The Physician Pharmacist: Gastrointestinal (GI)

Embryology:
-Foregut = esophagus to duodenum at level of pancreatic duct + common bile duct insertion (Ampulla of Vater)
-Midgut = lower duodenum to proximal 2/3 rds of Transverse colon
-Hindgut = distal 1/3 of Transverse colon to anal canal above the pectinate line
-Midgut:
- 6th week of development = physiologic herniation of midgut through umbilical ring
- 10th week of development = returns to abdominal cavity + rotates around superior mesenteric artery (SMA), Total 270 degrees counterclockwise

Ventral Wall Defects:
-developmental defects due to failure of rostral fold closure (sternal defects = Ectopia cordis; lateral fold closure = omphalocele, gastroschisis; caudal fold closure = bladder exstrophy)

1. Gastroschisis:
-Extrusion of abdominal contents through abdominal folds (typically right of umbilicus)
-NOT covered by peritoneum or amnion
-not associated w/ chromosome abnormalities
-favorable prognosis

2. Omphalocele:
-failure of lateral walls to migrate at umbilical ring → persistent midline herniation of abdominal contents into umbilical cord
-Covered by peritoneum + Amnion (light gray shiny sac)
-associated w/ **Congenital anomalies (Trisomy 13 and 18, Beckwith-Wiedemann Syndrom**e) + other structural abnormalities (Cardiac, GU, Neural Tube)

3. Congenital Umbilical Hernia:
-Failure of umbilical ring to close after physiologic herniation of midgut
-Covered by skin**
-protrudes w/ Intra-abdominal pressure (Crying)
-Associated w/ Congenital Disorders (Down Syndrome, Congenital Hypothyroidism)
-Small defects typically close spontaneously

Tracheoesophageal Anomalies:
-Esophageal Atresia (EA) w/ Distal Tracheoesophageal fistula (TEF) = most common + presents w/ Polyhydramnios in Utero (due to Fetus inability to swallow amniotic fluid)
-sxs = neonates drool, choke, vomit w/ first feeding
-TEFs allow air to enter the stomach (Visible on CXR)
-Cyanosis seen secondary to Laryngospasm (to avoid reflux-related aspiration)
-ddx = **failure to pass NG tube into stomach** (prominent gastric bubble in stomach due to air)

Intestinal Atresia:
-presents w/ bilious vomiting + abdominal distension within first (1-2 days of life)
-**Duodenal Atresia** = failure to recanalize (double Bubble = dilated stomach, proximal duodenum), associated w/ **Down Syndrome**
-**Jejunal and Ileal Atresia** = disruption of mesenteric vessels (Typically **SMA**) → ischemic necrosis of fetal intestine → segmental resorption; bowel becomes discontinuous
- "Triple Bubble" = dilated stomach, duodenum, proximal jejunum) + gasless Colon

Hypertrophic Pyloric Stenosis:
-Most common cause of Gastric Outlet obstruction in infants
-Palpable "Olive-Shaped" mass in Epigastric region, visible peristaltic waves, nonbilious projectile vomiting at 2-6 weeks
-Common in firstborn males; associated w/ exposure to macrolides
-sxs = **Hypokalemic Hypochloremic Metabolic Alkalosis** (secondary to vomiting of gastric acid + subsequent volume contraction)
-US = thickened + lengthened pylorus
-Tx = Surgical Incision of Pyloric Muscles (Pyloromyotomy)

Pancreas Embryo:
-derived from Foregut
-**Ventral pancreatic bud** contributes to uncinate process + main pancreatic duct***
-**Dorsal pancreatic bud** alone becomes the body, tail, isthmus, accessory pancreatic duct
-Both Ventral + Dorsal buds create the head
-**Annular Pancreas =** abnormal rotation of Ventral bud forms a ring encircling the duodenum (Duodenal Narrowing, vomiting)
-**Pancreas Divisum =** ventral + dorsal parts fail to fuse at 7 weeks of development (common anomaly; mostly asymptomatic, but may cause chronic abdominal pain/pancreatitis)

Splenic Embryo:
-Arises in mesentery of stomach (hence is Mesodermal) but has Foregut supply (Celiac Trunk → Splenic a.)

Anatomy:

Retroperitoneal Structures:
-posterior to (and outside of) the peritoneal cavity
-injuries here can cause blood/gas accumulation in the retroperitoneal space
-SAD PUCKER:
- Suprarenal (Adrenal) Glands
- Aorta and IVC
- Duodenum (2nd through 4th parts)
- Pancreas (except tail)
- Ureters
- Colon (Descending + Ascending)
- Kidneys
- Esophagus (Thoracic Portion)
- Rectum (partially)

Important GI Ligaments:

1. Falciform Ligament:
-Connects Liver to anterior Abd wall
-**Ligamentum Teres Hepatis** (Derivative of fetal umbilical vein), Patent Paraumbilical Veins
-Derivative of Ventral Mesentery
-"That big ugly worm looking thing on the liver"

2. Hepatoduodenal Ligament:
-connects Liver to duodenum
-**Portal Triad** = Proper Hepatic Artery, Portal Vein, Common Bile Duct
-Derivative of Ventral Mesentery
-Pringle Maneuver = ligament is compressed manually or with a vascular clamp in omental foramen to control bleeding from hepatic inflow source
-Borders of omental foramen, which connects the greater + lesser sacs
-Part of lesser omentum

3. Hepatogastric Ligament:
-Connects Liver to lesser curvature of stomach
-Gastric vessels
-Derivative of ventral mesentery separates greater + lesser sacs on the right
-May be cut during surgery to access lesser sac
-Part of Lesser Omentum

4. Gastrocolic Ligament:
-Connects Greater curvature + Transverse colon
-Gastroepiploic arteries
-Derivative of dorsal mesentery
-Part of Greater Omentum

5. Gastrosplenic Ligament:
-Connects greater curvature + spleen
-Short gastritis, left gastroepiploic vessels
-derivative of dorsal mesentery
-Separates greats + lesser sacs on the left
-Part of Greater Omentum

6. Splenorenal Ligament:
-connects spleen to left pararenal space
-splenic artery and vein, tail of pancreas
-derivative of dorsal mesentery

Digestive Anatomy:
-Inside to outside (layers of gut wall)
- Mucosa = epithelium, lamina propria, muscularis mucosa
- Submucosa = includes **submucosal nerve plexus (Meissner)**, secretes fluid
- Muscularis Externa = includes **Myenteric nerve Plexus (Auerbach),** motility
- Serosa (when intraperitoneal), Adventitia (when retroperitoneal)

-Ulcers = extend into submucosa, inner or outer muscular layer
-Erosions = mucosa only

Digestive Tract Histology:
1. Esophagus:
    a. Nonkeritonized stratified squamous epithelium
    b. Upper 1/3rd = striated muscle
    c. Middle and lower 2/3 = smooth muscle, w/ some overlap at the transition
2. Stomach:
    a. Gastric Glands
    b. Parietal Cells = eosinophilic
    c. Chief Cells = basophilic
3. Duodenum:
    a. Villi and Microvilli absorptive surface
    b. **Brunner Glands** (Bicarb-secreting cells of submucosa)
    c. Crypts of Lieberkuhn (Contain stem cells that replace enterocytes/goblet cells + Paneth cells (secrete defensins, Lysozyme, TNF
4. Jejunum:
    a. Villi, Crypts of Lieberkun, and Plicae circulares (also present in distal duodenum)
5. Ileum:
    a. Villi, Peyer Patches (Lymphoid Aggregates in Lamina Propria, Submucosa)
    b. Plicae Circulares (Proximal Ileum)
    c. Crypts of Lieberkuhn
    d. Largest # of Goblet Cells in the small intestine
6. Colon:
    a. Crypts of Lieberkuhn w/ Abundant goblet cells but no villi

Abdominal Aorta and Branches:
-Arteries supplying GI structures are single + branch anteriorly
-Arteries supplying non-GI structures are paired and branch laterally + posteriorly
-Dual-Blood Supply Regions/Watershed Regions → susceptible in colonic ischemia;
- Splenic Flexure = SMA and IMA
- Rectosigmoid Junction = last sigmoid arterial branch from the IMA and Superior Rectal Artery

1. Nutcracker Syndrome:
-Compression of LEFT renal Vein btw the **SMA and Aorta**
-sxs = Abd flank pain, gross hematuria (rupture of thin-walled renal varicosities), Left-side varicocele

2. Superior Mesenteric Artery Syndrome:
-"SMA/Aorta Pinch Duodenum = obstruction"
-Intermittent intestinal obstruction sxs (Postprandial pain) when SMA and Aorta compress transverse (third) portion of Duodenum
-occurs in conditions associated w/ Diminished Mesenteric Fat (Low Body Weight/Malnutrition)

-T12 = Inferior Phrenic a, Superior Suprarenal a, Middle Suprarenal a, Celiac a.
-L1 = SMA, Inferior Suprarenal a
-L1/L2 Border = Renal a.
-L2 = Gonadal a.
-L3 = IMA
-L4 = "BiFOURcation of Abdominal Aorta into R/L Common Iliac, Median Sacral a.
-L5 = Internal / External Iliacs

1. Foregut:
-Celiac artery supplies
-PSNS = Vagus
-Vertebral level = T12/L1
-Supplies Pharynx (Vagus n. only) and Lower Esophagus (Celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)

2. Midgut:
-SMA supplies
-PSNS = Vagus
-Vertebral level = L1
-supplies Distal duodenum to proximal 2/3rd of transverse colon

3. Hindgut:
-IMA
-PSNS = Pelvic
-Vertebral level = L3
-supplies Distal 1/3rd of Transverse colon to upper portion of anal canal

Celiac Trunk:
-Branches = Common Hepatic, Splenic, Left Gastric
-make up the main blood supply of Foregut
-Strong anastomose exist btw
- Left and Right Gastroepiploic
- Left and Right Gastrics

-Common Hepatic:
- Proper Hepatic
  - Left Hepatic
  - Right Hepatic
  - Cystic

-Left Gastric:
- Esophageal branches traveling proximally
- Anastomoses w/ Right Gastric

-Splenic:
- Short gastritis
- Left Gastroepiploic

-Gastroduodenal:
- Anterior Superior Pancreaticoduodenal
- Posterior Superior Pancreaticoduodenal
- Right Gastric (lesser curvature)
- Right Gastroepiploic (greater curvature)

Portosystemic Anastomoses:
1. Esophagus:
-sxs = **Esophageal Varices**
-Left gastric => <= Esophageal (Drains into Azygos)

2. Umbilicus:
-sxs = **Caput Medusae**
-Paraumbilical => <= small epigastric veins of the anterior abdominal wall

3. Rectum:
-sxs = **Anorectal varices**
-Superior Rectal => <= middle and inferior rectal

TIPS: "Transjugular Intrahepatic Portosystemic Shunt"
-btw the portal vein and hepatic vein relieves portal HTN by shunting blood to the systemic circulation bypassing liver
-precipitates Hepatic Encephalopathy due to clearance of Ammonia from Shunting

Pectinate Line:
-"Dentate Line" = formed where Endoderm (Hindgut) Meets Ectoderm

Above Pectinate Line:
-internal hemorrhoids, Adenocarcinoma
-Internal Hemorrhoids receive visceral innervation and are therefore NOT painful
-N = Visceral Innervation
-A = Superior Rectal (branch from IMA)
-V = Superior Rectal Vein → IMV → Splenic vein → portal Vein
-L = Drains to **internal iliac** LN

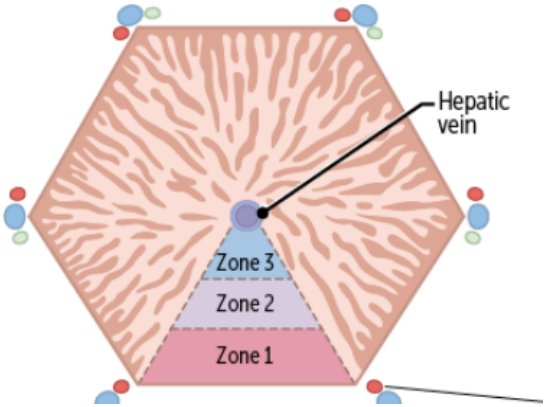
Below Pectinate Line:
-external hemorrhoids, anal fissures, squamous cell carcionoma
-External hemorrhoids receive somatic innervation (Inferior rectal branch of pudendal nerve) + are Painful if thrombosed
-N = SOmatic Innervation (Pudendal S2-4)
-A = Inferior Rectal a (branch of internal pudendal a)
-V = Inferior rectal vein → internal pudendal vein → internal iliac vein → common iliac vein → IVC
-L = Durian to superficial **Inguinal** LN
-**Anal Fissure**: "Tear in Anoderm Below Pectinate Line"
- Pain while pooping
- Blood on toilet paper
- Located in posterior midline b/c this area is poorly perfused
- Associated w/ low fiber diets and constipation

Liver Tissue Architecture:
-Functional unit of liver made up of Hexagonally arranged lobules surrounding the central vein w/ portal triads on the edes (Portal Vein, Hepatic a., Dile ducts, Lymphatics)
-Apical surface of hepatocytes faces bile canaliculi
-Basolateral surface faces sinusoids
-**Kupffer Cells** = Specialized macrophages located in Sinusoids
-Hepatic Stellare (Ito) Cells = in space of Disse, Store Vitamin A (when quiescent) and produce extracellular matrix (when activated)
- Responsible for Hepatic Fibrosis

-Zone I = Periportal Zone:
- Affected 1st by viral Hepatitis
- Best Oxygenated, most resistant to circulatory compromise
- Ingested Toxins

-Zone II = Intermediate Zone:
- Yellow Fever

-Zone III = Pericentral (Centrilobular) Zone:
- Affected 1st by Ischemia (Least Oxygenated)
- High Conc of CYP450
- Most sensitive to metabolic toxins (Ethanol, CCl4, Halothane, Rifampin, APAP)
- Site of Alcoholic Hepatitis



-Blood Flows toward the center
-Bile flows opposite (towards the outer edges)

Biliary Structure:
-Gallstones that reach the confluence of the common bile + pancreatic ducts at the ampulla of Vater can block common bile (cholangitis) and pancreatic ducts (pancreatitis) (Double Duct sign)
-Tumors that arise in head of pancreas (often Ductal Adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder w/ painless jaundice (Courvoisier's Sign)

Femoral Region: "Lateral to Medial" = NAVeL
-Femoral Triangle = Femoral Nerve, Artery, Vein
-Femoral Sheath = Fascial Tube below inguinal ligament (contains femoral vein, artery, and canal (Deep Inguinal Lymph Nodes) but **NOT Femoral Nerve**

Spermatic Cord (ICE tie): "From Inside to out"
-Internal Spermatic Fascia = Transversalis fascia
-Cremasteric Muscle and Fascia (Internal Oblique)
-External Spermatic Fascia (External Oblique)

Hernias:
-protrusion of peritoneum through an opening (site of weakness)
-At risk for Incarceration (not reducible back to where it came from) or strangulation (ischemia/necrosis)
-Complicated hernias can present w/ Tenderness, Erythema, Fever

1. Diaphragmatic Hernia:
-Abdominal structures enter the thorax
-Most common causes;
- Infants = congenital defect of pleuroperitoneal membrane → left-sided herniation (right hemidiaphragm is relatively protected by liver)
- Adults = Laxity/defect of phrenoesophageal membrane → **Hiatal hernia** (herniation of stomach through esophageal Hiatus)

-**Sliding Hiatal Hernia** = gastroesophageal junction is displaced upward as gastric cardia slides into hiatus; "Hourglass stomach" (most common type, associated w/ GERD)
-**Paraesophageal Hiatal Hernia** = gastroesophageal junction is usually normal BUT gastric fundus protrudes into the thorax (Stomach fundus pushes through)

2. Indirect Inguinal Hernia:
-Goes through the Internal (Deep) Inguinal Ring, External (Superficial) inguinal Ring, and into the Groin
-Enters internal inguinal ring **lateral to inferior epigastric vessels**
-Caused by failure of **Processus Vaginalis** to close (can form Hydrocele)
-Males more common
-Follows pathway of testicular descent (Covered by all three layers of Spermatic Cord Fascia)****

3. Direct Inguinal Hernia:
-Protrudes through **inguinal (Hesselbach) Triangle**
-Bulges directly through parietal peritoneum **MEDIAL to Inferior Epigastric Vessels** but Lateral to Rectus Abdominis
-Goes through External (Superficial) Inguinal Ring ONLY
-Covered by external spermatic fascia
-Older males due to acquired weakness of transversalis fascia

MDs don't LIe = Media/Direct, Lateral/Intirect

4. Femoral Hernias:
-protrudes **below Inguinal ligament** through femoral canal below and lateral to pubic tubercle
-More common in Females (but overall inguinal hernias are most common)
-Most likely to present w/ Incarceration or Strangulation (vs. Inguinal hernias)

GI Regulatory Substances:

Gastrin:
-G cells (Antrum of Stomach, Duodenum)
-Acts on Enterochromaffin-like Cells → Histamine
-Role:
- Gastric H+ secretion
- Growth of gastric mucosa
- gastric motility

-Regulation:
- by stomach distention/alkalinization, AAs, Peptides, Vagal Stimulation via Gastrin-releasing peptide (GRP)
- by pH < 1.5

- by Chronic PPI use
- in Chronic Atrophic Gastritis (H Pylori)
- in Zollinger-Ellison Syndrome (Gastrinoma)

Somatostatin:
-D Cells (pancreatic Islets, GI mucosa)
-Role:
- gastric acid and Pepsinogen secretion
- Pancreatic and Small intestine fluid secretion
- gallbladder contraction
- insulin + glucagon release

-Regulation:
- by Acid
- by Vagal Stimulation

-Inhibits secretion of Various Hormones (encourages "Somato-stasis")
-Analog to treat acromegaly, Carcinoid Syndrome, VIPoma, Variceal Bleeding

Cholecystokinin (CCK):
-I Cells (Duodenum, Jejunum)
-Role:
- Pancreatic Secretion
- Gallbladder Contraction
- Gastric Emptying
- Sphincter of Oddi Relaxation

-Release by Fatty acids, AAs
-Acts on neural muscarinic pathways to cause pancreatic secretion

Secretin:
-S cells (Duodenum)
-Role:
- pancreatic bicarb secretion
- gastric acid secretion
- bile secretion

- by acid, Fatty acids in lumen of duodenum
- bibarb neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function

Glucose-Dependent Insulinotropic Peptide (GIP):
-"Gastric Inhibitory Peptide (GIP)"
-K cells (Duodenum, Jejunum)
-Role:
- Exocrine = Gastric H+ secretion
- Endocrine = Insulin Release

- by Fatty acids, AAs, Oral Glc

-Oral Glucose load insulin much more compared to IV equivalent due to GIP secretion**

Motilin:
-Small Intestine
-Produces Migrating Motor Complexes (MMCs)
- in Fasting State
-Motilin Receptor agonist (Erythromycin) are used to Stimulate intestinal peristalsis

Vasoactive Intestinal Polypeptide (VIP:
-PSNS Ganglia in Sphincters, Gallbladder, Small Intestine
-Role:
- Intestinal water and electrolyte secretion
- relaxation of intestinal smooth muscle and Sphincters

-Regulation:
- by Distension and vagal stimulation
- by Adrenergic Input

-**VIPoma** = non-a, non-B islet cell pancreatic tumor that secretes VIP; watery diarrhea, hypokalemia (K+), Achlorhydria, "Pancreatic Cholera"

Nitric Oxide (NO):
- Smooth muscle relaxation, including LES

-Loss of NO secretion → LES tone → Achalasia

Ghrelin:
-Stomach
-Role = Appetite
- release in fasting state, by food intake

-Prader-Willi Syndrome (Maternal disomy) Ghrelin
-Gastric Bypass SUrgery = Ghrelin

Secretory Products:

Intrinsic Factor:
-Parietal Cells (Stomach)
-Vitamin B12-Binding Protein (Required for B12 uptake in terminal ileum)
-Autoimmune Destruction of Parietal Cells → chronic gastritis and Pernicious Anemia

Gastric Acid:
-Parietal Cells (Stomach)
- Stomach pH
-Regulation:
- by Histamine, Vagal stimulation (ACh), Gastrin
- by Somatostatin, GIP, PGs, Secretin

Pepsin:
-Chief Cells (Stomach)
-Protein Digestion
- Vagal stimulation, Local Acid
-Pepsinogen (Inactive) is Converted to Pepsin (Active) in the presence of H+

Bicarbonate:
-Mucosal cells (Stomach, Duodenum, Salivary Glands, Pancreas) + Brunner Glands (Duodenum)
-Neutralizes Acid
- by pancreatic and biliary secretion w/ Secretin
-Trapped in Mucus that covers the gastric epithelium

Pancreatic Secretions:
-Isotonic fluid
-**low flow → high Chloride; high flow → high bicarb**

1. A-amylase = digests starch (secreted in active form)
2. Lipases = fat digestion
3. Proteases = protein digestion (Trypsin, Chymotrypsin, Elastase, Carboxypeptidases), Secreted as "Proenzymes" = "Zymogen"
4. Trypsinogen:
- Converted to active enzyme Trypsin → activation of other proenzymes + cleaving of additional trypsinogen molecules into active Trypsin (Positive Feedback Loop)
- Converted to Trypsin by Enterokinase/Enteropeptidase (Brush-border enzyme on Duodenal and Jejunal Mucosa)

Carbohydrate Absorption:
-SGLT-1 and GLUT-5 on Apical surface
-Na/K ATPase and GLUT-2 on basolateral surface
-Only monosaccharides (Glc, Galactose, Fructose) are absorbed by Enterocytes
- SGLT-1 = Glc, Galactose, and are Na+ dependent
- GLUT-5 = Fructose uptake via facilitated diffusion

-D-xylose Test = passively absorbed in intestine (blood and urine levels decrease w/ mucosal damage, normal in pancreatic insufficiency)

Vitamin & Mineral Absorption:
-Iron (Fe2+) in Duodenum
- Heme Iron enters enterocyte, accumulates as Ferritin
- Ferroportin (basolateral) allows Iron to exit and bind Transferrin in blood stream
- Ferroportin activity is inhibited by Hepcidin (from Liver)

-Folate = small bowel
-Vit B12 = terminal ileum along w/ bile salts (requires Intrinsic Factor = from Parietal Cells in stomach)

Peyer's Patches;
-Unencapsulated Lymphoid tissue found in Lamina Propria + Submucosa of Ileum
-Contains **M-Cells** (sample and present antigens to Immune Cells)
-B-cells stimulated in germinal centers of Peyer patches differentiate into **IgA-Secreting plasma cells** (which reside in Lamina Propria)
-IgA receives Protective secretory component and is then transported across the epithelium to the gut to deal w/ intraluminal antigen

Bile:
-Bile Salts (bile acids conjugated to glycine, taurine, make them water soluble), Phospholipids, Cholesterol, Bilirubin, Water, Ions
-Cholesterol **7a-Hydroxylase** Catalyzes RDS of Bile Acid Synthesis
-Functions:
- Digestion/absorption of lipids + fat-sol vitamins
- Bilirubin + Cholesterol Excretion
- Antimicrobial activity (via membrane disruption)

- absorption of enteric bile salts as distal ileum prevents normal fat absorption +cause bile acid diarrhea
-Calcium (normally binds Oxalate) gets bound to Fat so oxalate is absorbed → Calcium Oxalate

Bilirubin:
-Heme is metabolized by **Heme oxygenase** to biliverdin → reduced to Bilirubin
-Unconjugated bilirubin is removed from blood by liver, conjugated w/ glucuronate, excreted in bile
- UDP-Glucuronosyl-Transferase

-**Direct Bilirubin** = conjugated w/ Glucuronic Acid; Water Soluble
-**Indirect Bilirubin** = Unconjugated (Water Insoluble)

-RBC → Heme → Unconjugated (Indirect) Bilirubin → unconjugated Bilirubin-Albumin → UDP-Glucuronyosyl-Transferase → Conjugated (Direct Bilirubin - in liver) → release into gut as bile → Urobilinogen → 20% participates in Enterohepatic circulation + small amount released in urine as Urobilin (Yellow color of urine), rest excreted in feces as Stercobilin (brown stool)

Sialothiiasis:
-Stone in salivary gland duct
-Parotid, Submandibular, Sublingual salivary glands
-Single stone more common in Submandibular (Wharton Duct)
-Associated w/ Salivary stasis (dehydration) and Trauma
-Recurrent Pre/Periprandial pain + swelling in affected gland
-**Sialadenitis** = inflammation of salivary gland due to obstruction, infection (Staph aureus, mumps, virus) or immune-mediated mechs (Sjogrens)

Salivary Gland Tumors:
-mostly benign + usually parotid gland (85%)
-Submandibular gland/Sublingual gland tumors are generally malignant
1. Pleomorphic Adenoma (Benign Mixed Tumor) = most common salivary gland tumor
- Composed of chondromyxoid stroma + epithelium
- Recurs if incompletely excited or ruptured intraoperatively
- Can undergo malignant transformation

2. Mucoepidermoid Carcinoma:
- Most common malignant tumor (has mucinous and squamous Components)

3. Warthin Tumor (papillary cystadenoma Lymphomatosum)
- Benign cystic tumor w/ **Germinal Centers**
- Smoking**, Bilateral and multifocal in 10%

Achalasia:
-Failure of LES to relax due to **degeneration of Inhibitory neurons** (Containing NO and VIP) **in the Myenteric (Auerbach) Plexus** of Esophageal Wall
-Primary Achalasia = Idiopathic
-Secondary Achalasia = **Chagas Disease** (Trypanosoma Cruzi Infection) or Extraesophageal malignancies (Paraneoplastic, Mass effect)
-Progressive Dysphagia to **solids + Liquids** (vs. Obstruction - Primarily Solids)
- risk of Esophageal Cancer
-Manometry = uncoordinated or absent peristalsis w/ LES resting pressure
-Barium Swallow = dilated esophagus w/ area of distal stenosis **("Birds-Beak")**
-Tx = Surgery, Endoscopic Botulinum Toxin Injection

Esophageal Pathologies:
1. GERD:
-heartburn, regurgitation, dysphagia, chronic cough, hoarseness (Laryngopharyngeal reflux)
-Associated w/ Asthma
-Caused by Transient decreases in LES tone

2. Eosinophilic Esophagitis:
-infiltration of eosinophils in the esophagus often in atrophic pts
-cause = multifactorial
-Food allergens → dysphagia, food impaction
-Esophageal Rings + Linear Furrows often seen on endoscopy

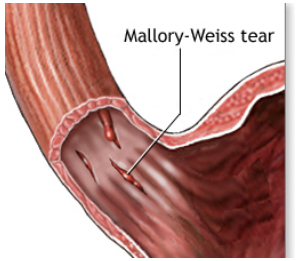
3. Esophagitis:
-Associated w/ reflux, infxn in immunocompromised (Candida = White Pseudomembrane; HSV-1 = Punched-out Ulcers; CMV = linear ulcers), caustic ingestion, pill-induced esophagitis (Bisphosphonates, TCNs, NSAIDs, Iron, K+)

4. Esophageal Strictures:
-Associated w/ Caustic Ingestion, Acid Reflux, Esophagitis

5. Plummer-Vinson Syndrome:
-Triad:
- **Dysphagia**
- **Iron Def (IDA)**
- **Esophageal Webs******

Nephrolithiasis

6. Mallory-Weiss Syndrome:
"Tear/laceration of the mucous membrane at the point where esophagus and stomach meet → severe bleeding"
-partial thickness, Longitudinal lacerations of Gastroesophageal junction, confined to mucosa/submucosa due to severe vomiting
-Often presents w/ Hematemesis +/- Abdominal/back pain
-Usually found in pts w/ Alcohol use Disorder, Bulimia Nervosa



7. Esophageal Varices:
-Dilated submucosal veins in lower 1/3rd of Esophagus secondary to portal HTN
-common in pts w/ cirrhosis
-potentially life-threatening bleeds
-Tx = somatostatin (Octreotide), Banding

8. Distal Esophageal Spasm:
-"Diffuse Esophageal Spasm"
-Spontaneous, Non Peristaltic (Uncoordinated) contractions of the esophagus w/ Normal LES pressure
-**Presents w/ dysphagia + angina-like chest pain**
-Barium swallow reveals **"Corkscrew"** Esophagus
-Manometry = often diagnostic
-Tx = Nitrates + CCBs

9. Scleroderma Esophageal Involvement:
-Esophageal Smooth Muscle Atrophy → LES pressure and Distal Esophageal Dysmotility → Acid Reflux and Dysphagia → stricture, Barrett esophagus, Aspiration
-Part of CREST Syndrome

10. Esophageal Perforation:
-Most commonly iatrogenic following esophageal instrumentation
-Iatrogenic causes = spontaneous rupture, foreign body ingestion, trauma, malignancy
-Present w/ **Pneumomediastinum** (air in mediastinum)
-SQ emphysema may be due to dissecting air (Crepitus in the neck region or chest wall)

Barrett Esophagus:
-specialized intestinal metaplasia
-Replacement of **Nonkeratinized Stratified Squamous Epithelium → Intestinal Epithelium** (Nonciliated Columnar **w/ Goblet Cells**) in Distal Esophagus
-Occurs due to Chronic Gastroesophageal Reflux Disease (GERD)
-Associated w/ Risk of Esophageal **Adenocarcinoma**

Esophageal Cancer:
-Typically presents w/ progressive dysphagia (first solids, then liquids) + Weight loss
-Aggressive course due to lack of serosa in esophageal wall → allowing rapid extension/metastasis
-Poor prognosis due to Advanced dx at presentation

1. Squamous Cell Carcinoma (SCC):
-Upper 2/3rds of Esophagus
-RF = **Alcohol, Hot Liquids, Caustic Strictures, Smoking, Achalasia**
-More common around the world

2. Adenocarcinoma:
-Lower 1/3rd
-RF = Chronic **GERD, Barrett Esophagus, Obesity, Smoking**
-More common in America

Menetrier Disease:
-Hyperplasia of Gastric Mucosa → Hypertrophied Rugae (Imaging of stomach looks "Wavy" like brain gyri)
-Causes excess mucus production w/ protein loss + Parietal Cell Atrophy (Acid Production + Intrinsic Factor)
-Precancerous
-Sxs: "WAVEE"
- Weight loss
- Anorexia
- Vomiting
- Epigastric pain
- Edema (due to protein loss)

- risk of Squamous Cell Carcinoma
-Associated w/ Glossitis

Gastritis:
1. Acute Gastritis:
-Erosions caused by;
- NSAIDs → PGE2 → Gastric Mucosa protection
- Burns (Curling Ulcer) → Hypovolemia --. Mucosal Ischemia
- Brain Injury (Cushing Ulcer) → vagal stimulation → ACh → H+ production

-Especially common in pts w/ alcohol use disorder, chronic NSAID use

2. Chronic Gastritis:
-mucosal inflammation → atrophy (hypochlorhydria → hypergastrinemia) and Intestinal Metaplasia (risk of gastric cancers)
-**H. Pylori** = Most common cause, risk of PUD, MALT Lymphoma, Affects **Antrum** first + spread to body of stomach
-**Autoimmune** = autoantibodies to the H/K ATPase on Parietal Cells and to Intrinsic Factor → risk of Pernicious Anemia; More commonly affecting Body/Fundus of stomach

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Gastric Cancer:
-Most commonly Gastric Adenocarcinoma
-Early aggressive local spread w/ node/liver metastasis
-Often presents late, w/ weight loss, abdominal pain, early satiety, and acanthosis nigricans or **Leser-Trelat Sign** (abrupt appearance of multiple seborrhoeic keratoses on skin)
-Intestinal = associated w/ H. pylori, Dietary nitrosamines (smoked foods), smoking, achlorhydria, chronic gastritis
- Often on Lesser curvature; looks like Ulcer w/ raised margins

-Diffuse = **not associated w/ H pylori** (most causes due to **E-cadherin Mutation; Signet Ring Cells** = mucin-filled cells w/ peripheral nuclei)
- Stomach wall is grossly thickened and leathery (Linitis Plastica)

1. Virchow Node = involvement of **Left Supraclavicular node** by metastasis from stomach

-Boerhaave Syndrome = Transmural, usually distal esophageal rupture due to violent retching

3. Sister Mary Joseph Nodule = SQ periumbilical Metastasis (indicates poor prognosis w/ advanced disease)

4. Blumer Shelf = Palpable mass on digital rectal exam suggesting mets to rectouterine ouch (Pouch of Douglas)

Peptic Ulcer Disease (PUD):
-Ulcer Hemorrhage is the most common complication
-ruptured ulcer on lesser curvature = bleeding from Left Gastric a.
-rupture on posterior wall of duodenum = bleeding from gastroduodenal a.
-**Pneumoperitoneum** (Free air under Diaphragm) often from anterior duodenal ulcers can perforate into the anterior abdominal cavity
- Sxs = Referred pain to shoulder via irritation of phrenic nerve + CXR visualization of air

1. Gastric Ulcer:
-pain worse w/ intake/eating (weight loss)
-H. Pylori infection (70% cases), or Chronic NSAIDs
- Mucosal protection against gastric acid
- Risk of Carcinoma

-Biopsy margins to rule out malignancy

2. Duodenal Ulcer:
-pain DECREASES w/ meals (weight gain)
-H. Pylori infection (90% cases)
- mucosal protection or gastric acid secretion

-can occur from Zollinger-Ellison Syndrome
-Generally benign w/ minimal increase in risk of malignancy
-Benign-appearing ulcers (not routinely biopsied)

Acute GI Bleeding:

-Upper GI Bleed:
- Originates **Proximal** to **ligament of Treitz** (suspensory ligament of Duodenum)
- Presents w/ Hematemesis and or Melena
- Seen in PUD or Variceal bleeds

-Lower GI Bleeds:
- Originates **distal** to Ligament of Treitz
- Hematochezia (fresh bright red blood) passage

Malabsorption Syndromes:

Celiac Disease:
-"Gluten-Sensitive Enteropathy" = "Celiac Sprue"
-**Autoimmune-mediated intolerance of Gliadin** (Gluten protein found in wheat, barley, rye)
-Associated w/ HLA-**DQ2**, HLA-**DQ8**, Northern European Descent
-Affects Distal Duodenum +/or Proximal Jejunum → malabsorption and Steatorrhea
-Associated w/ **Dermatitis Herpetiformis, Bone Density, risk of Malignancy (T-Cell Lymphoma)**
-DDx = D-Xylose Test is Abnormal
-Serology = (+) IgA anti-tissue Transglutaminase (IgA-tTG), Anti-endomysial, Anti-deamidated Gliadin Peptide antibodies
-Histology = **Villous Atrophy, Crypt Hyperplasia, Intraepithelial Lymphocytosis**
-Tx = Gluten-Free Diet

Lactose Intolerance:
-Lactase Deficiency
-Normal-appearing Villi (except if caused by Viral Enteritis)
-Osmotic Diarrhea w/ stool pH (Colonic Bacteria Ferment Lactose)
-Lactose Hydrogen Breath Test = (+) for Lactose Malabsorption if Post-lactose breath hydrogen value rises > 20 ppm compared to baseline

Pancreatic Insufficiency:
-Due to chronic pancreatitis, CF, Obstructing Cancer
-Causes Malabsorption of fat (ADEK + B12)
- Duodenal Bicarb (pH) and Fecal Elastase

-D-xylose Test = **NORMAL**

Tropical Sprue:
-Similar findings to Celiac Sprue (affects small bowel) but responds to Antibiotics
-seen in pts recently traveling to tropics (unknown cause)
- mucosal absorption affecting duodenum + jejunum

-(+) Megaloblastic Anemia (due to folate + B12 def)

Whipple Disease:
-Infxn w/ **Tropheryma Whipplei** (Intracellular Grm (+))
-PAS (+) Foamy Macrophages in Intestinal Lamina

2. Krukenberg Tumor = metastasis to ovaries (typically bilateral), Abundant Mucin-secreting signet Ring cells

Inflammatory Bowel Diseases (IBD):

1. Crohn's Disease:
-Any portion of the GI tract (Ileum, colon most common)
-Skip lesions and rectal sparing
-**Transmural** inflammation → fistulas
-Cobblestone mucosa, creeping fat, bowel wall thickening ("string sign" on small bowel follow-through), linear ulcers/fissures
-Hist = Noncaseating granulomas + lymphoid aggregates **(Th1 Mediated)**
-Malabsorption/malnutrition, colorectal cancer (Risk w/ Pancolitis)
-Complications = fistulas (Enterovesical fistulae, which causes recurrent TI and Pneumaturia), Phelgmon/abscess, strictures (causing obstruction), perianal disease
- Diarrhea +/- blood
- Rash **(Pyoderma Gangrenosum, Erythema Nodosum)**
- Eye inflammation (Episcleritis, Uveitis), Oral ulcerations (Aphthous Stomatitis), Arthritis (Peripheral Spondylitis)
- Kidney stones (Calcium Oxalate), Gallstones
- (+) antibodies for anti-saccharomyces cerevisiae (ASCA)

-Tx = Steroids, AZA, Abx (Cipro/Metro), Biologics (Infliximab, Adalimumab)

2. Ulcerative Colitis:
-Colitis = colon inflammation
-Continuous colonic lesions, always w/ rectal invomvelent
-Mucosal and submucosal inflammation ONLY
-Friable mucosa w/ superficial and/or deep ulcerations
-**Loss of Haustra → Lead pipe appearance**
-Crypt abscesses and ulcers, bleeding, **No Granulomas (Th2)**
-Malabsorption/malnutrition, colorectal cancer (risk w/ pancolitis) (same as above)
-Complications = fulminant colitis, toxic megacolon, perforation
in stool
- Associated w/ IBD, Diverticulosis, Angiodysplasia, Hemorrhoids, Cancer

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Microscopic Colitis:
-inflammatory dx of colon = causing watery diarrhea
-More common in older females
-colonic mucosa appears normal on endoscopy
-Histo = **inflammatory infiltrates** in **lamina propria** w/ thickened subepithelial collagen band or intraepithelial Lymphocytes

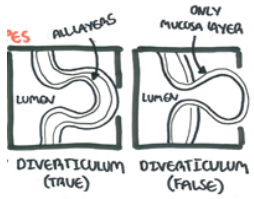
Irritable Bowel Syndrome (IBS):
-Recurrent Abd pain associated w/ ≥ 2 of the following;
- Related to defecation
- Change in stool frequency
- Change in form (consistency) of stool

-No structural abnormalities
-Most common in Middle-aged females
-Chronic sxs may be IBS-D, IBS-C, IBS-Mixed
-Tx = Lifestyle modification + dietary changes

Appendicitis:
-Acute inflammation of Appendix
-due to obstruction by faclith (adults) or lymphoid hyperplasia (children)
-Proximal obstruction of appendiceal lumen produces closed-loop obstruction → intraluminal pressure → stim of Visceral Afferent Nerve at T8-T10 → initial Diffuse Periumbilical pain → inflammation extend to serosa + irritates parietal peritoneum
-Pain at RLQ/McBurney Point (1/3rd distance from Right Anterior Superior Iliac Spine to Umbilicus
-Sxs = Pain, Nausea, fever, Psoas, Obturator, Rovsing Signs (RLQ Pain seen when palpating LLQ), Guarding and rebound tenderness on exam
-Complications = Perforation → Peritonitis
-Tx = Appendectomy

Diverticular of the GI Tract:

1. Diverticulum:
-Blind pouch protruding from the alimentary tract (communicates w/ lumen of gut)
-Most are "false Diverticula" or acquired
-**True Diverticulum** = all gut



Propria, Mesenteric Nodules
-Cardiac Sxs, Arthralgias, Neurologic sxs = Early
-Diarrhea/steatorrhea = later in dx course
-Most common in older males

2. Diverticulosis:
-**"many false diverticula of the colon, commonly sigmoid"**
-50% of people >60 yo
-caused by **intraluminal pressure** + focal weakness in colonic wall
-Associated w/ obesity + diets low in fiber, high intotal fat/red meat
-Often asymptomatic or vague discomfort
-Complications = diverticular bleeding (**painless hematochezia**), Diverticulitis

3. Diverticulitis:
-Inflammation of diverticula w/ wall thickening classically causing LLQ pain, fever, leukocytosis
-Complications = Abscess, Fistula (Colovesical Fistula → Pneumaturia), Obstruction (Inflammatory Stenosis), Perforation leading to Peritonitis
-Hematochezia is rare
-Tx = Abx

Zenker Diverticulum:
-pharyngoesophageal "False" Diverticulum
-Esophageal dysmotility causes herniation of mucosal tissue at Killian Triangle btw the Thyropharyngeus Muscle + Cricopharyngeus muscle (parts of Inferior Pharyngeal Constrictor)
-sxs = Dysphagia, Obstruction, Gurgling, Aspiration, Foul Breath, Neck Mass
-Most common in elderly males

Meckel Diverticulum:
-"True Diverticulum"
-Persistence of **Vitelline Duct** (Omphalomesenteric)
-May contain ectopic acid → **secreting gastric mucosa and/or pancreatic tissue**
-Most common congenital anomaly in GI
-Can cause Hematochezia/Melena (Less common), RLQ pain, Intussusception, Volvulus, Obstruction near terminal ileum
-Ddx = 99mTc-Pertechnetate Scan (Meckel Scan) looking for uptake by Heterotopic Gastric Mucosa
-Rule of 2's
- **2x as likely in Males**
- **2 inches long**

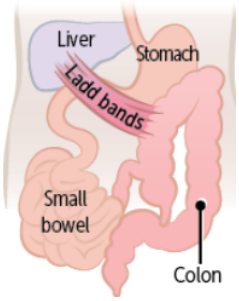
- Bloody diarrhea***
- Same Skin, Eye, Oral Ulcerations, Arthritis as above
- Primary sclerosing cholangitis (MPO-ANCA/p-ANCA

-Tx = 5-ASA (Mesalamine), 6-MP, Infliximab etc.

Hirschsprung Disease:
-Congenital megacolon = **Lack of Ganglion** cells/enteric nervous plexus (**Auerbach and Meissner Plexuses**) in Distal segment of colon
-caused by **failure of Neural Crest Cell migration**
-Loss of Function **mutations in *RET***
-sxs = bilious emesis, abd distention, failure to pass meconium within 48 hrs → chronic constipation
-Normal portion of colon proximal to aganglionic segment is dilated (creating a "Transition Zone")
- Risk w/ Down Syndrome

-Explosive expulsion of Feces ("**Squirt Sign**") --. Empty rectum on digital exam
-ddx = absence of ganglion cells on rectal suction biopsy
-Tx = Resection

Malrotation:
-anomaly of midgut rotation during fetal development → improper positioning of bowel
-Small bowel clumped on the right side + formation of fibrous bands ("Ladd Bands")
- risk of Volvulus, Duodenal obstruction



Intussusception:
-"telescoping of proximal bowel segment into distal segment"
-common at Ileocecal junction
-often Idiopathic or due to a "lead point"
-Compromised blood supply → intermittent severe, abdominal pain w/ "Currant Jelly" Dark red stools (Not "Currant Jelly" for Klebsiella)
-Infants > > Adults
-Common Lead Points:
- Children = Meckel Diverticulum
- Adults = Intraluminal Mass/tumor

-PE = Sausage-shaped mass in Right abdomen, pt may draw **legs to chest to ease pain**

wall layers outpouch (Meckel)
-False Diverticulum/Pseudodiverticulum = only mucosa + submucosa outpouch (occurs especially where vasa recta perforate muscularis externa)

Volvulus:
-twisting of portion of bowel around its mesentery → lead to obstruction + infarction
-can occur anywhere in GI
- Midgut Volvulus = infants/children
- SIgmoid Volvulus = "Coffee Bean Sign", Elderly

Acute Mesenteric Ischemia:
-Critical blockage of intestinal blood flow (embolic occlusion of **SMA**) → small bowel necrosis → abdominal pain out of proportion to physical findings
-"Currant Jelly" Stool

Adhesion:
-Fibrous band of scar tissue (commonly seen after surg)
-most common cause of small bowel obstruction
-multiple dilated small bowel loops on x-ray

Angiodysplasia:
-Tortuous dilation of vessels → Hematochezia
-Most often found in right -sided colon
-more common in older pts
-confirmed by angiography
-associated w/ ESRD, Von Willebrand Dx, Aortic Stenosis

Chronic Mesenteric Ischemia:
-"Intestinal Angina" = atherosclerosis of **Celiac Artery**, **SMA, IMA** → Intestinal Hypoperfusion → **postprandial epigastric pain** → food aversion + weight loss

Colonic Ischemia:
-Crampy abdominal pain followed by Hematochezia
-occurs at "Watershed" areas (Splenic Flexure, Rectosigmoid Junction)
-Typically affects elderly
-Thumbprint sign on imaging due to Mucosal edema/hemorrhage

Ileus:
-intestinal hypomotility without obstruction → constipation + flatus; distended/tympanic abdomen w/ bowel sounds

- **2 feet from ileocecal valve**
- **2% of population**
- **Presents in the first 2 years of life**
- **May have 2 types of epithelia (Gastric/Pancreatic)**

Meconium Ileus:
-plug obstructs intestine, prevents stool passage at birth (often in Ileum)
-Associated w/ CF***

Necrotizing Enterocolitis:
-Premature, formula-fed infants w/ immature immune system
-necrosis of intestinal mucosa (commonly terminal ileum, proximal colon) → pneumatotiss intestinalis, Pneumoperitoneum, portal venous gas

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Colonic Polyps:
-Growths of tissue within the colon
-Grossly characterized as "Flat, sessile, pedunculated" on basic of protrusion into colonic lumen

Generally Nonneoplastic:
1. Hamartomatous Polyps:
-Solitary lesions do NOT have significant risk of transformation
-Growths of normal colonic tissue w/ distorted architecture
-associated w/ **Peutz-Jeghers Syndrome** (polyp production in GI tract + cancers of breast, colon, rectum, pancreas, stomach, testicles, ovaries etc.) **+ Juvenile Polyposis**

2. Hyperplastic Polyps;
-most common
-generally smaller + predominantly located in rectosigmoid region
-occasionally evolves into serrated polyps and more advanced lesions

3. Inflammatory Pseudopolyps:
-due to mucosal erosion in inflammatory bowel disease

4. Mucosal Polyps:
-small, usually < 5 mm
-look similar to normal mucosa

-Imaging/US = "**Target Sign**"
-associated w/ IgA Vasculitis (HSP), Recent Viral infection (Adenovirus; Peyer Patch Hypertrophy creates lead point)

-seen w/ Abd surgeries, opiates, hypokalemia, sepsis
-No transition zone on imaging** **(vs. Hirshsprungs)**
-Tx = Bowel rest, electrolyte correction, cholinergic drugs to stimulate GI motility

-clinically insignificant

5. Submucosal Polyps:
-Lipomas, Leiomyomas, Fibromas, other lesions

Potentially Malignant:
1. Adenomatous Polyps:
-neoplastic, via chromosomal instability pathway w/ mutations in **APC** and **KRAS**
-Tubular histology has less malignant potential than villous ("Villous Histology is Villainous")
-Tubulovillous has intermediate malignant potential
-usually asymptomatic; may present w/ occult bleeding

2. Serrated Polyps:
-neoplastic
-characterized by **CpG island methylator** phenotype (CIMP; cytosine base followed by guanine, liked by a Phosphodiester bond)
-Defect may silence MMR gene (DNA Mismatch repair) expression
-Mutations lead to microsatellite instability + mutations in BRAF
-"Sawtooth" Pattern of Crypts on Biopsy

Polyposis Syndromes:
1. Familial Adenomatous Polyposis (FAP):
-Autosomal dominant mutation of APC tumor suppressor gene on chromosome 5q21-q22
-2-Hit hypothesis
-Thousands of polyps arise starting after puberty
-Pancolonic (always involves rectum)
-Prophylactic Colectomy or 100% guaranteed progression to Colorectal Cancer (CRC)

2. Gardner Syndrome:
-FAP + Osseous/Soft tissue tumors (Osteomas of Skull or Mandible)
-Congenital Hypertrophy of Retinal Pigment epithelium, impacted/supernumerary teeth

3. Turcot Syndrome:
-FAP or Lynch Syndrome + Malignant CNS tumor (Medulloblastoma, Glioma)

4. Peutz-Jeghers Syndrome:
-Autosomal dominant syndrome w/ numerous

Lynch Syndrome;
-"Hereditary nonpolyposis Colorectal Cancer (HNPCC)"
-Autosomal dominant
-Mutation of **mismatch repair genes (MLH1, MSH2)** w/ **microsatellite instability**
-80% progress to CRC
-Proximal colon is Always involved
-associated w/ Endometrial, Ovarian, Skin cancers

Colorectal Cancer (CRC):
-ddx:
- IDA in Males (esp if > 50 yo) + posmenopausal women
- Screening:
  - Average risk:
    - Colonoscopy at 50 yo
  - 1st degree relative w/ colon cancer;
    - Colonoscopy at 40 yo
    - Colonoscopy 10 years prior to relatives age or presentation
  - IBD? "Screened more regularly"
  - "Apple Core" lesion seen on barium enema x-ray
- **CEA Tumor marker** = good for monitoring recurrence, should not be used for screening

-Most pts > 50 yo (25% have family hx)
-Presentation:
- Rectosigmoid > ascending > descending
- Most asymptomatic
- Right side (Cecal, Ascending) = associated w/ occult bleeding
- Left side (rectosigmoid) associated w/ Hematochezia + Obstruction (narrower lumen → Stool caliber)
- Ascending = exophytic mass, IDA, Weight loss
- Descending = Infiltrating mass, partial obstruction, colicky pain, hematochezia
- Can present w/ Strep Bovis (Gallolyticus) bacteremia/endocarditis or an episode of diverticulitis

-RF = Adenomatous + serrated polyps, familial cancer syndromes, IBD, Tobacco use, diet of processed meat

"Normal" → loss of APC gene (intracellular adhesion, proliferation → "Colon at risk" → KRAS mutation (unregulated intracellular signaling) → "Adenoma" → loss of tumor suppressor (TP53, DCC) (tumorigenesis → "Carcinoma"

Cirrhosis:
-diffuse bridging fibrosis (via stellate cells) + regenerative nodules disrupt normal architecture of liver
- risk of HCC
-Causes = alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary dx, genetic/metabolic disorders

Portal HTN:
- pressure in portal venous system
-Causes = cirrhosis, Vascular obstruction (Portal vein thrombosis, Budd-Chiari syndrome), Schistosomiasis

- Jaundice
- Spider angiomas*
- Palmar erythema*
- Purpura
- Petechiae
- Esophageal varices
- Gastric varices → melena
- Caput medusa
- Ascites
- Anorectal varices
- Testicular atrophy*
- gynecomastia*
- Amenorrhea
- Hepatic encephalopathy
- Asterixis
- Anorexia
- Dull abdominal pain, N/V
- Fetor Hepaticus (garlic/rotten eggs breath)
- Thrombocytopenia (platelets)
- Anemia (Hb, RBCs)
- Coagulation disorders
- Splenomegaly

Hamartomas throughout GI tract
-**Hyperpigmented Macules on mouth/lips, hands, genitalia**
- risk of Breast and GI cancers (Colorectal, stomach, small bowel, pancreatic)

5. Juvenile Polyposis Syndrome: (< 5 yo)
-numerous hamartomatous polyps in GI (CRC)

Spontaneous Bacterial Peritonitis (SBP):
-potentially fatal bacterial infection in pts w/ cirrhosis + ascites
-asymptomatic but can cause fevers, chills, abd pain, ileus, worsening encephalopathy
-caused by Grm (-) organisms (E coli, Kleb) or less commonly Grm (+) (Strep)
-ddx = paracentesis w/ ascitic fluid absolute neutrophil count (ANC) > 250
-ppx often needed (bactrim)
-Tx = 3rd Gen ceph (Cefotaxime, Ceftriaxone)

Serum Markers of Pathology:

Enzymes Released in Liver Damage:
1. AST/ALT:
- in liver dx (ALT > AST)
- Alcoholic Liver Dx (AST > ALT in 2:1 ratio), AST usually doesn't exceed 500
-AST > ALT in Nonalcoholic Liver Dx suggests progression to advanced fibrosis or cirrhosis
- AST/ALT (> 1000) = Drug induced Liver injury (APAP), Ischemic Hepatitis, Acute Viral infxn, Autoimmune Hepatitis

2. Alk Phos:
- in Cholestasis (Biliary obstruction), Infiltrative disorders, bone disease

3. gamma-Glutamyl Transpeptidase (g-GTP):
- in liver and biliary dx, but NOT in bone dx (associated w/ alcohol use)

Functional Liver Markers:
1. Bilirubin:
- in liver dx (biliary obstruction, alcoholic/viral hepatitis, cirrhosis) or Hemolysis

2. Albumin:
- in advanced liver dx (marker of livers biosynthetic function)

w/ low fiber
-Pathogenesis:
- Chromosomal instability pathway (mutations in APC cause FAP)
- Microsatellite instability pathway; Mutations or Methylation of Mismatch Repaire Genes (MLH1) cause Lynch Syndrome
- Overexpression of COX-2(NSAIDs protective?)

Reye Syndrome:
-rare but fatal childhood hepatic encephalopathy
-associated w/ viral infxn (esp VZV and Influenza) that has been Tx w/ ASA
-ASA metabolites B-oxidation by reversible inhibition of mitochondrial enzymes
-Findings = mitochondrial abnormalities, fatty liver (microvesicular fatty changes), hypoglycemia, vomiting, hepatomegaly, coma
- **Steatosis of Liver/Hepatocytes**
- **Hypoglycemia/Hepatomegaly**
- **Infxn (VZV, Influenza)**
- **Not awake (coma)**
- **Encephalopathy**

-**Avoid ASA in children, except Kawasaki Dx (Medium Vessel Vasculitis)**

Alcoholic Liver Disease:

1. Hepatic Steatosis:
-macrovesicular fatty change (reversible / alcohol cessation)

2. Alcoholic Hepatitis:
-requires sustained, long-term consumption
-swollen + necrotic hepatocytes w/ neutrophilic infiltration
-**Mallory Bodies =** Intracytoplasmic eosinophilic inclusions of damaged keratin filaments)

3. Alcoholic Cirrhosis:
-final + usually irreversible form
-sclerosis around central vein
-regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal HTN and ESLD

Nonalcoholic Fatty Liver Dx:
-Metabolic syndrome (Insulin resistance)
-Obesity → fatty infiltration of hepatocytes → cellular **"ballooning"** and eventual necrosis
-May cause cirrhosis + HCC
- Hepatorenal syndrome
- Hyperbilirubinemia
- Hyponatremia
- Cardiomyopathy
- Peripheral edema

Hepatic Encephalopathy:
-Cirrhosis → Portosystemic Shunts → NH3 metabolism → neuropsychiatric dysf
-Reversible neuropsychiatric dysfunction ranging from disorientation/asterixis (mild) to difficult arousal or coma (severe)
-Trigger;
- NH3 production and absorption (due to GI bleed, Constipation, Infxn)
- NH3 removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS)

-Tx = Lactulose (NH4+ generation) and Rifaximin (NH3-production by bacteria in gut)

Liver Tumors:
1. Hepatic Hemangioma:
-"Cavernous Hemangioma"
-most common benign liver tumor (venous Malformation)
-30-50 yo
-biopsy contraindicated b/c of risk of hemorrhage**

2. Focal Nodular Hyperplasia:
-Second most common benign liver tumor
-Mostly females (35-50 yo)
-Hyperplastic rxn of hepatocytes to aberrant dystrophic artery

3. Hepatic Adenoma:
-Rare benign tumor
-related to oral contraceptive or anabolic steroid use (most regress spontaneously or rupture → abd pain/shock)

4. Hepatocellular Carcinoma (HCC):
-"Hepatoma"
-Most common primary liver tumor in adults
-associated w/ HBV (+/- Cirrhosis) and all other causes of Cirrhosis (HVC, Alcoholic and nonalcoholic fatty liver dx, autoimmune dx , hemochromatosis,

3. Prothrombin Time:
- in advanced liver dx (production of clotting factors, measuring livers biosynthetic function)

4. Platelets:
- in liver dx (thrombopoietin, liver sequestration) and portal HTN (Splenomegaly/Splenic sequestration)

5. Hepatic Angiosarcoma:
-rare malignant tumor of endothelial origin; associated w/ exposure to arsenic, vinyl chloride

6. Metastases:
-most common malignant liver tumors overall
-common primary sources = GI, Breast, Lung Cancers
-Mets are rarely solitary

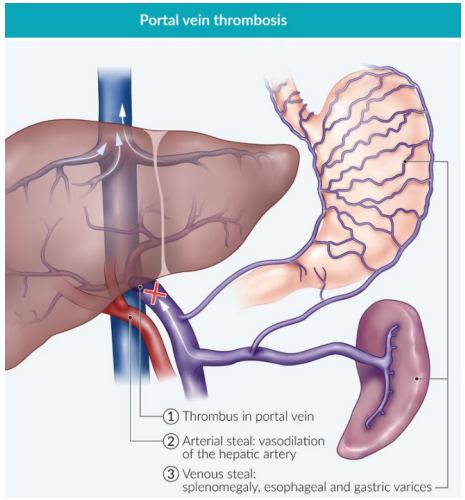
a1-Antitrypsin Deficiency:
-misfolded gene product protein aggregates in hepatocellular ER --. Cirrhosis w/ PAS (+) Globules in Liver
-Codominant trait
-"young pts w/ liver damage + SOB w/o hx of tobacco smoking"
-In lungs; a1-antitrypsin → uninhibited elastase in alveoli → Elastic Tissue → Panacinar emphysema (respir bronchioles + distal alveoli affected)

Budd-Chiari Syndrome:
-**Hepatic venous outflow tract obstruction** (due to thrombosis, compression) w/ Centrilobular congestion + necrosis → Congestive Liver Dx
- Portal Vein Thrombosis → No Hepatosplenomegaly

-sxs = Hepatomegaly, ascites, varices, abdominal pain, liver failure
-Absence of JVD***
-Associated w/ Hypercoagulable states, Polycythemia vera, Postpartum State, HCC
-**Nutmeg Liver** (Mottled Appearance)

-Independent of alcohol use

Autoimmune Hepatitis;
-chronic inflammatory liver dx
-more common in females
-Asymptomatic or fatigue, nauseous, pruritus
-Associated w/ (+) Antinuclear, anti-smooth muscle and anti-liver/kidney microsomal-1 Abs (ALT/AST)
-Histo = portal/periportal lymphoplasmacytic infiltrates



Jaundice:
-Abnormal yellowing of the skin/sclera (scleral icterus) due to bilirubin deposition
-Hyperbilirubinemia, secondary to production or clearance (impaired hepatic uptake, conjugation, excretion)
-Common causes of Bili; "HOT Liver"
- Hemolysis
- Obstruction
- Tumor
- Liver Dx

Conjugated (Direct) Hyperbilirubinemia:
-biliary tract obstruction → Gallstones, Cholangiocarcinoma, Pancreatic/Liver Cancer, Liver Fluke
-Biliary Tract Dx:
- Primary Sclerosing Cholangitis
- Primary Biliary Cholangitis

-Excretion Defect = **Dubin-Johnson Syndrome, Rotor Syndrome**

Wilson Dx, a1-antitrypsin def., Carcinogens (Aflatoxin from Aspergillus))
-Findings = Anorexia, Jaundice, Tender hepatomegaly, decompensation of previously stable cirrhosis (ascites), Budd-Chiari Syndrome
-Spreads Hematogenously
-ddx = **AFP, Ultrasound or contrast CT/MRI, Biopsy**

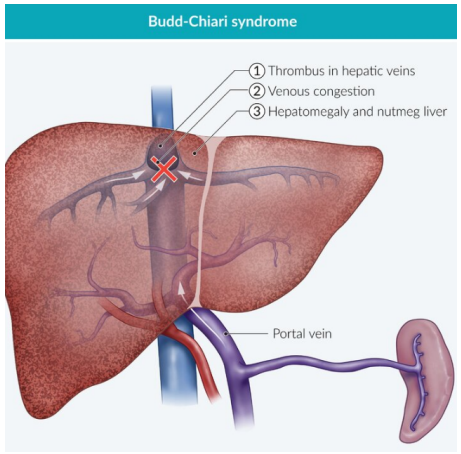
Physiologic Neonatal Jaundice:
-at birth, lower activity of **UDP-Glucuronosyltransferase** → unconjugated hyperbilirubinemia (Unconj Bili) → Jaundice/Kernicterus (Deposition of Unconj, lipid-soluble bilirubin in the brain/basal ganglia)
-Occurs after 1st 24 hrs of life + usually resolves w/o treatment in 1-2 weeks
-Tx = Phototherapy (non-UV) Isomerizes Unconj Bili to Water-Sol form

Biliary Atresia:
-most common reason for pediatric liver transplantation
-**Fibro-obliterative destruction of bile ducts → cholestasis**
-Often presents as a newborn w/ persistent jaundice **after 2 weeks of life** → darkening of urine, acholic stools, hepatomegaly
-Labs = **Direct Bilirubin and GGT**

Hereditary Hyperbilirubinemias:
-All autosomal recessive

1. Gilbert Syndrome:
-mildly **UDP-Glucuronosyltransferase** conjugation
-Asymptomatic or mild jaundice usually w/ stress, illness, or fasting
- Unconjugated bilirubin w/o overt hemolysis
-Relatively common, benign condition

2. Crigler-Najjar Syndrome, Type I:
-**Absent UDP-Glucuronosyltransferase**
-presents early in life, but some pts may not have neurologic signs until later in life
-Findings = Jaundice, Kernicterus (Bilirubin deposition in brain), **Unconjugated bilirubin**
-Tx = Plasmapheresis and Phototherapy (does not conjugate UCB; but does polarity and water solubility to allow excretion



Unconjugated (indirect) Hyperbilirubinemia:
-Hemolytic, Physiologic (newborns), Crigler-Najjar, Gilbert Syndrome

Mixed (Direct/Indirect) Hyperbilirubinemia:
-Hepatitis, Cirrhosis

3. Dubin-Johnson Syndrome:
-**Conjugated hyperbilirubinemia** due to defective Liver excretion (Benign)
-Grossly Black liver due to impaired excretion of Epinephrine metabolites

4. Rotor Syndrome:
-Phenotypically similar to Dubin-Johnson but milder presentation without Black liver
-Due to **impaired hepatic storage of conjugated bili**

Wilson Disease:
-"Hepatolenticular Degeneration"
-Autosomal recessive mutations in **hepatocyte copper-transporting ATPase (ATP7B gene; Chr13)**
- Copper Incorporation into apoceruloplasmin + excretion into bile → serum ceruloplasmin
-COpper accumulates, especially in liver, brain (basal ganglia), cornea, kidneys
- Copper in Urine
- < 40 yo w/ Liver Dx
  - Hepatitis, Acute Liver Failure, Cirrhosis
  - Neurologic Dx (Dysarthria, Dystonia, Tremor, Parkinsonism)
  - Psychiatric Dx
  - **Kayser-Fleischer rings** (deposits in Descemet membrane of Cornea)
  - Hemolytic Anemia
  - Renal Dx (Fanconi Syndrome)

-Tx = Chelation w/ **Penicillamine** or **Trientine, Zinc**, Liver Transplant in acute liver failure related to Wilson Dx

Hemochromatosis:
-Autosomal recessive
-Mutation in **HFE gene; Chr 6**
-leads to abnormal **Iron Sensing** and intestinal absorption (**Ferritin, Iron, TIBC → Transferrin saturation)**
-Iron overload (can also be secondary to chronic transfusion therapy (B-thalassemia Major)
-Iron accumulates in liver, pancreas, skin, heart, pituitary, joints

Biliary Tract Disease:
-Pruritus (itching), dark urine, light-colored stool, hepatosplenomegaly
-Cholestatic Pattern in LFTs (**Conjugated Bili, Cholesterol, Alk phos, GGT,** AST/ALT only mildly elevated)

1. Primary Sclerosing Cholangitis (PSC):
-Unknown cause of Concentric "**Onion Skin**" bile Duct Fibrosis → Alternating Strictures + Dilation **w/ "beading"** of intra/extrahepatic bile ducts on ERCP/MRCP
-Middle-aged males w/ UC
-Associated w/ Ulcerative Colitis (UC)
-MPO-ANCA/p-ANCA (+)
- IgM
-can lead to secondary biliary cirrhosis
- risk of cholangiocarcinoma + Gallbladder cancer

2. Primary Biliary Cholangitis (PBC):
-Autoimmune rxn → Lymphocytic Infiltrate +/- Granulomas → Destruction of Lobular Bile Ducts
-**Middle-Aged Females**
-anti-Mitochondrial antibody (+)
- IgM
-Associated w/ other autoimmune disorders (Hashimoto Thyroiditis, RA, Celiac Dx)
-Tx = **Ursodiol**

3. Secondary Biliary Cirrhosis:
-Extrahepatic Biliary obstruction (outside liver blockage) → Pressure in intrahepatic ducts → injury/fibrosis + bile stasis

Cholelithiasis and Related Pathology:
- cholesterol +/or Bilirubin, Bile salts, Gallbladder stasis → all lead to stones
-Stone Types:
  - Cholesterol Stones:
    - Radiolucent w/ 10-20% opaque due to calcifications
    - Account for 80% of all stones
    - Obesity, Crohn dx, Advanced age, Estrogen therapy, multiparity, rapid weight loss, meds (Fibrates)
  - Pigment Stones:
    - Black = Radiopaque; Ca2+ bilirubinate, hemolysis
    - Brown = radiolucent; infection
    - Crohns, Chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, TPN

-Mech:
  - Sex (female), age, obestity, genetics, Cholesterol 7a-Hydroxylase → cholesterol, bile salts, gallbladder stasis → supersaturation of bile w/ cholesterol → cholesterol stones form
  - Chronic hemolysis, biliary tract infection → unconjugated bili, gallbladder stasis → supersaturation of bile w/ Calcium bilirubinate → pigment stones

-RF:
  1. **Female**
  2. **Fat (Obese)**
  3. **Fertile (Multiparity)**
  4. **Forty (> 40 yo)**

-Hemosiderin (Iron) seen on MRI or w/ Prussian Blue
-**Presents > 40 yo** (after enough iron has accumulated over life)
-Iron loss through menstruation slows progression in females
-Triad:

1. **Cirrhosis**
2. **DM**
3. **Skin pigmentation ("Bronze DM")**
4. **+/- Restrictive Cardiomyopathy or dilated (reversible)**

-Hypogonadism, Arthropathy (Calcium Pyrophosphate deposition; espe metacarpophalangeal joints)
-**HCC is common cause of death**
-Tx = Repeated phlebotomy, Iron Chelation (**Deferasirox, Deferoxamine, Dferiprone**

<u>Cholecystitis</u>:
-acute or chronic inflammation of Gallbladder
-**Murphy Sign** = inspiratory arrest on RUQ palpation due to pain (may radiate to Right shoulder - due to irritation of phrenic nerve)

- Alk phos if bile duct becomes involved (Acute Cholangitis)

-DDx w/ US or Cholescintigraphy (HIDA Scan), failure to visualize gallbladder on HIDA suggests obstruction

1. Calculus Cholecystitis = most common type
-due to gallstone impaction in the Cystic Duct resulting in inflammation + gallbladder wall thickening (can produce secondary infection)
2. Acalculous Cholecystitis = due to gallbladder stasis, Hypoperfusion, infection (CMV); seen in critically ill pts
3. Gallstone Ileus = fistula btw Gallbladder and GI tract → stone enters GI lumen → obstruction at Ileocecal Valve (Narrowest point)

- Can see air in biliary tree (pneumobilia)
- Rigler Triad:
  - Pneumobilia
  - Small bowel Obstruction
  - Gallstone (Iliac Fossa)

<u>Porcelain Gallbladder</u>:
-Calcified Gallbladder = from chronic cholecystitis (often found incidentally w/ imaging)
-Tx = prophylactic Cholecystectomy generally
-Pts w/ Known Obstructive lesions (Gallstones, Biliary Strictures, Pancreatic Carcinoma)
-may be complicated by acute Cholangitis

Courvoisier's Sign:
-palpable gallbladder over skin + jaundice
-Suspect Obstructing Pancreatic or Biliary Neoplasm (Often **Pancreatic Adenocarcinoma**)

Cullen's Sign:
-Periumbilical bruising
-Suspect **Hemorrhagic Pancreatitis or Ectopic Pregnanc**y

Murphy's Sign:
-RUQ tenderness exacerbated by inspiration
-suspect **Acute Cholecystitis**

<u>Acute Pancreatitis</u>:
-Autodigestion of pancreas by pancreatic enzymes
-Causes:

- Idiopathic
- Gallstones
- Ethanol
- Trauma
- Mumps
- Autoimmune Dx
- Scorpion Sting
- Hypercalcemia/Hypertriglyceridemia (> 1000)
- ERCP
- Drugs (SUlfa, NRTIs, Protease Inhibs,Steroids)

-DDx = 2 out of the 3

- **Acute epigastric pain radiating to back**
- **serum Amylase or Lipase to 3x ULN**
- Imaging findings

-Complications = Pseudocyst (lined by granulation tissue, NOT epithelium),Abscess, Necrosis, Hemorrhage, Infection, Organ Failure (ALI/ARDS, Shock, Renal failure), Hypocalcemia (precipitation of ca2+ soaps)

<u>Chronic Pancreatitis</u>:
-Chronic inflammation, atrophy, calcification of pancreas
-RF = Alcoholism, Genetics (CF), Idiopathic
-Complications = pancreatic insufficiency + pseudocysts
-Pancreatic Insuff seen w/ < 10% of residual pancreas function (steatorrhea, fat-soluble vit def, DM)
-Amylase, Lipase /normal (ALWAYS Elevated in Acute Pancreatitis)
-most common complication is **cholecystitis** (can cause acute pancreatitis, acute cholangitis)
-Ddx w/ US
-Tx = elective cholecystectomy if symptomatic

<u>Biliary Colic</u>:
-associated w/ Nausea/Vomiting + Dull RUQ pain
-neurohormonal activation (by CCK after fatty meal) triggers contraction of gallbladder → forcing stone into cystic duct
-Labs normal
-US shows cholelithiasis (stone)

<u>Choledocholithiasis</u>:
-Presence of gallstone(s) in common bile duct, leading to elevated Alk Phos, GGT, direct bilirubin, and/or AST/ALT

<u>H2-Blockers</u>:
-Cimetidine, Famotidine
-mech = reversible blocking of H2 receptors → H+ secretion by Parietal Cells
-sxs = Cimetidine

- CYP inhibitor → drug intxns
- Prolactin release
- Gynecomastia
- Impotence
- libido in males
- Crosses BBB (Confusion, Dizziness, HA)
- Crosses placenta
- renal clearance of Creatinine (SCr)

-Other H2 blockers have none of these issues

<u>PPIs</u>:
-Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole
-mech = irreversibly inhibit H/K ATPase in stomach parietal cells
-sxs = risk for C.diff infxn, pneumonia, acute interstitial nephritis, Vit B12 malabsorption (B12), Mg2+ , Ca2+ absorption (leading to potential in fracture risk)

<u>Antacids</u>:
-affect absorption, bioavailability, urinary excretion of other drugs by changing gastric pH and delaying gastric emptying
-All can cause hypokalemia (K+)

recommended due to risk of Gallbladder Cancer (Mostly Adenocarcinoma)

Acute Cholangitis:
-"ascending cholangitis"
-infection of biliary tree (often due to obstruction → statis/bacterial growth)
-**Charcot Triad:**
- **Cholangitis**
- **Jaundice**
- **Fever/RUQ pain**

-Reynolds Pentad = Charcot + AMS + Shock (Hypotension)

Misoprostol:
-Mech = PGE1 analog → production and secretion of gastric mucosal barrier + acid production
-prevention of NSAID-induced PUD
-Induction of labor/abortifacient

Octreotide:
-somatostatin analog (inhibiting splanchnic vasodilatory hormones)
-sxs = Nausea, cramps, steatorrhea, risk of Cholelithiasis due to CCK inhibition

Sulfasalazine:
-combo of Sulfapyridine (Antibacterial) and 5-ASA (Antiinflammatory)
-Activated by colonic bacteria
-sxs = malaise, nausea, sulfamide toxicity, reversible oligospermia

Loperamide:
-agonist of Mu-opioid receptors slowing gut motility (poor CNS penetration so very little addictive potential)
-sxs = constipation, nausea

Ondansetron;
-5HT3 antagonist (acts peripherally → vagal stimulation) and centrally (potent antiemetic)
-sxs = HA, Constipation, QT prolongation, serotonin syndrome

Pancreatic Adenocarcinoma:
-very aggressive tumor arising from pancreatic DUCTs (disorganized glandular structure w/ cellular infiltration)
-often metastatic at presentation (average survival ~ 1year)
-Tumors most commonly in Pancreatic Head (leads to obstructive jaundice)
-Associated w/ **CA 19-9 Tumor Marker (CEA) (KRAS)**
-RF:
- Smoking
- Chronic pancreatitis (> 20 yrs)
- DM
- Age >50

-Sxs = Abdominal pain radiating to back, weight loss (due to malabsorption/anorexia), Migratory Thrombophlebitis - redness/tenderness on palpation of extremities (Trousseau syndrome), Obstructive Jaundice w/ Palpable Gallbladder (Courvoisier Sign)

Orlistat:
-inhibits gastric and pancreatic lipase → Breakdown and absorption of Dietary fats
-taken w/ fat containing meals
-use = weight loss
-sxs = flatulence, steatorrhea, fat sol vits

-Bulk-forming laxatives = Psyllium, Methylcellulose
-Osmotic Laxatives = magnesium hydroxide, Mag cit, polyethylene glycol, lactulose
-Stimulants = Senna, Bisacodyl (enteric nerve stimulation → colonic contraction)
-Emollients = Doculase (promotes incorporation of water into fat)

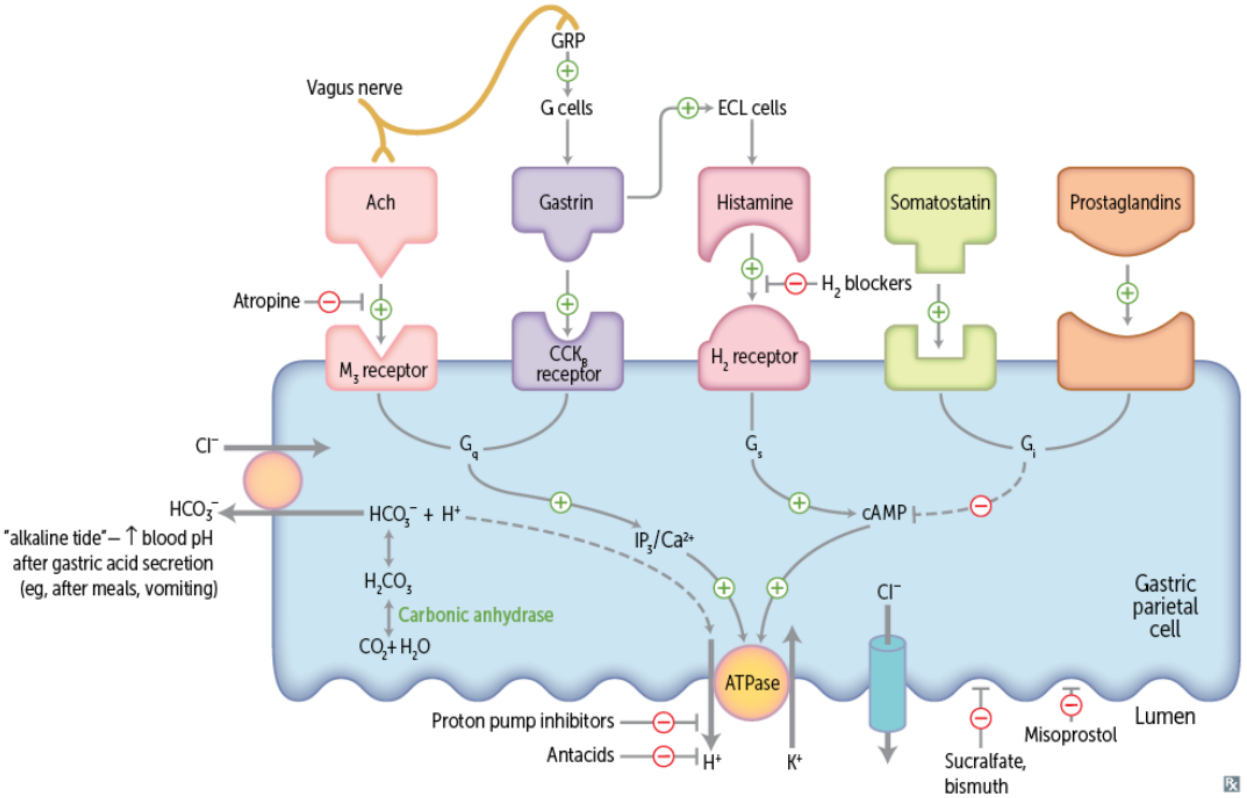
1. Aluminum Hydroxide:
-**Constipation**, Hypophos, Osteodyrstorphy, Proximal muscle weakness, Seizures
2. Calcium Carb:
-hypercalcemia (Milk-Alkali Syndrome), Rebound Acid

-Can chelate and effectiveness of other drugs (TCNs)
3. MagnesiumOH:
-**Diarrhea**, hyporeflexia, hypotension, cardiac arrest

Bismuth, Sucralfate:
-mech = bind ulcer base, providing physical barrier protection and allowing bicarb secretion to reestablish pH gradient in mucous layer
-Sucralfate requires acidic environment (not given w/ PPIs/H2)
-use = ulcer healing, Traveler's Diarrhea (Bismuth) and H.Pylori (Bismuth)

Aprepitant:
-Substance P antagonist (via blockade of NK1 receptors in brain)
-CINV - good for delayed nausea

Metoclopramide:
-D2 receptor antagonist (resting tone, contractility, LES tone, motility, promotes gastric emptying (does NOT influence colon transport time)
-sxs = parkinsonian effects, Tardive dyskinesia, diarrhea, drug intxns (Digoxin)
-Contraindicated in small bowel obstruction, Parkinson's Dx, seizure threshold



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