatory change → fibrosis

**SX:**
- Portal hypertension, pulmonary disease
- AR on Chrom. 14; PIZZ = bad news
- Neonatal hepatitis

**Diagnosis:**
- Quantitative serum levels, biopsy and demonstration of globules; phenotyping requirement, prenatal diagnosis
- No treatment
- Liver transplant for advanced disease is curative
- Gene therapy trials

### Granulomatous Disease

**Slide 73**

- Circumscribed aggregates of macrophages and lymphocytes within the liver – epithelioid histiocytes or lipogranuloma
- Infectious, foreign body, drug-induced, auto-immune
- Sarcoidosis: confluent granulomas → cirrhosis, portal hypertension; star shaped asteroid bodies in giant cells

**SX:**
- Typical patient is young with fatigue, jaundice, pruritis
- Patients may progress to cirrhosis

**Diagnosis:**
- Investigate TB, sarcoidosis, drug history
- Treat underlying disorder – Immunosuppression: steroids, methotrexate, azathioprine; Ursodeoxycholic acid
| **Budd-Chiari Syndrome** | **Slide 74** | - Gross: liver swollen and hyperemic due to outflow obstruction  
- Histo: sinusoidal dilation, congestion and acute hemorrhage in perivenular zone; ischemic necrosis of perivenular hepatocytes; extravasation of RBCs into space of Disse  
- In chronic syndrome – bridging fibrosis → cirrhosis  
- Thrombotic occlusion of major hepatic veins due to hyper-coagulable disorders  
- When Chronic the caudate lobe is often spared and can undergo hypertrophy  |
| **Herpes Hepatitis** | **Slide 75** | - Randomly located (not restricted to a specific histologic compartment, i.e. centrilobular), variably-sized, often geographically-shaped zones of parenchymal "dirty necrosis"  
- Multi-nucleation, molding of nuclei, margination of nuclear chromatin around central ground glass nucleoplasm  
- Occurs in premature infants and during neonatal period  
- Rare and usually fatal cause of acute hepatitis in adults  
- Uncommon in healthy individuals  |
| **Lymphoma and acute hepatitis** | **Slide 76** | - Gross: Hepatic enlargement from massive infiltration; enlarged spleen and mesenteric LNs; hilar LN enlargement → compression of biliary tree and cholestasis  
- Histo: diffuse or nodular pattern of infiltration; failure results from parenchyma destruction  |
| **Acetaminophen toxicity** | **Slide 77** | - Toxic intermediate causes hepatocellular necrosis  
- Gross: With massive hepatocellular necrosis and resorption of necrotic material the liver can undergo considerable shrinkage; RBCs can replace where the liver was  
- Necrosis from toxic metabolite  
- Usually overdose or high therapeutic dose with concurrent alcohol abuse or high dose when glutathione stores are low (protein deficient or fasting)  
- ARDS/ renal failure  
- N-acetylcysteine (mucomist) can be given up to 24 hours after ingestion to keep the glutathione-dependent pathway from being overwhelmed and diminish liver injury |
### Hepatitis A

**General Acute Hepatitis Markers:**
- Spotty necrosis (Councilman or acidophil bodies)
- Lobular sinusoidal inflammation
- Lobular disarray
- +/- cholestasis, zone 3
- Portal inflammation variable
- Reticulin framework preserved, no fibrosis

- Fecal-Oral transmission; incubation period avg. 30 days; patients who are older have more jaundice
- Greatest concentration in the feces
- Travelers, drug users, people with chronic liver dx

- Diagnosis: ALT rises and peaks 1-2 months after exposure; Total anti-HAV rises to max 12-24 months after exposure; anti-HAV IgM peaks 3 months after exposure
- Routine Childhood vaccination

### Hepatitis B

**General Severe Acute markers:**
- Confluent hepatic necrosis: varies from bridging necrosis to fulminating hepatitis with submassive or massive necrosis

- Transmission is sexual, parenteral, perinatal
- Infants > risk of chronic infection
- Can have concurrent HDV infection

- Serologies: HBsAg = current infection; Anti-HBs = resolution; HBcAg = exposure; HBeAg = replication (activity); Anti-HBe = resolution of activity
- TXT: Interferon, Lamivudine, Adefovir
- VACCINATE

### Hepatitis C

**General Chronic Hep Markers:**
- Predominant location of lesion: portal → periportal
- Portal inflammation: lymphocytes, plasma cells
- Piecemeal necrosis or interface hepatitis: destruction of the limiting plate of hepatocytes
- Lobular spotty necrosis (Councilman bodies)
- Periportal fibrosis

- Risk factors: IVDU, transplants, transfusions
- More common in males around age 40
- Often presents with autoimmune complications: Cryoglobulinemia
- Does not usually cause acute symptoms

- Abnormal ALT
- First test is ELISA with fair number of false positives
- Then go on to RIVA test
- High false positive rates in low-risk groups
- Window phase prior to seroconversion in acute HCV
- Confirming diagnosis with PCR
- PEG Inferon +RBV

### Primary Biliary Cirrhosis

- Cyto-toxic T-cell - mediated immune destruction of small interlobular bile ducts
- Liver Biopsy: Stage I → infiltration of the portal tract with inflammatory cells "florid duct lesion" Stage II: Spilling of inflammatory infiltrate into hepatic lobule, formation of

- Sx: Fatigue, pruritis, jaundice
- Signs: hyperpigmentation hepatomegaly, splenomegaly, xanthelasma
- Various associated auto-immune disorders
- Malabsorption and portal hypertension

- Lab studies: Alkaline phosphatase, anti-mitochondrial Ab, increased IgM, transaminases, bilirubin, cholesterol, bile acids
- Rule out obstruction, ERCP is normal
- Liver Biopsy: Stage
<table>
<thead>
<tr>
<th>Primary Sclerosing Cholangitis</th>
<th>Stage III: Fibrosis, which links portal tracks, fewer interlobular and septal bile ducts. Stage IV Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The bigger ducts</strong></td>
<td>- Inflammatory reaction in bile ducts from chronic or recurrent entry of bacteria into the portal circulation. - Bile duct cells express antigens that cross-react with colonic epithelial cells and HLA class II antigens. - Diffuse and irregular narrowing and dilatation of the intrahepatic +/- or extrahepatic bile ducts, diverticulum-like outpouchings, resulting in a beaded appearance. - Fibrous obliteration of medium and large bile ducts with concentric replacement by connective tissue in “onion skin” pattern.</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>- Fatigue, jaundice, pruritus, weight loss. Fever; same signs as PBC. - Disease of men; strong association with IBD → stronger with UC. - Secondary Sclerosing Cholangitis – arises from other causes.</td>
</tr>
<tr>
<td><strong>Diagnosis and Therapy</strong></td>
<td>- 50% have elevated IgM. - Look at XRay. - Antibodies directed against cytoplasmic and nuclear antigens of neutrophils with perinuclear staining pattern (pANCA) found in 80%. - Elevated CD4+ cells in liver; elevated serum alkaline phosphatase, hyper-gamma-globulinemia, serum bilirubin, p-ANCA. - Ultrasound → abnormal ducts; Cholangiogram confirms diagnosis. - Increased prevalence of cholangiocarcinoma and colon cancer. - Disease progressive and median time from diagnosis to transplant = 10yrs. - Treatment limited to management of recurrent cholangitis antibiotics.</td>
</tr>
</tbody>
</table>
| Autoimmune Hepatitis | Portal and periportal mononuclear cell infiltration
- Plasma cells, with their eccentric, clock-faced nucleus and perinuclear cytoplasmic crescent, are characteristic of AIH, but are neither pathognomonic of the disease or required for its diagnosis | Common symptoms are fatigue and acute hepatitis
- PE: hepatomegaly and jaundice
- Associated with other auto-immune diseases
- No single feature distinguishes it from other forms of hepatitis
- Occurs more often in young women
- Likely immune mediated | Responds to immuno-suppressive therapy
- Circulating Ab useful for diagnosis --- ANA, anti-SMa and IgG hyper-gamaglobulonemia
- Three types of AIH and most are type I with ANA and ASMA
- Elevated transaminases
- Liver biopsy and determine disease activity and extent of fibrosis
- With cirrhosis have lower life expectancy
- Corticosteroids may induce remission
- Transplant an option but recurrence a problem |
| --- | --- | --- | --- |
| Extra-Hepatic Biliary Atresia | Gross: marked cholestasis; progressive fibrosis evolves to biliary cirrhosis
- Histology: similar to large duct obstruction in adults; Edematous expansion of portal areas with ductular proliferation at the limiting plate associated with a neutrophilic infiltrate; bile lakes and infarcts | Jaundice @ 2-3 weeks of age
- Congenital absence or post-natal shrinkage of extra-hepatic bile ducts
- Possibly due to virus or auto-immunity | A Kasai procedure must be performed by 2 months of age to have a significant probability of restoring biliary drainage – slows progression until transplant is required; Bacteria within the jejunum can enter the biliary tree resulting in bacterial cholangitis |
| Cirrhosis | Diffuse hepatic fibrosis with the formation of regenerative nodules which together markedly reduce functional liver tissue and alter vascular-parenchymal anatomic relationships diminishing hepatic function
- Hepatocellular injury (whatever the cause) stimulates stellate (Ito) cells to become | Clinical outcomes: jaundice, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal and hepatopulmonary syndromes, hypersplenism, and hepatocellular carcinoma
- Decrease in functional capacity | --- |
| Alcoholic Liver Disease | fibrogenic leading to the end stage of chronic liver disease  
- Macronodular vs. micronodular  
- Fibrosis mediated by release of TGF-B and growth factors  
- Subendothelial accumulation of collagen in Disse’s space leading to “capillarization” of the sinusoids which results in decreased metabolic exchange between blood and hepatocytes  
- Nodules of regenerative parenchyma without portal areas are encased in dense fibrous connective tissue septa  
- In alcoholic fibrosis: Fibrosis beginning in the perivenular area and extends in a chicken-wire fashion into the space of Disse of the surrounding lobule (perisinusoidal fibrosis) | and an increase in portal venous pressure  
- In advanced cirrhosis, as little as 13% of portal blood flow perfuses the liver and exits via hepatic veins  
- Alcohol is empty calories  
- Enlarged, often tender liver; jaundice  
- 30% of heavy drinkers develop steatohepatitis; 10% develop cirrhosis  
- Other complications: cardiomyopathy, myopathy, neurological symptoms, pancreatitis, hyperlipemias, anemia, liver disease  
- CAGE  
- MILT: increased MCV; Increased iron, amylase; elevated liver enzymes; increased triglycerides  
- First get increased GGT and then the AST/ALT split  
- Best index of severity is PT  
- Bilirubin in the urine  
- TXT: use drugs sparingly, correct metabolic disturbances, abstinence, multi-vitamins  
- Intervention |
### Non-Alcoholic Fatty Liver Disease/ NASH

- Encompasses steatosis and steatohepatitis
- Requires steatosis, inflammation, and ballooning degeneration
  - A morphologic appearance identical to alcoholic steatohepatitis
- Steatosis may activate fibrogenesis
- Oxidative stress leads to expression of inflammatory cytokines
  - Histo-path: Macrovesicular steatosis; mixed lobular inflammation; lipogranulomas and Mallory bodies
- Associated with diabetes, obesity, metabolic syndrome
- Insulin resistance associated with primary type
- Secondary Type: drugs, etc
- A diagnosis of exclusion
- Associated with cryptogenic cirrhosis
- Risk factors: Increasing age > 45; Obesity and or diabetes; AST/ALT ratio > 1.
- Treatment of NASH is behavioral

### Benign Cysts of the Liver

**Slide 88**

- Unilocular cyst lined by simple cuboidal epithelium, surrounded by normal liver
- In polycystic liver disease could find more cysts
- Usually found at autopsy – incidental findings

### Hydatid Cysts

**Slide 89**

- Caused by larvae of Echinococcus tape worms
- Gross: spherical with fibrous rim; lined by germinal membrane that the worms come from
- Micro: worms have hooks arranged in circular pattern
- Cysts form space occupying lesion that blocks the biliary tree
- Many asymptomatic and are discovered incidentally
- Rarely compresses portal vein → portal hypertension
- Diagnosis: made by radiology or hydatid serology
- Needle biopsy contraindicated b/c leakage → anaphylaxis

### Hepatic Adenoma

**Slide 90**

- Benign tumor composed of hepatocytes and associated CT
- Gross: Solitary, well-defined with dilated blood vessels; tumor yellow to tan with areas of necrosis, cystic degeneration and hemorrhage
- Micro: Hepatocytes arranged in 2-3 layered trabeculae, having an irregular pattern with no portal areas or bile ducts; usually larger
- Consequence: Rupture of necrotic and peliotic areas with significant intra-abdominal bleeding
- Primarily in women
- Associated with OCPs
- Risk of hemorrhage or malignant degeneration
- Diagnostic test: MRI with gadolinium, hepatic angiography demonstrates radiating vessels
- Some regress when estrogen discontinued
- Surgery if no regression, >4 cm, symptomatic, increasing in size, hemorrhage
- Biopsy- risk of hemorrhage
<table>
<thead>
<tr>
<th>Focal Nodular Hyperplasia</th>
<th>Hepatocellular Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slide 91</strong></td>
<td><strong>Slide 92</strong></td>
</tr>
</tbody>
</table>

**than normal hepatocytes with cytoplasm rich in fat;**
Free floating vessels with no CT framework;
areas of peliosis (blood filled cavities not lined by epithelium) present;
eosinophilic inclusions

- **Gross:** Small irregular nodule divided by CT septa often with stellate scar differing in color
- **Micro:** looks like cirrhosis; hepatocytes arranged in 2-3 layer plates; the stellate scar has proliferating ductules; arteries with fibromuscular hyperplasia; contains bile ductular structures; usually arrayed in and around bands of fibrous tissue within the lesion

- **Greater predominance in females but not associated with estrogen usage**
- **Maybe the result of an anomalous arterial branch**
- **1/3 asymptomatic**
- **Relationship with angiopoietin**

- **Liver biopsy rarely needed**
- **Distinguish from fibrolamellar hepatocellular carcinoma**
- **Difficult to distinguish from adenoma**
- **Diagnosis:** Technetium-99m sulfur colloid scan; MRI with Gadolinium
- **Prognosis is good:** rarely rupture, no malignant degeneration

- **Tumor nodules are soft, hemorrhagic, and bile-stained and may be single or multiple, small or large, expanding or infiltrative, with or without a fibrous capsule**
- **Micro:** trabecular, atypical hepatocytes arranged in irregular trabeculae greater than 2 layers thick covered by non-fenestrated endothelium; no Kupffer cells; Pale round PAS+ inclusions; Mallory’s hyaline common; does not display normal reticulin stain

- **Malignant tumor almost always seen in cirrhotic liver**
- **Hep B and C are risk factors**
- **TMN classification**
- **Okuda staging system:** considers other factors of liver failure:
  - ascites, albumin levels, tumor size, bilirubin level

- **Diagnosis:** radiographically directed percutaneous needle biopsy; abnormal serum alpha fetoprotein
- **Fine needle aspirate yield abundant diagnostic trabecular material**
- **TXT:** radio frequency ablation for patients who are not good surgery candidates --- complete tumor necrosis likely with small tumors; necrotic tumor gradually resorbed and replaced with fibrotic scar tissue
- **10-30% of tumors are resectable**
- **Screening with alpha-fetoprotein and ultrasound**
<table>
<thead>
<tr>
<th><strong>Fibro-lamellar HCC</strong></th>
<th>A variant of HCC - Tumor cells are large with abundant eosinophilic cytoplasm; clear areas of cytoplasm (pale bodies) are frequent; dense PAS positive cytoplasmic inclusions may also be present; Abundant CT – dense layers of collagen</th>
<th>• Usually occurs in normal liver and strikes younger folks • Survival rate is higher than regular HCC</th>
<th>• Normal serum alpha fetoprotein</th>
</tr>
</thead>
</table>
| **Hepatoblastoma**     | - Malignant tumor composed of cells resembling primitive hepatic parenchymal cells 
- Gross: large, sharply delimited, grayish-yellow variegated tumor with hemorrhagic areas 
- Micro: Can be embryonal, fetal or small cell undifferentiated anaplastic | • Poor Prognosis: Age <1 year, large size, involvement of vital structures, predominance of small anaplastic cells |  |
| **Hemangiomas**        | - Composed of vascular channels lined by a single layer of flat endothelium 
- Gross: solitary purple subcapsular nodule, with variable degrees of fibrosis, calcification 
- Micro: Cavernous vascular spaces lined by flattened endothelium with variable amounts of fibrous septae, thrombosis, phleboliths, and calcification | • Most common benign hepatic tumor • Complications: rupture; Kasabach-Merritt syndrome (platelet sequestration and consumptive coagulopathy) | • Diagnosis: CT, ultrasound; Technetium-labeled red blood cell scan; MRI - diagnostic test of choice, frequently not needed; Liver biopsy - rarely needed but can be performed safely; Prognosis is quite good, rarely hemorrhage or severe symptoms • TXT: rarely require surgery; if there are symptoms; new lower dose estrogen OCPs are safe; size alone not indication for surgery |