

# Gastrointestinal

*“A good set of bowels is worth more to a man than any quantity of brains.”*  
—Josh Billings

*“Man should strive to have his intestines relaxed all the days of his life.”*  
—Moses Maimonides

*“All right, let’s not panic. I’ll make the money by selling one of my livers. I can get by with one.”*  
—Homer Simpson, *The Simpsons*

*“The truth does not change according to our ability to stomach it emotionally.”*  
—Flannery O’Connor

When studying the gastrointestinal system, be sure to understand the normal embryology, anatomy, and physiology and how the system is affected by various pathologies. Study not only disease pathophysiology, but also its specific findings, so that you can differentiate between two similar diseases. For example, what specifically makes ulcerative colitis different from Crohn disease? Also, be comfortable with basic interpretation of abdominal x-rays, CT scans, and endoscopic images.

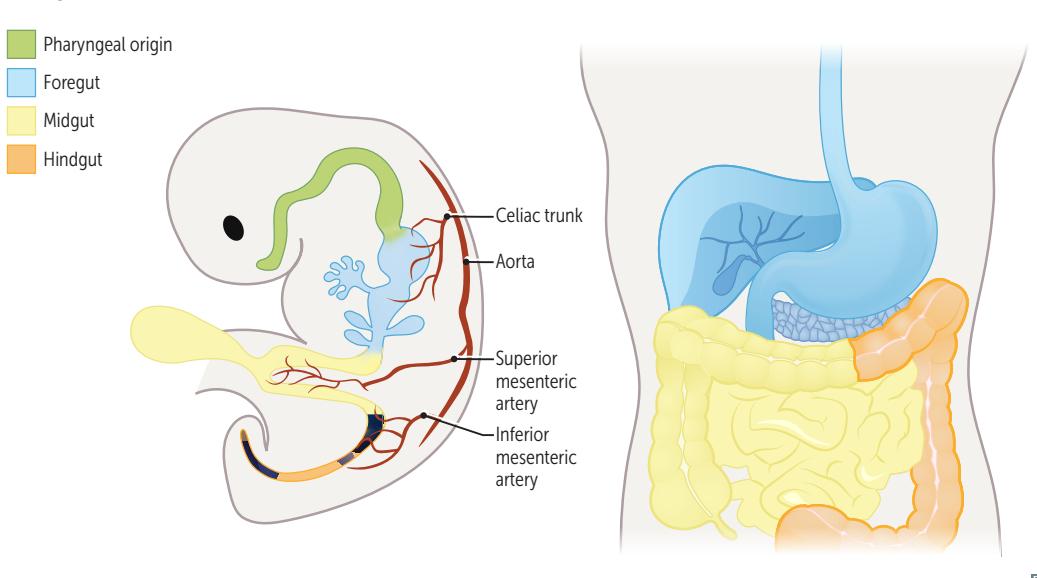
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## ► GASTROINTESTINAL—EMBRYOLOGY

**Normal  
gastrointestinal  
embryology**

Foregut—esophagus to duodenum at level of pancreatic duct and common bile duct insertion (ampulla of Vater).

- 4th-6th week of development—stomach rotates 90° clockwise.
  - Left vagus becomes anteriorly positioned, and right vagus becomes posteriorly positioned.
- Midgut—lower duodenum to proximal 2/3 of transverse colon.
- 6th week of development—physiologic herniation of midgut through umbilical ring.
  - 10th week of development—returns to abdominal cavity rotating around superior mesenteric artery (SMA), 270° counterclockwise (~180° before 10th week, remaining ~90° in 10th week).
- Hindgut—distal 1/3 of transverse colon to anal canal above pectinate line.



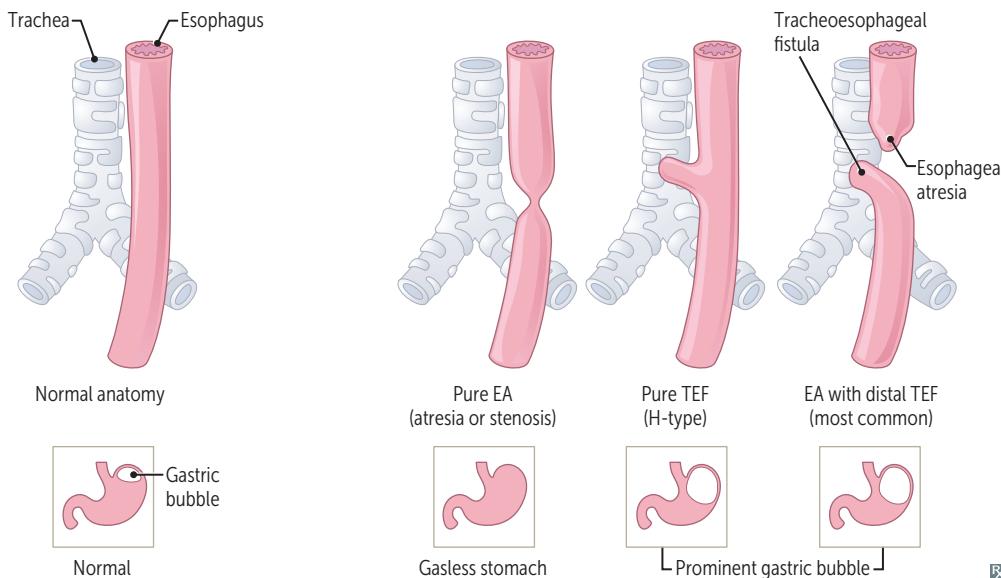
Ventral wall defects	Developmental defects due to failure of rostral fold closure (eg, sternal defects [ectopia cordis]), lateral fold closure (eg, omphalocele, gastroschisis), or caudal fold closure (eg, bladder exstrophy).	
<b>PRESENTATION</b>	<b>Gastroschisis</b>	<b>Omphalocele</b>
	Paraumbilical herniation of abdominal contents through abdominal wall defect	Herniation of abdominal contents through umbilicus
<b>COVERAGE</b>	Not covered by peritoneum or amnion <b>A</b> : “the <b>g</b> uts come out of the <b>g</b> ap ( <b>s</b> chism) in the letter <b>G</b> ”	Covered by peritoneum and amnion <b>B</b> (light gray shiny sac); “abdominal contents are <b>sealed</b> in the letter <b>O</b> ”
<b>ASSOCIATIONS</b>	Not associated with chromosome abnormalities; <b>good prognosis</b>	Associated with congenital “ <b>O</b> nomalies” (eg, trisomies 13 and 18, Beckwith-Wiedemann syndrome) and other structural abnormalities (eg, cardiac, GU, neural tube)



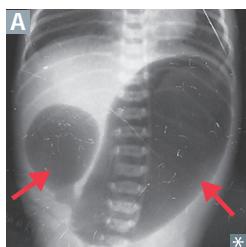
### Tracheoesophageal anomalies

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%) and often presents as polyhydramnios in utero (due to inability of fetus to swallow amniotic fluid). Neonates drool, choke, and vomit with first feeding. TEFs allow air to enter stomach (visible on CXR). Cyanosis is  $2^{\circ}$  to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach.

In **H-type**, the fistula resembles the letter **H**. In pure EA, CXR shows gasless abdomen.



### Intestinal atresia

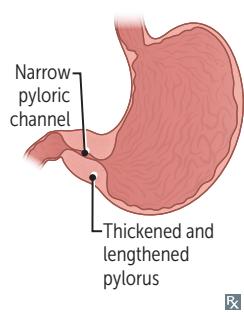


Presents with bilious vomiting and abdominal distension within first 1–2 days of life.

**Duodenal atresia**—failure to recanalize. X-ray **A** shows “double bubble” (dilated stomach, proximal duodenum). Associated with **Down syndrome**.

**Jejunal and ileal atresia**—disruption of mesenteric vessels (typically SMA) → ischemic necrosis of fetal intestine → segmental resorption: bowel becomes discontinuous. X-ray may show “triple bubble” (dilated stomach, duodenum, proximal jejunum) and gasless colon. Associated with cystic fibrosis and gastroschisis. May be caused by tobacco smoking or use of vasoconstrictive drugs (eg, cocaine) during pregnancy.

### Hypertrophic pyloric stenosis



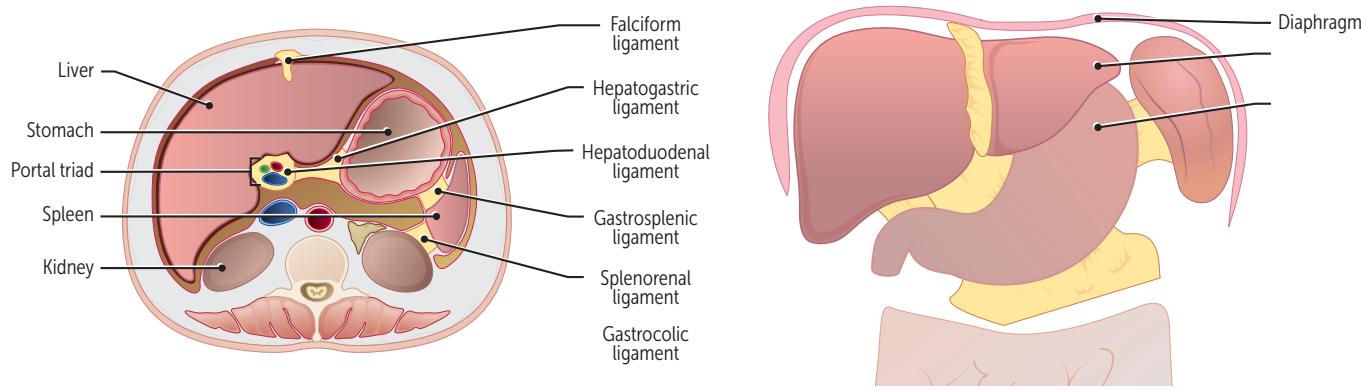
Most common cause of gastric outlet obstruction in infants. Palpable olive-shaped mass (due to hypertrophy and hyperplasia of pyloric sphincter muscle) in epigastric region, visible peristaltic waves, and nonbilious projectile vomiting at ~ 2–6 weeks old. More common in firstborn **males**; associated with exposure to **macrolides**.

Results in hypokalemic hypochloremic **metabolic alkalosis** ( $2^{\circ}$  to vomiting of gastric acid and subsequent volume contraction).

Ultrasound shows thickened and lengthened pylorus.

Treatment: surgical incision of pyloric muscles (**pyloromyotomy**).



**Important gastrointestinal ligaments**

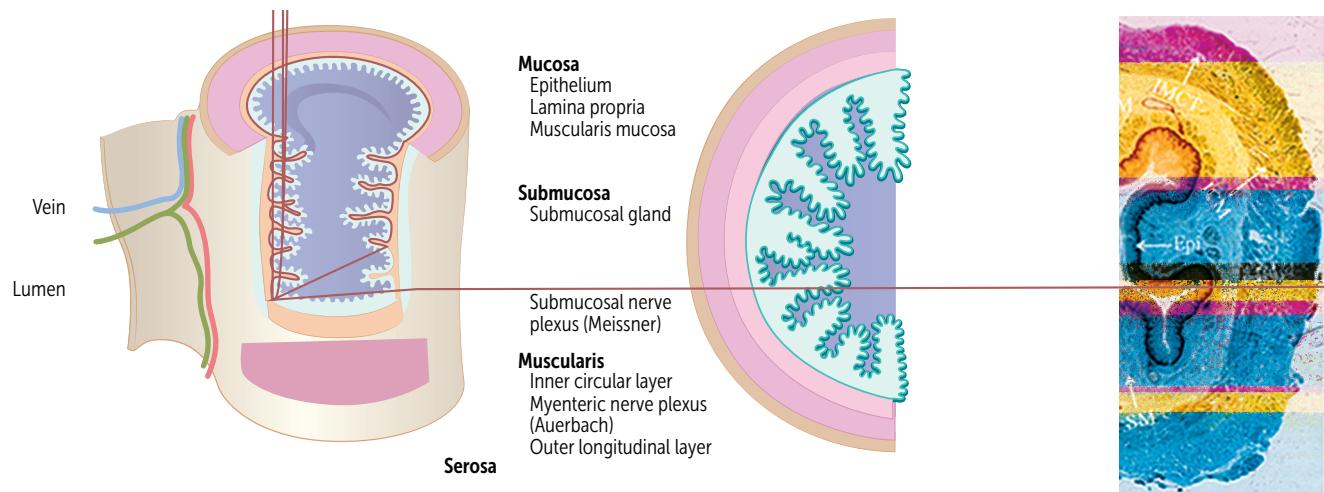

**Digestive tract anatomy**

Layers of gut wall A (inside to outside—MSMS):

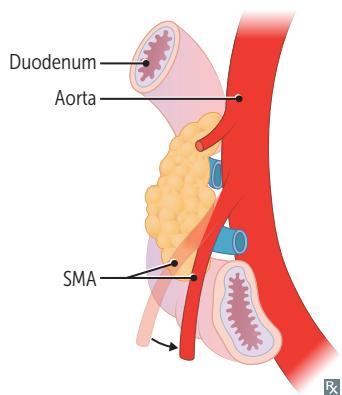
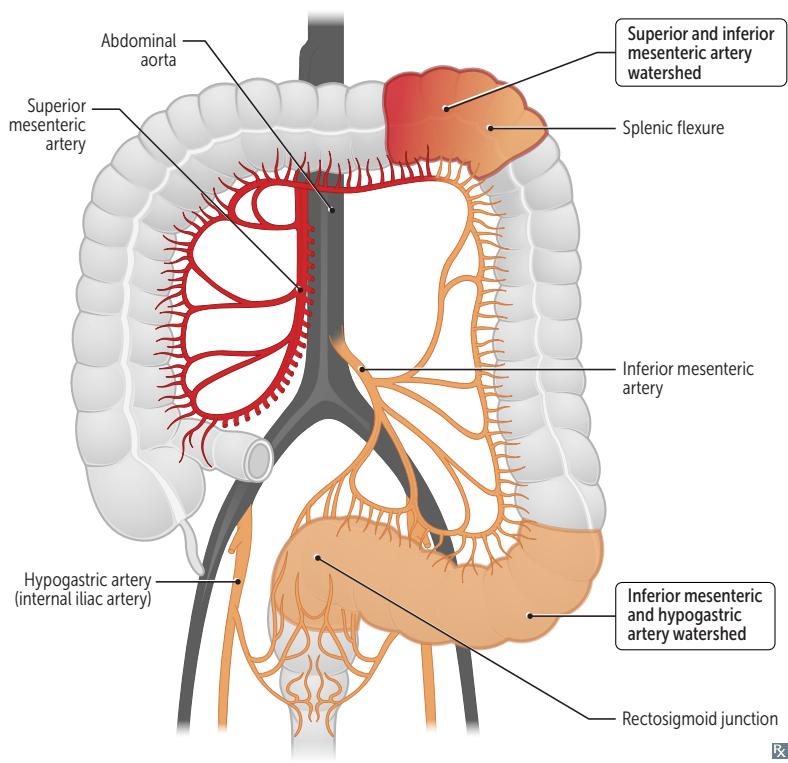
- **Mucosa**—epithelium, lamina propria, muscularis mucosa
- **Submucosa**—includes submucosal nerve plexus (Meissner), secretes fluid
- **Muscularis externa**—includes myenteric nerve plexus (Auerbach), motility
- **Serosa** (when intraperitoneal), adventitia (when retroperitoneal)

Ulcers can extend into submucosa, inner or outer muscular layer. Erosions are in mucosa only.

Frequency of basal electric rhythm (slow waves), which originate in the interstitial cells of Cajal: duodenum > ileum > stomach.



### Abdominal aorta and branches



Arteries supplying GI structures are single and branch anteriorly.

Arteries supplying non-GI structures are paired and branch laterally and posteriorly.

Two areas of the colon have dual blood supply from distal arterial branches (“watershed areas”) → susceptible in colonic ischemia:

- Splenic flexure—SMA and IMA
- Rectosigmoid junction—IMA branches (last sigmoid arterial branch and superior rectal artery)

**Nutcracker syndrome**—compression of left renal vein between superior mesenteric artery and aorta. May cause abdominal (flank) pain, gross hematuria (from rupture of thin-walled renal varicosities), left-sided varicocele.

**Superior mesenteric artery syndrome**—characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when SMA and aorta compress transverse (third) portion of duodenum.

Typically occurs in conditions associated with diminished mesenteric fat (eg, rapid weight loss, low body weight, malnutrition, gastric bypass surgeries).

### Gastrointestinal blood supply and innervation

EMBRYONIC GUT REGION	ARTERY	PARASYMPATHETIC INNERVATION	VERTEBRAL LEVEL	STRUCTURES SUPPLIED
Foregut	Celiac	Vagus	T12/L1	Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)
Midgut	SMA	Vagus	L1	Distal duodenum to proximal 2/3 of transverse colon
Hindgut	IMA	Pelvic	L3	Distal 1/3 of transverse colon to upper portion of anal canal

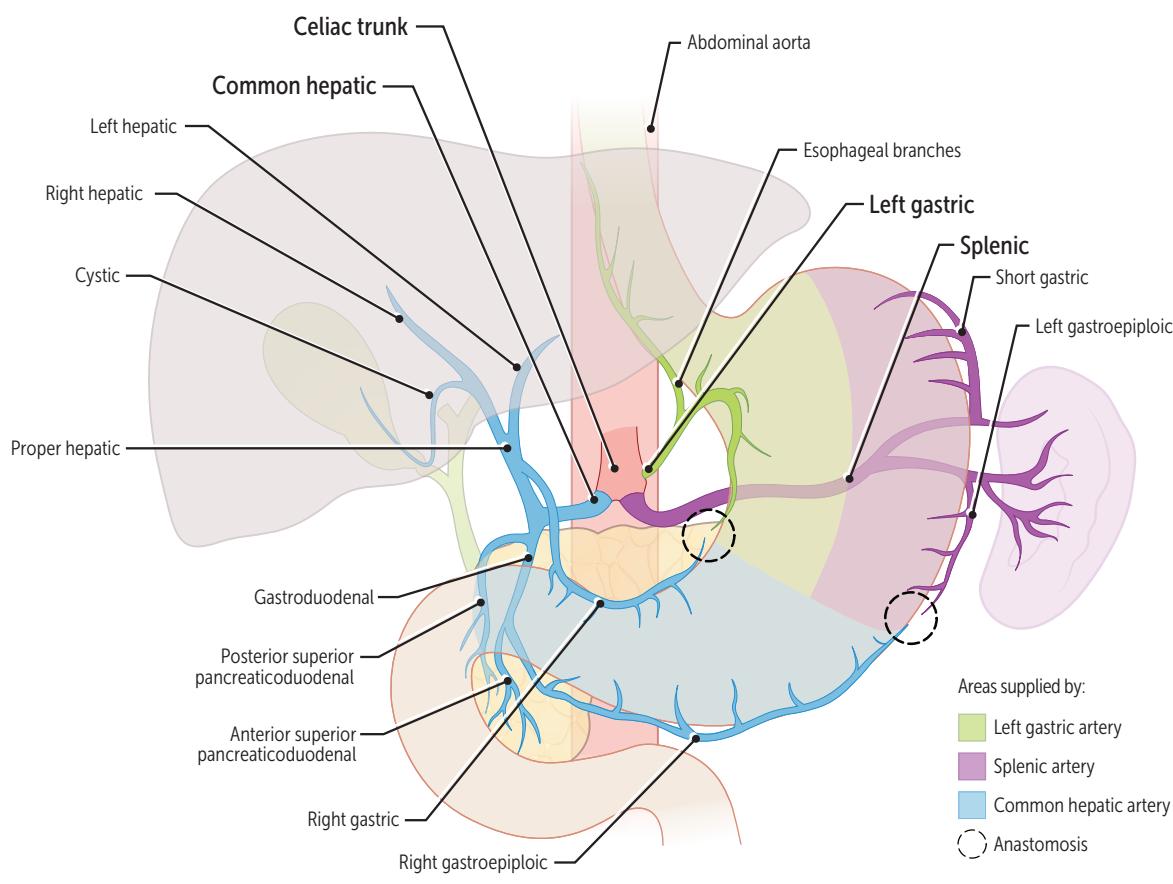
Sympathetic innervation arises from abdominal prevertebral ganglia: celiac, superior mesenteric, and inferior mesenteric.

### Celiac trunk

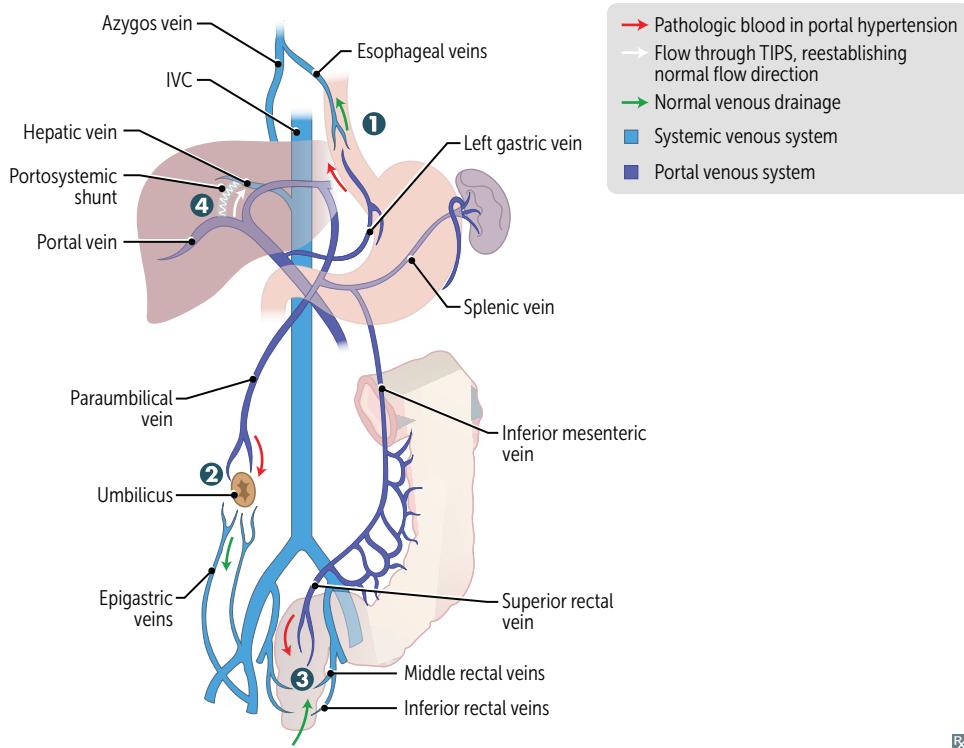
Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the foregut.

Strong anastomoses exist between:

- Left and right gastroepiploics
- Left and right gastrics



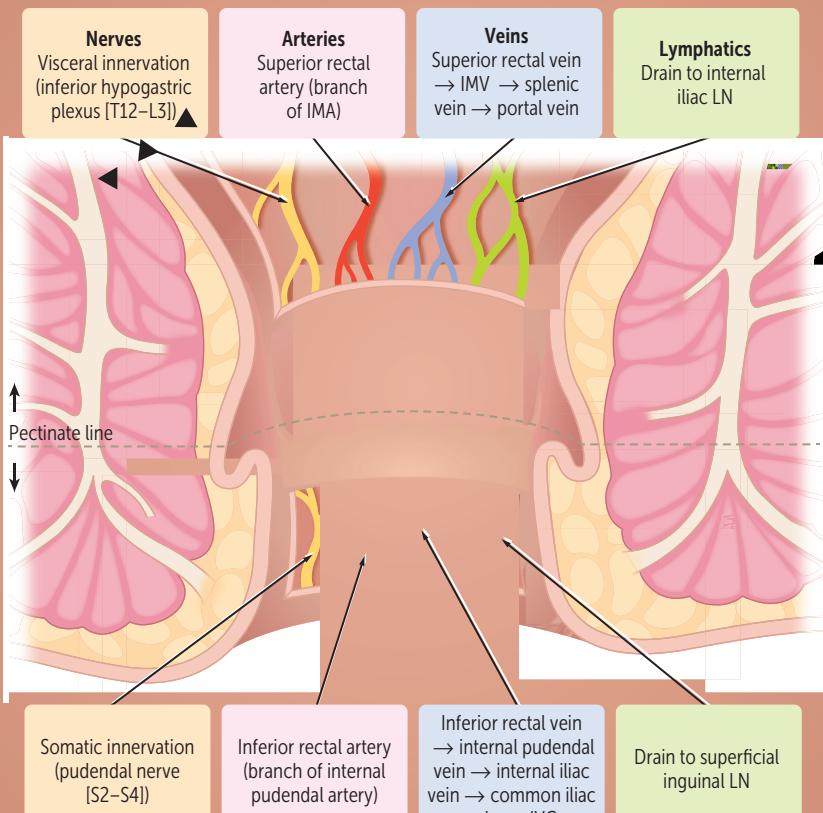
### Portosystemic anastomoses



SITE OF ANASTOMOSIS	CLINICAL SIGN	PORTAL ↔ SYSTEMIC
<b>① Esophagus</b>	Esophageal varices	Left gastric ↔ esophageal (drains into azygos)
<b>② Umbilicus</b>	<b>Caput</b> medusae	Paraumbilical ↔ small epigastric veins (branches of inferior and superficial epigastric veins) of the anterior abdominal wall
<b>③ Rectum</b>	Anorectal varices	Superior rectal ↔ middle and inferior rectal

Varices of **gut**, **butt**, and **caput** (medusae) are commonly seen with portal hypertension.

- ④** Treatment with a **Transjugular Intrahepatic Portosystemic Shunt (TIPS)** between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. TIPS can precipitate hepatic encephalopathy due to ↓ clearance of ammonia from shunting.



**Above pectinate line:** internal hemorrhoids, adenocarcinoma.

**Internal hemorrhoids**—abnormal distention of anal venous plexus **A**. Risk factors include older age and chronic constipation. Receive visceral innervation and are therefore **not painful**.

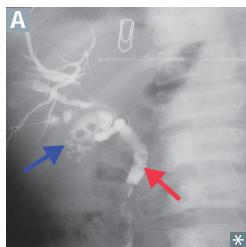


**Below pectinate line:** external hemorrhoids, anal fissures, squamous cell carcinoma.

**External hemorrhoids**—receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed.

**Anal fissure**—tear in anoderm below pectinate line. Pain while pooping; blood on toilet paper. Located in the posterior midline because this area is poorly perfused. Associated with low-fiber diets and constipation.

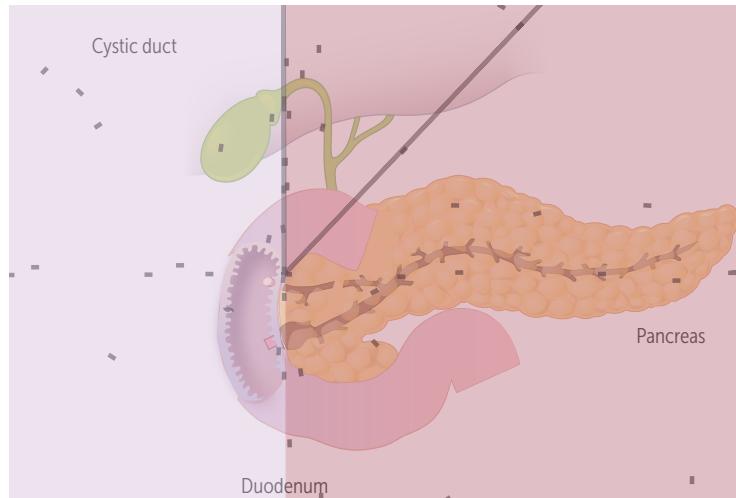


**Biliary structures**

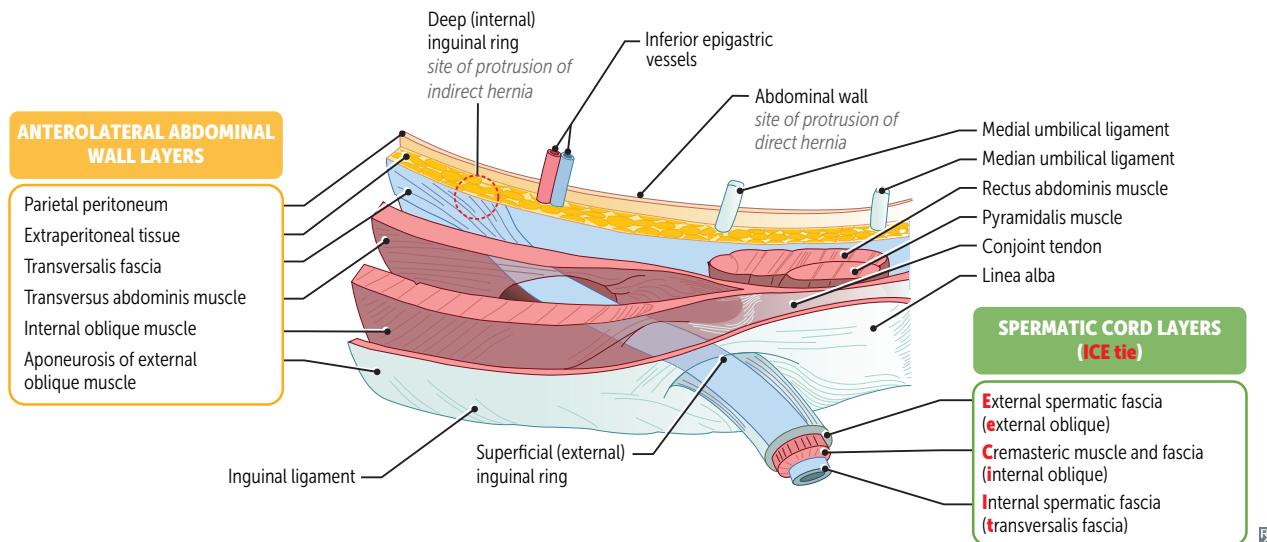
Cholangiography shows filling defects in gallbladder (blue arrow in A) and common bile (red arrow in A).

Gallstones that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

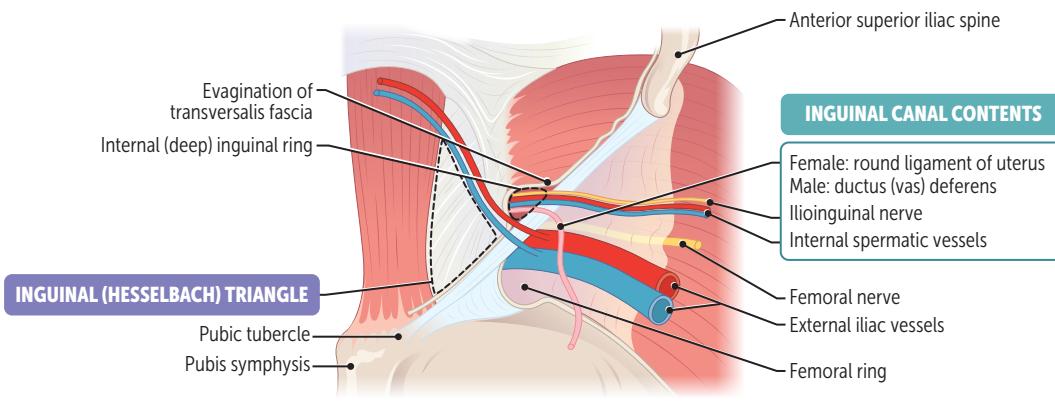
Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder with painless jaundice (Courvoisier sign).



### Inguinal canal



### Myopectineal orifice



### Hernias

Protrusion of peritoneum through an opening, usually at a site of weakness. Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis). Complicated hernias can present with tenderness, erythema, fever.

#### Spigelian hernia

Also called spontaneous lateral ventral hernia or hernia of semilunar line. Occurs through defects between the rectus abdominis and the semilunar line in the Spigelian aponeurosis. Most occur in the lower abdomen due to lack of the posterior rectus sheath. Presentation is variable but may include abdominal pain and a palpable lump along the Spigelian fascia. Diagnosis: ultrasound and CT scan.



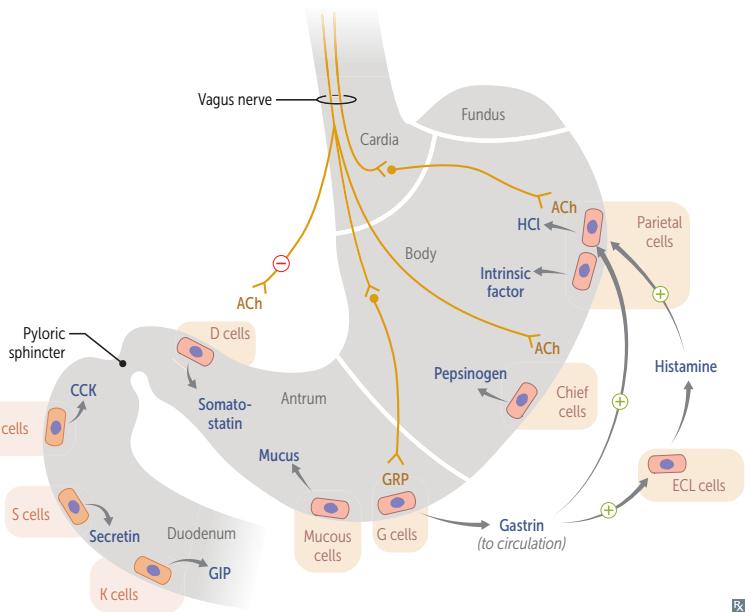
## ► GASTROINTESTINAL—PHYSIOLOGY

## Gastrointestinal regulatory substances

REGULATORY SUBSTANCE	SOURCE	ACTION	REGULATION	NOTES
Gastrin	G cells (antrum of stomach, duodenum)	↑ gastric H <sup>+</sup> secretion ↑ growth of gastric mucosa ↑ gastric motility	↑ by stomach distention/ alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP) ↓ by pH < 1.5	↑ by chronic PPI use ↑ in chronic atrophic gastritis (eg, <i>H pylori</i> ) ↑↑ in Zollinger-Ellison syndrome (gastrinoma)
Somatostatin	D cells (pancreatic islets, GI mucosa)	↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release	↑ by acid ↓ by vagal stimulation	Inhibits secretion of various hormones (encourages somato-stasis) Octreotide is an analog used to treat acromegaly, carcinoid syndrome, VIPoma, and variceal bleeding
Cholecystokinin	I cells (duodenum, jejunum)	↑ pancreatic secretion ↑ gallbladder contraction ↓ gastric emptying ↑ sphincter of Oddi relaxation	↑ by fatty acids, amino acids	Acts on neural muscarinic pathways to cause pancreatic secretion
Secretin	S cells (duodenum)	↑ pancreatic HCO <sub>3</sub> <sup>-</sup> secretion ↓ gastric acid secretion ↑ bile secretion	↑ by acid, fatty acids in lumen of duodenum	↑ HCO <sub>3</sub> <sup>-</sup> neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function
Glucose-dependent insulinotropic peptide	K cells (duodenum, jejunum)	Exocrine: ↓ gastric H <sup>+</sup> secretion Endocrine: ↑ insulin release	↑ by fatty acids, amino acids, oral glucose	Also called gastric inhibitory peptide (GIP) Oral glucose load ↑ insulin compared to IV equivalent due to GIP secretion
Motilin	Small intestine	Produces migrating motor complexes (MMCs)	↑ in fasting state	Motilin receptor agonists (eg, erythromycin) are used to stimulate intestinal peristalsis.
Vasoactive intestinal polypeptide	Parasympathetic ganglia in sphincters, gallbladder, small intestine	↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters	↑ by distention and vagal stimulation ↓ by adrenergic input	VIPoma—non-α, non-β islet cell pancreatic tumor that secretes VIP; associated with Watery Diarrhea, Hypokalemia, Achlorhydria (WDHA syndrome)
Nitric oxide		↑ smooth muscle relaxation, including lower esophageal sphincter (LES)		Loss of NO secretion is implicated in ↑ LES tone of achalasia
Ghrelin	Stomach	↑ appetite (“ghrowlin’ stomach”)	↑ in fasting state ↓ by food	↑ in Prader-Willi syndrome ↓ after gastric bypass surgery



### Locations of gastrointestinal secretory cells



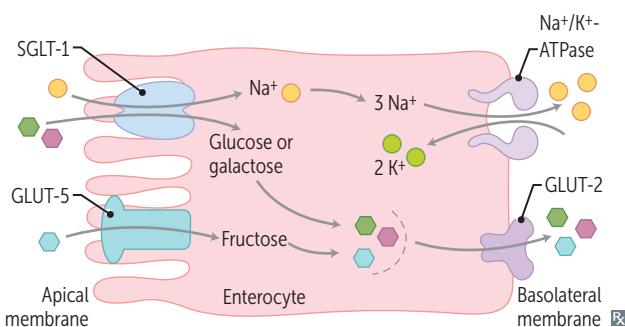
Gastrin ↑ acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

### Pancreatic secretions

Isotonic fluid; low flow → high Cl<sup>-</sup>, high flow → high HCO<sub>3</sub><sup>-</sup>.

ENZYME	ROLE	NOTES
$\alpha$ -amylase	Starch digestion	Secreted in active form
Lipases	Fat digestion	
Proteases	Protein digestion	Includes trypsin, chymotrypsin, elastase, carboxypeptidases Secreted as proenzymes also called zymogens Dipeptides and tripeptides degraded within intestinal mucosa via intracellular process
Trypsinogen	Converted to active enzyme trypsin → activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop)	Converted to trypsin by enterokinase/enteropeptidase, a brush-border enzyme on duodenal and jejunal mucosa

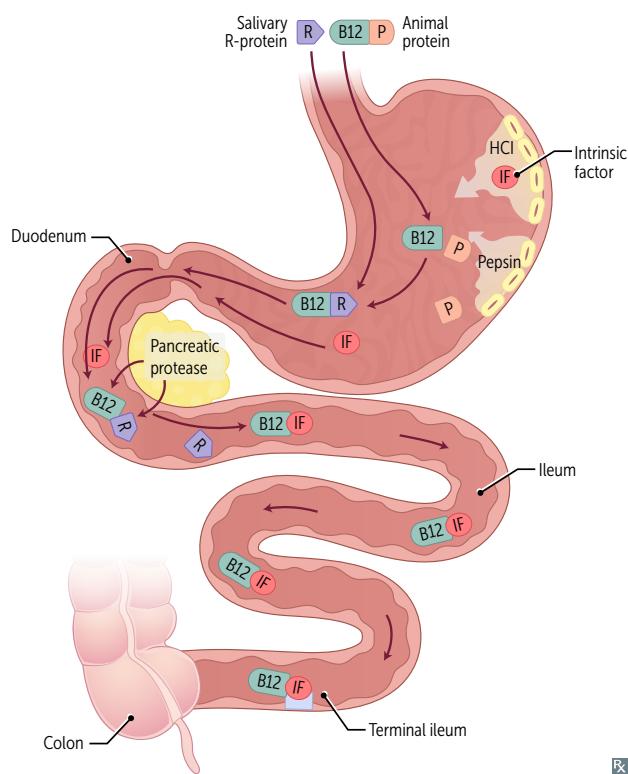
### Carbohydrate absorption



Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGlt1 (Na<sup>+</sup> dependent). Fructose is taken up via facilitated diffusion by GLUT5. All are transported to blood by GLUT2.

D-xylose test: simple sugar that is passively absorbed in proximal small intestine; blood and urine levels ↓ with mucosal damage, normal in pancreatic insufficiency.

### Vitamin and mineral absorption



Vitamin and mineral deficiencies may develop in patients with small bowel disease, bowel resection, intestinal failure (also called short bowel syndrome), or bariatric surgery (eg, vitamin B<sub>12</sub> deficiency after terminal ileum resection).

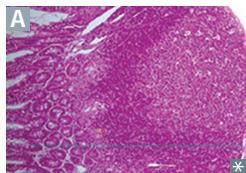
**Iron** absorbed as Fe<sup>2+</sup> in duodenum.

**Folate** absorbed in small bowel.

Vitamin **B**<sub>12</sub> absorbed in terminal ileum along with bile salts, requires intrinsic factor.

**Iron fist, Bro**

### Peyer patches



Unencapsulated lymphoid tissue **A** found in lamina propria and submucosa of ileum. Contain specialized **Microfold (M)** cells that sample and present antigens to **iM**mune cells. B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Think of **IgA**, the **Intra-gut Antibody**

**Bile**

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol 7 $\alpha$ -hydroxylase catalyzes rate-limiting step of bile acid synthesis.

Functions:

- Digestion and absorption of lipids and fat-soluble vitamins
- Bilirubin and cholesterol excretion (body's 1° means of elimination)
- Antimicrobial activity (via membrane disruption)

↓ absorption of enteric bile salts at distal ileum (as in short bowel syndrome, Crohn disease) prevents normal fat absorption and may cause bile acid diarrhea.

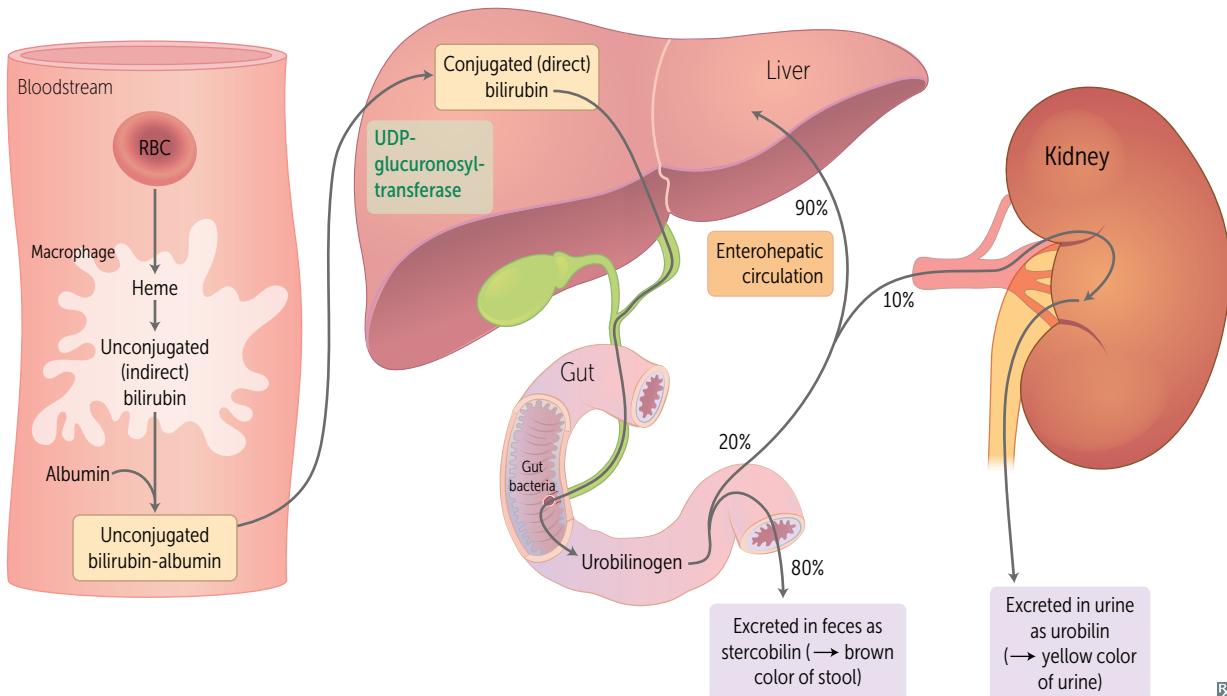
Calcium, which normally binds oxalate, binds fat instead, so free oxalate is absorbed by gut  
→ ↑ frequency of calcium oxalate kidney stones.

**Bilirubin**

Heme is metabolized by heme oxygenase to biliverdin (green), which is subsequently reduced to bilirubin (yellow-brown). Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile.

**Direct bilirubin:** conjugated with glucuronic acid; water soluble (**dissolves in water**).

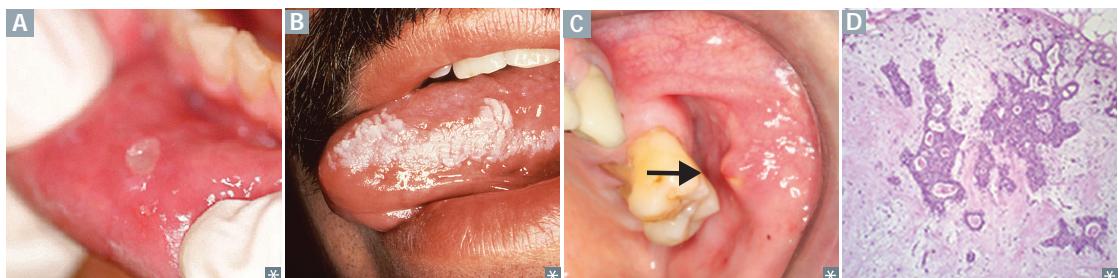
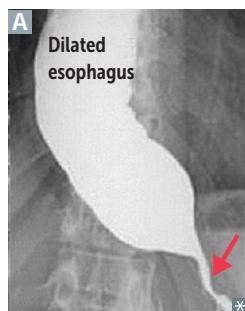
**Indirect bilirubin:** unconjugated; water **insoluble**.



## ► GASTROINTESTINAL—PATHOLOGY

## Oral pathologies

<b>Aphthous ulcers</b>	Also called canker sores. Common oral lesions that appear as painful, shallow, round to oval ulcers covered by yellowish exudate <b>A</b> . Recurrent aphthous stomatitis is associated with celiac disease, IBD, SLE, Behçet syndrome, HIV infection.
<b>Squamous cell carcinoma</b>	Most common malignancy of oral cavity. Usually affects the tongue. Associated with tobacco, alcohol, HPV-16. Presents as nonhealing ulcer with irregular margins and raised borders. Leukoplakia (white patch <b>B</b> ) and erythroplakia (red patch) are precursor lesions.
<b>Sialolithiasis</b>	Stone formation in ducts of major salivary glands (parotid <b>C</b> , submandibular, or sublingual). Associated with salivary stasis (eg, dehydration) and trauma. Presents as recurrent pre-/periprandial pain and swelling in affected gland.
<b>Sialadenitis</b>	Inflammation of salivary gland due to obstruction, infection (eg, <i>S aureus</i> , mumps virus), or immune-mediated mechanisms (eg, Sjögren syndrome).
<b>Salivary gland tumors</b>	Usually benign and most commonly affect the parotid gland. Submandibular, sublingual, and minor salivary gland tumors are more likely to be malignant. Typically present as painless mass/swelling. Facial paralysis or pain suggests malignant involvement. <ul style="list-style-type: none"> <li>▪ <b>Pleomorphic adenoma</b> (benign mixed tumor)—most common salivary gland tumor <b>D</b>. Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively. May undergo malignant transformation.</li> <li>▪ <b>Warthin tumor</b> (papillary cystadenoma lymphomatosum)—benign cystic tumor with <b>germinal</b> centers. May be bilateral or multifocal. Typically found in people who <b>smoke</b>. “<b>Warriors from Germany love smoking.</b>”</li> <li>▪ <b>Mucoepidermoid carcinoma</b>—most common malignant tumor. Mucinous and squamous components.</li> </ul>

**Achalasia**

Failure of LES to relax due to degeneration of inhibitory neurons (containing NO and VIP) in the myenteric (Auerbach) plexus of esophageal wall.

1° achalasia is idiopathic. 2° achalasia may arise from Chagas disease (*T cruzi* infection) or extraesophageal malignancies (mass effect or paraneoplastic). **Chagas** disease can cause **achalasia**.

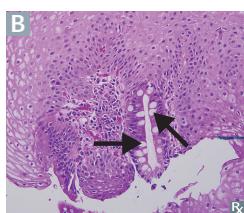
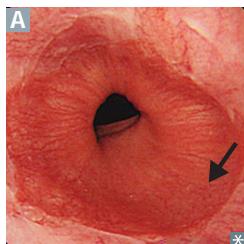
Presents with progressive dysphagia to solids and liquids (vs obstruction—primarily solids). Associated with ↑ risk of esophageal cancer.

Manometry findings include uncoordinated or absent peristalsis with ↑ LES resting pressure. Barium swallow shows dilated esophagus with area of distal stenosis (“bird’s beak” **A**).

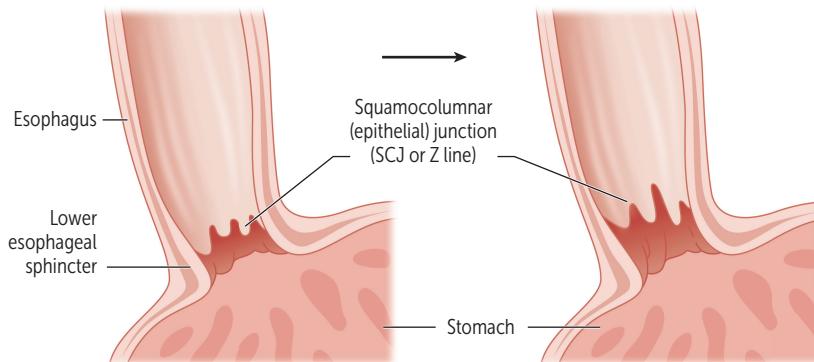
Treatment: surgery, endoscopic procedures (eg, botulinum toxin injection).

**Other esophageal pathologies**

Gastroesophageal reflux disease	Transient decreases in LES tone. Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma. Complications include erosive esophagitis, strictures, and Barrett esophagus.
Esophagitis	Inflammation of esophageal mucosa. Presents with odynophagia and/or dysphagia. Types: <ul style="list-style-type: none"><li>▪ <b>Reflux (erosive) esophagitis</b>—most common type. 2° to GERD.</li><li>▪ <b>Medication-induced esophagitis</b>—2° to bisphosphonates, tetracyclines, NSAIDs, ferrous sulfate, potassium chloride.</li><li>▪ <b>Eosinophilic esophagitis</b>—chronic, immune-mediated, eosinophil-predominant. Associated with atopic disorders (eg, asthma). Esophageal rings and linear furrows on endoscopy.</li><li>▪ <b>Infectious esophagitis</b>—<i>Candida</i> (most common; white pseudomembranes <b>A</b>), HSV-1 (punched-out ulcers), CMV (linear ulcers). Associated with immunosuppression.</li><li>▪ <b>Corrosive esophagitis</b>—2° to caustic ingestion.</li></ul>
Plummer-Vinson syndrome	Triad of <b>dysphagia</b> , <b>iron deficiency anemia</b> , <b>esophageal webs</b> . ↑ risk of esophageal <b>squamous cell carcinoma</b> ("Plumber dies"). May be associated with glossitis.
Mallory-Weiss syndrome	Partial thickness, <b>longitudinal lacerations</b> of gastroesophageal junction, confined to mucosa/submucosa, due to severe vomiting. Often presents with hematemesis +/- abdominal/back pain. Usually found in patients with alcohol use disorder, bulimia nervosa.
Esophageal varices	Dilated submucosal veins (red arrows in <b>B</b> ) in lower 1/3 of esophagus 2° to portal hypertension. Common in patients with cirrhosis, may be source of life-threatening hematemesis.
Distal esophageal spasm	Formerly called diffuse esophageal spasm. Spontaneous, nonperistaltic (uncoordinated)

**Barrett esophagus**

Specialized intestinal metaplasia (arrow in **A**)—replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [arrows in **B**]) in distal esophagus. Due to chronic gastroesophageal reflux disease (GERD). Associated with ↑ risk of esophageal adenocarcinoma.

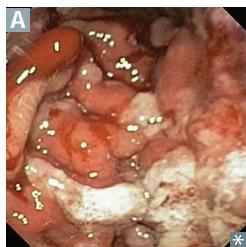
**Esophageal cancer**

Typically presents with progressive dysphagia (first solids, then liquids) and weight loss. Aggressive course due to lack of serosa in esophageal wall, allowing rapid extension. Poor prognosis due to advanced disease at presentation.

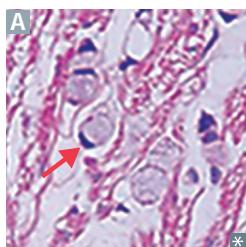
CANCER	PART OF ESOPHAGUS AFFECTED	RISK FACTORS	PREVALENCE
<b>Squamous cell carcinoma</b>	Upper 2/3	Alcohol, hot liquids, caustic strictures, smoking, achalasia, nitrosamine-rich foods	More common worldwide
<b>Adenocarcinoma</b>	Lower 1/3	Chronic GERD, Barrett esophagus, obesity, tobacco smoking	More common in America

**Gastritis**

<b>Acute gastritis</b>	Erosions can be caused by: <ul style="list-style-type: none"> <li>▪ NSAIDs—<math>\downarrow</math> PGE<sub>2</sub> <math>\rightarrow</math> <math>\downarrow</math> gastric mucosa protection</li> <li>▪ <b>Burns (Curling ulcer)</b>—hypovolemia <math>\rightarrow</math> mucosal ischemia</li> <li>▪ <b>Brain</b> injury (<b>Cushing ulcer</b>)—<math>\uparrow</math> vagal stimulation <math>\rightarrow</math> <math>\uparrow</math> ACh <math>\rightarrow</math> <math>\uparrow</math> H<sup>+</sup> production</li> </ul>	Especially common among patients with alcohol use disorder and those taking daily NSAIDs (eg, for rheumatoid arthritis) <b>Burned</b> by the <b>Curling</b> iron Always <b>Cushion</b> the <b>brain</b>
<b>Chronic gastritis</b>	Mucosal inflammation, often leading to atrophy (hypochlorhydria $\rightarrow$ hypergastrinemia) and intestinal metaplasia ( $\uparrow$ risk of gastric cancers)	
<i>H pylori</i>	Most common. $\uparrow$ risk of peptic ulcer disease, MALT lymphoma	Affects antrum first and spreads to body of stomach
<b>Autoimmune</b>	Autoantibodies (T-cell induced) to the H <sup>+</sup> /K <sup>+</sup> -ATPase on parietal cells and to intrinsic factor. $\uparrow$ risk of pernicious anemia	Affects body/fundus of stomach

**Ménétrier disease**

Hyperplasia of gastric mucosa  $\rightarrow$  hypertrophied rugae (“wavy” like brain gyri **A**). Causes excess mucus production with resultant protein loss and parietal cell atrophy with  $\downarrow$  acid production. Precancerous.  
Presents with **Weight loss**, **Anorexia**, **Vomiting**, **Epigastric pain**, **Edema** (due to protein loss; pronounce “**WAVEE**”).

**Gastric cancer**

Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with **Weight loss**, **Early satiety**, **Abdominal Pain**, **Obstruction**, and in some cases acanthosis Nigricans or Leser-Trélat sign (**WEAPON**).  

- **Intestinal**—associated with *H pylori*, dietary nitrosamines (smoked foods common in East Asian countries), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.
- **Diffuse**—not associated with *H pylori*; most cases due to E-cadherin mutation; signet ring cells (mucin-filled cells with peripheral nuclei) **A**; stomach wall grossly thickened and leathery (linitis plastica).

**Virchow node**—involvement of left supraclavicular node by metastasis from stomach.

**Krukenberg tumor**—metastasis to ovaries (typically bilateral). Abundant mucin-secreting, signet ring cells.

**Sister Mary Joseph nodule**—subcutaneous periumbilical metastasis.

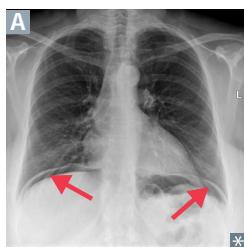
**Blumer shelf**—palpable mass on digital rectal exam suggesting metastasis to rectouterine pouch (pouch of Douglas).

**Peptic ulcer disease**

	Gastric ulcer	Duodenal ulcer
PAIN	Can be <b>greater</b> with meals—weight loss	<b>Decreases</b> with meals—weight gain
H PYLORI INFECTION	~ 70%	~ 90%
MECHANISM	↓ mucosal protection against gastric acid	↓ mucosal protection or ↑ gastric acid secretion
OTHER CAUSES	NSAIDs	Zollinger-Ellison syndrome
RISK OF CARCINOMA	↑ Biopsy margins to rule out malignancy	Generally benign Not routinely biopsied

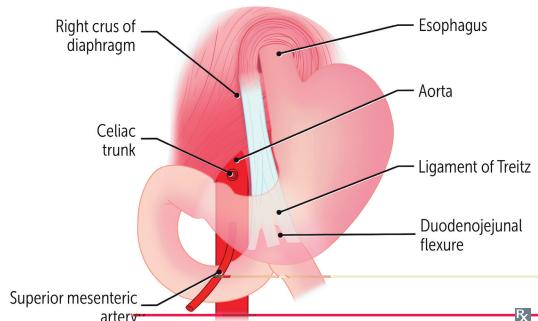
**Ulcer complications**

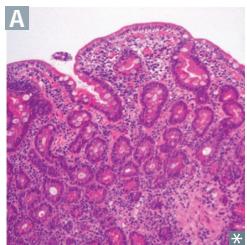
<b>Hemorrhage</b>	Gastric, duodenal (posterior > anterior). Most common complication. Ruptured gastric ulcer on the <b>lesser curvature</b> of stomach → bleeding from <b>left gastric artery</b> . An ulcer on the posterior wall of duodenum → bleeding from <b>gastroduodenal artery</b> .
<b>Obstruction</b>	Pyloric channel, duodenal.
<b>Perforation</b>	Duodenal (anterior > posterior). Anterior duodenal ulcers can perforate into the anterior abdominal cavity, potentially leading to <b>pneumoperitoneum</b> . May see free air under diaphragm (pneumoperitoneum) <b>A</b> with referred pain to the shoulder via irritation of phrenic nerve.

**Acute gastrointestinal bleeding**

**Upper GI bleeding**—originates **proximal** to ligament of Treitz (suspensory ligament of duodenum). Usually presents with hematemesis and/or melena. Associated with peptic ulcer disease, variceal hemorrhage.

**Lower GI bleeding**—originates **distal** to ligament of Treitz. Usually presents with hematochezia. Associated with IBD, diverticulosis, angiodysplasia, hemorrhoids, anal fissure, cancer.



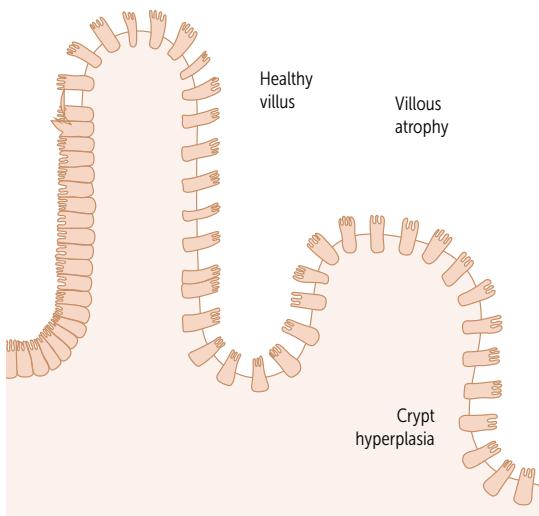
**Malabsorption syndromes****Celiac disease**

Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies. Screen for fecal fat (eg, Sudan stain).

Also called gluten-sensitive enteropathy, celiac sprue. Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat, barley, rye). Associated with HLA-DQ2, HLA-DQ8, northern European descent.

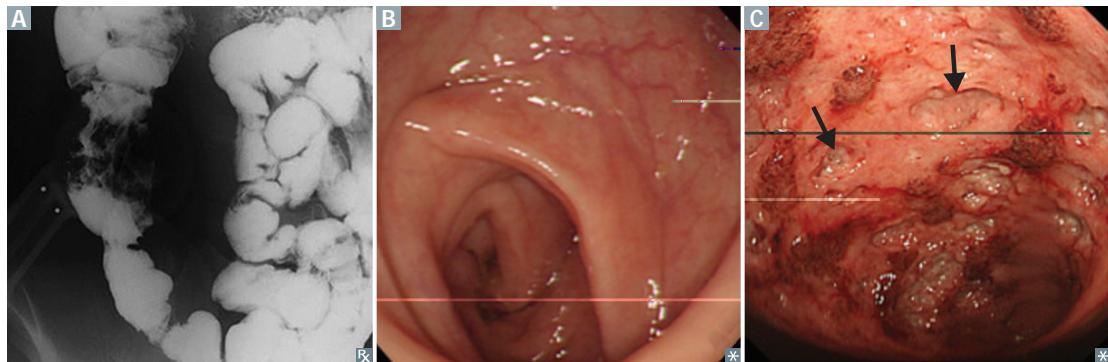
Primarily affects distal duodenum and/or proximal jejunum → malabsorption and steatorrhea.

Treatment: gluten-free diet.



## Inflammatory bowel diseases

	Crohn disease	Ulcerative colitis
LOCATION	Any portion of the GI tract, usually the terminal ileum and colon. Skip lesions, rectal sparing.	Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement.
GROSS MORPHOLOGY	Transmural inflammation → fistulas. Cobblestone mucosa, creeping fat, bowel wall thickening (“string sign” on small bowel follow-through <b>A</b> ), linear ulcers, fissures.	Mucosal and submucosal inflammation only. Friable mucosa with superficial and/or deep ulcerations (compare normal <b>B</b> with diseased <b>C</b> ). Loss of haustra → “lead pipe” appearance on imaging.
MICROSCOPIC MORPHOLOGY	Noncaseating granulomas, lymphoid aggregates.	Crypt abscesses/ulcers, bleeding, no granulomas.
COMPLICATIONS	Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis). Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.	Fulminant colitis, toxic megacolon, perforation.
INTESTINAL MANIFESTATION	Diarrhea that may or may not be bloody.	Bloody diarrhea (usually painful).
EXTRAINTESTINAL MANIFESTATIONS	Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis).	1° sclerosing cholangitis. Associated with MPO-ANCA/p-ANCA.
TREATMENT	Glucocorticoids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), biologics (eg, infliximab, adalimumab).	5-aminosalicylic acid preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.
DISEASE ACTIVITY	Fecal calprotectin used to monitor activity and distinguish from noninflammatory diseases (irritable bowel).	



## Microscopic colitis

Inflammatory disease of colon that causes chronic watery diarrhea. Most common in older females. Colonic mucosa appears normal on endoscopy. Histology shows lymphocytic infiltrate in lamina propria with intraepithelial lymphocytosis or thickened subepithelial collagen band.

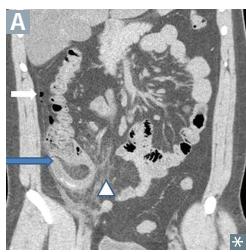
**Irritable bowel syndrome**

Recurrent abdominal pain associated with ≥ 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 symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted. May be associated with fibromyalgia and mood disorders (anxiety, depression).

First-line treatment is lifestyle modification and dietary changes.

**Appendicitis**

Acute inflammation of the appendix (blue arrow in **A**), can be due to obstruction by fecalith (in adults) or lymphoid hyperplasia (in children).

Proximal obstruction of appendiceal lumen → closed-loop obstruction → ↑ intraluminal pressure → stimulation of visceral afferent nerve fibers at T8-T10 → initial diffuse periumbilical pain → inflammation extends to serosa and irritates parietal peritoneum. Pain localized to RLQ/McBurney point (1/3 the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate → peritonitis. May elicit psoas, obturator, and Rovsing (severe RLQ pain with palpation of LLQ) signs; guarding and rebound tenderness on exam.

Treatment: appendectomy.

**Diverticula of the GI tract****Diverticulum**

Blind pouch **A** protruding from the alimentary tract that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed “false diverticula.”

**“True” diverticulum**—all gut wall layers outpouch (eg, Meckel).

**“False” diverticulum** or **pseudodiverticulum**—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa.

**Diverticulosis**

Many false diverticula of the colon **B**, commonly sigmoid. Common (in ~ 50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with obesity and diets low in fiber, high in total fat/red meat.

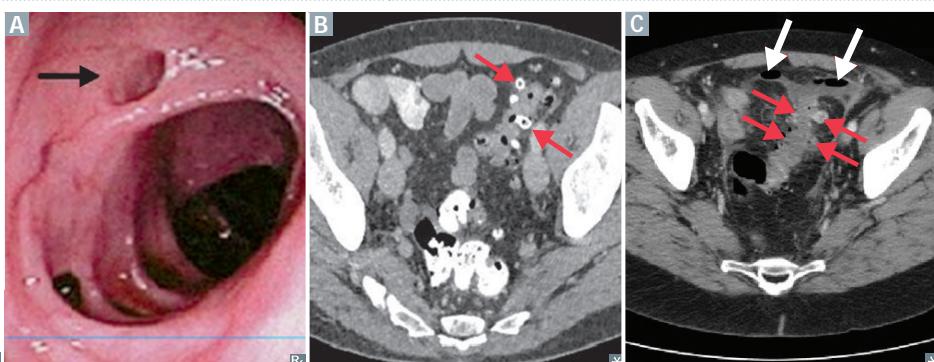
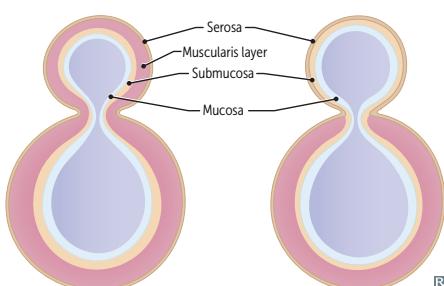
Often asymptomatic or associated with vague discomfort.

Complications include diverticular bleeding (painless hematochezia), diverticulitis.

**Diverticulitis**

Inflammation of diverticula with wall thickening (red arrows in **C**) classically causing LLQ pain, fever, leukocytosis. Treat with supportive care (uncomplicated) or antibiotics (complicated).

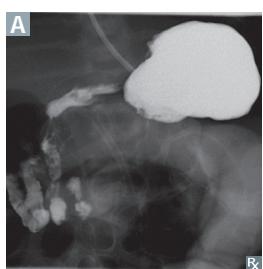
Complications: abscess, fistula (colovesical fistula → pneumaturia), obstruction (inflammatory stenosis), perforation (white arrows in **C**) (→ peritonitis). Hematochezia is rare.



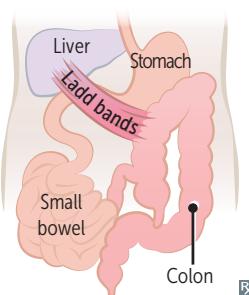
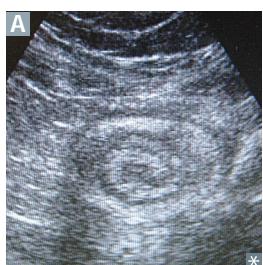
**Zenker diverticulum****Pharyngoesophageal false diverticulum A.**

Esophageal dysmotility causes herniation of mucosal tissue at an area of weakness between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor (Killian triangle). Presenting symptoms: dysphagia, obstruction, gurgling, aspiration, foul breath, neck mass. Most common in older males.



**Malrotation**

Anomaly of midgut rotation during fetal development → improper positioning of bowel (small bowel clumped on the right side) **A**, formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

**Intussusception**

Telescoping of a proximal bowel segment into a distal segment, most commonly at ileocecal junction. Typically seen in infants; rare in adults.

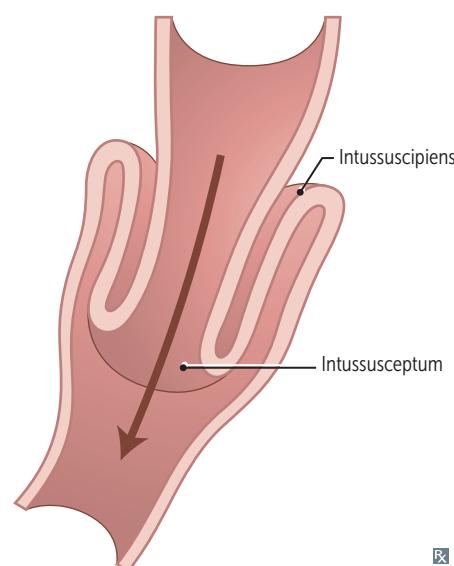
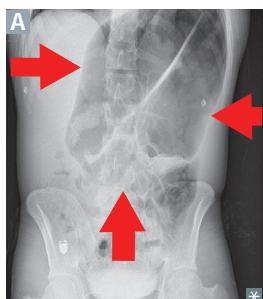
Usually idiopathic in children, less frequently due to an identifiable lead point. Idiopathic form is associated with recent viral infections (eg, adenovirus), rotavirus vaccine → Peyer patch hypertrophy may act as a lead point. Common lead points:

- Children—Meckel diverticulum, small bowel wall hematoma (IgA vasculitis).
- Adults—intraluminal mass/tumor.

Causes small bowel obstruction and vascular compromise → intermittent abdominal pain, vomiting, bloody “currant jelly” stools.

Physical exam—sausage shaped mass in right abdomen, patient may draw their legs to chest to ease pain.

Imaging—ultrasound/CT may show “target sign” **A**.

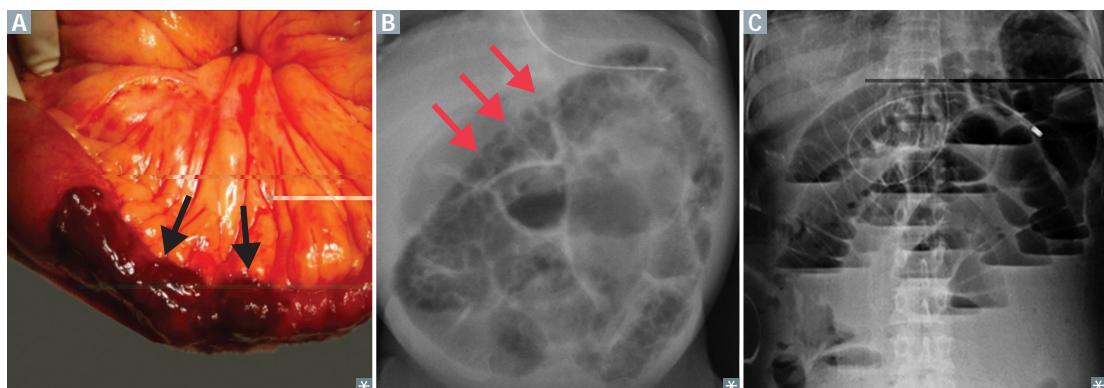
**Volvulus**

Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. Can occur throughout the GI tract.

- Gastric volvulus more common with anatomic abnormalities (paraesophageal hernia), and presents with severe abdominal pain, dry heaving, and inability to pass nasogastric tube
- Midgut volvulus more common in infants and children (**minors**)
- Sigmoid volvulus (coffee bean sign on x-ray **A**) more common in older adults (**seniors**)

### Other intestinal disorders

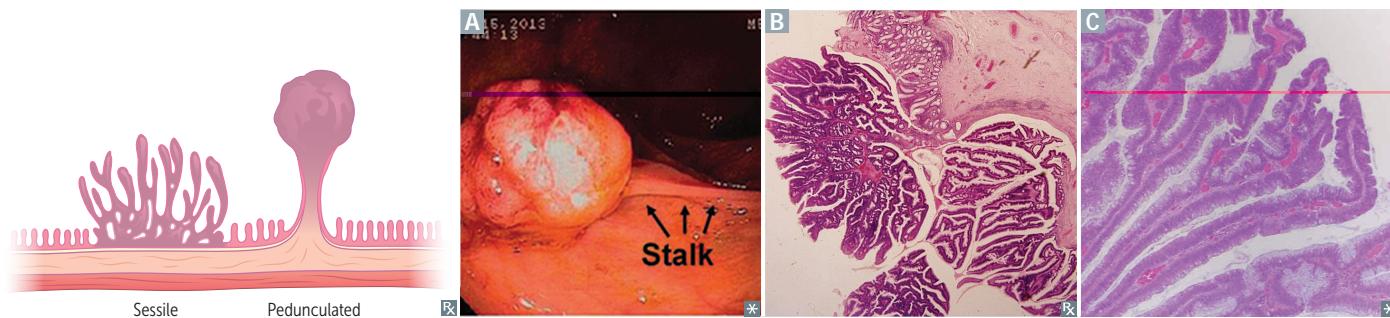
<b>Acute mesenteric ischemia</b>	Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis <b>A</b> → abdominal pain out of proportion to physical findings. May see red “currant jelly” stools. Risk factors: atrial fibrillation, peripheral arterial disease, recent MI, CHF.
<b>Angiodysplasia</b>	Tortuous dilation of vessels → hematochezia. Most often found in the right-sided colon. More common in older patients. Confirmed by angiography. Associated with end-stage renal disease, von Willebrand disease, aortic stenosis.
<b>Chronic mesenteric ischemia</b>	“Intestinal angina”: atherosclerosis of celiac artery, SMA (most commonly affected), or IMA → intestinal hypoperfusion → postprandial epigastric pain → food aversion and weight loss.
<b>Colonic ischemia</b>	Crampy abdominal pain followed by hematochezia. Commonly occurs at watershed areas (splenic flexure, rectosigmoid junction). Typically affects older adults. Thumbprint sign on imaging due to mucosal edema/hemorrhage.
<b>Ileus</b>	Intestinal hypomotility without obstruction → constipation and ↓ flatus; distended/tympanic abdomen with ↓ bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. No transition zone on imaging. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility).
<b>Necrotizing enterocolitis</b>	Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (most commonly terminal ileum and proximal colon), which can lead to pneumatosis intestinalis (arrows in <b>B</b> ), pneumoperitoneum, portal venous gas.
<b>Proctitis</b>	Inflammation of rectal mucosa, usually associated with infection ( <i>N gonorrhoea</i> , <i>Chlamydia</i> , <i>Campylobacter</i> , <i>Shigella</i> , <i>Salmonella</i> , HSV, CMV), IBD, and radiation. Patients report tenesmus, rectal bleeding, and rectal pain. Proctoscopy reveals inflamed rectal mucosa (ulcers/vesicles in the case of HSV). Rectal swabs are used to detect other infectious etiologies.
<b>Small bowel obstruction</b>	Normal flow of intraluminal contents is interrupted → fluid accumulation and intestinal dilation proximal to blockage and intestinal decompression distal to blockage. Presents with abrupt onset of abdominal pain, nausea, vomiting, abdominal distension. Compromised blood flow due to excessive dilation or strangulation may lead to ischemia, necrosis, or perforation. Most commonly caused by intraperitoneal adhesions (fibrous band of scar tissue), tumors, and hernias (in rare cases, meconium plug in newborns → meconium ileus). Upright abdominal x-ray shows air-fluid levels <b>C</b> . Management: gastrointestinal decompression, volume resuscitation, bowel rest.
<b>Small intestinal bacterial overgrowth</b>	Abnormal bacterial overgrowth in the small intestine (normally low bacterial colony count). Risk factors: altered pH (eg, achlorhydria, PPI use), anatomical (eg, small bowel obstruction, adhesions, fistula, gastric bypass surgery, blind loop), dysmotility (eg, gastroparesis), immune mediated (IgA deficiency, HIV). Presents with bloating, flatulence, abdominal pain, chronic watery diarrhea, malabsorption (vitamin B <sub>12</sub> ) in severe cases. Diagnosis: carbohydrate breath test or small bowel culture.



**Colonic polyps**

Growths of tissue within the colon **A**. Grossly characterized as flat, sessile, or pedunculated on the basis of protrusion into colonic lumen. Generally classified by histologic type.

HISTOLOGIC TYPE	CHARACTERISTICS
<b>Generally nonneoplastic</b>	
<b>Hamartomatous polyps</b>	Solitary lesions do not have significant risk of transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.
<b>Hyperplastic polyps</b>	Most common; generally smaller and predominantly located in rectosigmoid region. Occasionally evolves into serrated polyps and more advanced lesions.
<b>Inflammatory pseudopolyps</b>	Due to mucosal erosion in inflammatory bowel disease.
<b>Mucosal polyps</b>	Small, usually < 5 mm. Look similar to normal mucosa. Clinically insignificant.
<b>Submucosal polyps</b>	May include lipomas, leiomyomas, fibromas, and other lesions.
<b>Potentially malignant</b>	
<b>Adenomatous polyps</b>	Neoplastic, via chromosomal instability pathway with mutations in APC and KRAS. Tubular <b>B</b> histology has less malignant potential than villous <b>C</b> (“villous histology is villainous”); tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding.
<b>Serrated polyps</b>	Neoplastic. Characterized by CpG island methylator phenotype (CIMP; cytosine base followed by guanine, linked by a phosphodiester bond). Defect may silence mismatch repair gene (eg, MLH1) expression. Mutations lead to microsatellite instability and mutations in BRAF. “Saw-tooth” pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.

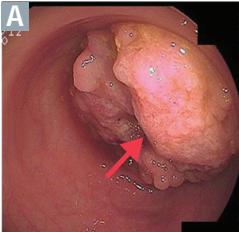
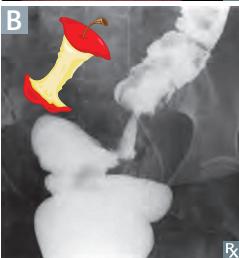
**Polypsis syndromes**

<b>Familial adenomatous polyposis</b>	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 else 100% progress to CRC.
<b>Gardner syndrome</b>	FAP + osseous and soft tissue tumors (eg, osteomas of skull or mandible), congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth.
<b>Turcot syndrome</b>	FAP or Lynch syndrome + malignant CNS tumor (eg, medulloblastoma, glioma). <b>Turcot = Turban.</b>
<b>Peutz-Jeghers syndrome</b>	Autosomal dominant syndrome featuring numerous hamartomatous polyps throughout GI tract, along with hyperpigmented macules on mouth, lips, hands, genitalia. Associated with ↑ risk of breast and GI cancers (eg, colorectal, stomach, small bowel, pancreatic).
<b>Juvenile polyposis syndrome</b>	Autosomal dominant syndrome in children (typically < 5 years old) featuring numerous hamartomatous polyps in the colon, stomach, small bowel. Associated with ↑ risk of CRC.
<b>MUTYH-associated polyposis syndrome</b>	Autosomal recessive disorder of the <i>MUTYH</i> gene responsible for DNA repair. Associated with significantly ↑ risk of CRC, polyps (adenomatous; may be hyperplastic or serrated), and serrated adenomas. Also associated with duodenal adenomas, ovarian and bladder cancers.

**Lynch syndrome**

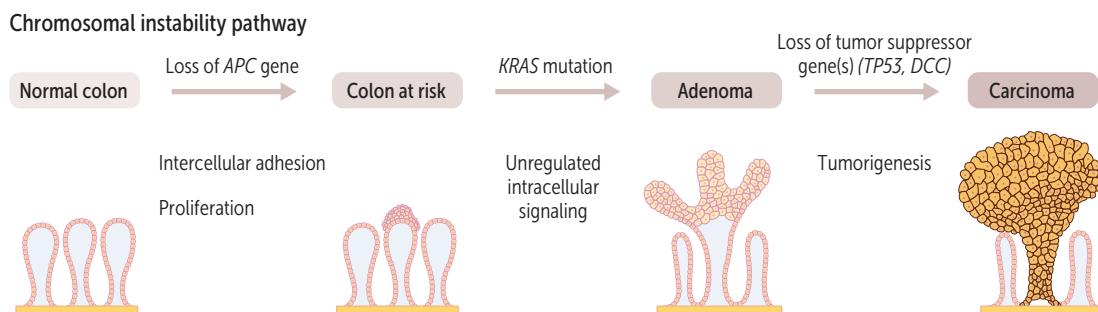
Also called hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of mismatch repair genes (eg, *MLH1*, *MSH2*) with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal Colon is always involved. Associated with Endometrial, Ovarian, and Skin cancers. Merrill Lynch has **CEOS**.

**Colorectal cancer**

<b>EPIDEMIOLOGY</b>	Most patients are > 50 years old. ~ 25% have a family history.
<b>RISK FACTORS</b>	Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.
<b>PRESSENTATION</b>	Rectosigmoid > ascending > descending. Most are asymptomatic. Right side (cecal, ascending) associated with occult bleeding; left side (rectosigmoid) associated with hematochezia and obstruction (narrower lumen → ↓ stool caliber). Ascending—exophytic mass, iron deficiency anemia, weight loss. Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia. Can present with <i>S bovis (gallopticus)</i> bacteremia/endocarditis or as an episode of diverticulitis.
<b>DIAGNOSIS</b>	Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screening: <ul style="list-style-type: none"> <li>Average risk: screen at age 45 with colonoscopy (polyp seen in <b>A</b>); alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), FIT-fecal DNA, CT colonography.</li> <li>Patients with a first-degree relative who has colon cancer: screen at age 40 with colonoscopy, or 10 years prior to the relative's presentation.</li> <li>Patients with IBD: screen 8 years after onset.</li> </ul> “Apple core” lesion seen on barium enema x-ray <b>B</b> . CEA tumor marker: good for monitoring recurrence, should not be used for screening.
 	

**Molecular pathogenesis of colorectal cancer**

Chromosomal instability pathway: mutations in APC cause FAP and most sporadic cases of CRC (commonly right-sided) via adenoma-carcinoma sequence.  
Microsatellite instability pathway: mutations or methylation of mismatch repair genes (eg, *MLH1*) cause Lynch syndrome and some sporadic CRC via serrated polyp pathway.  
Overexpression of COX-2 has been linked to CRC, NSAIDs may be chemopreventive.



**Cirrhosis and portal hypertension**

**Cirrhosis**—diffuse bridging fibrosis (via stellate cells) and regenerative nodules disrupt normal architecture of liver; ↑ risk for hepatocellular carcinoma. Can lead to various systemic changes **A**. Etiologies include alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

**Portal hypertension**—↑ pressure in portal venous system. Etiologies include cirrhosis (most common cause in developed countries), vascular obstruction (eg, portal vein thrombosis, Budd-Chiari syndrome), schistosomiasis.

**Serum ascites albumin gradient (SAAG)**—difference between albumin levels in serum and ascitic fluid.

$$\text{SAAG} = \text{albumin}_{\text{serum}} - \text{albumin}_{\text{ascites}}$$

Used to evaluate the etiology of ascites.

$\text{SAAG} \geq 1.1$  = portal hypertension.

$\text{SAAG} < 1.1$  = consider other causes.

<b>Spontaneous bacterial peritonitis</b>	Also called 1° bacterial peritonitis. Common and potentially fatal bacterial infection in patients with cirrhosis and ascites. Often asymptomatic, but can cause fevers, chills, abdominal pain, ileus, or worsening encephalopathy. Commonly caused by gram $\ominus$ organisms (eg, <i>E coli</i> , <i>Klebsiella</i> ) or less commonly gram $\oplus$ <i>Streptococcus</i> . Diagnosis: paracentesis with ascitic fluid absolute neutrophil count (ANC) $> 250$ cells/mm $^3$ . Empiric first-line treatment is 3rd generation cephalosporin (eg, ceftriaxone).
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## Serum markers of liver pathology

### ENZYMES RELEASED IN LIVER DAMAGE

<b>Aspartate aminotransferase and alanine aminotransferase</b>	↑ in most liver disease: ALT > AST ↑ in <b>alcoholic</b> liver disease: <b>AST</b> > ALT (ratio usually $> 2:1$ , AST does not typically exceed 500 U/L in alcoholic hepatitis). Make a to <b>AST</b> with <b>alcohol</b> AST > ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis ↑↑↑ aminotransferases ( $> 1000$ U/L): differential includes drug-induced liver injury (eg, acetaminophen toxicity), ischemic hepatitis, acute viral hepatitis, autoimmune hepatitis
<b>Alkaline phosphatase</b>	↑ in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease
<b><math>\gamma</math>-glutamyl transpeptidase</b>	↑ in various liver and biliary diseases (just as ALP can), but not in bone disease (located in canalicular membrane of hepatocytes like ALP); associated with alcohol use

### FUNCTIONAL LIVER MARKERS

<b>Bilirubin</b>	↑ in various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis
<b>Albumin</b>	↓ in advanced liver disease (marker of liver's biosynthetic function)
<b>Prothrombin time</b>	↑ in advanced liver disease (↓ production of clotting factors, thereby measuring the liver's biosynthetic function)
<b>Platelets</b>	↓ in advanced liver disease (↓ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration)

## Reye syndrome

Rare, often fatal childhood hepatic encephalopathy.  
Associated with viral infection (especially VZV and influenza) that has been treated with aspirin. Aspirin metabolites ↓  $\beta$ -oxidation by reversible inhibition of mitochondrial enzymes.  
Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty changes), hypoglycemia, vomiting, hepatomegaly, coma. ↑ ICP ↑ morbidity and mortality. Renal and cardiac failure may also occur. Requires expert review.

Avoid aspirin (**ASA**) in children, except in Kaw**ASA**ki disease.  
Salicylates aren't a ray (**Reye**) of sun**SHINE** for kids:  
**Steatosis of liver/hepatocytes**  
**Hypoglycemia/Hepatomegaly**  
**Infection (VZV, influenza)**  
**Not awake (coma)**  
**Encephalopathy**

**Alcoholic liver disease****Hepatic steatosis**

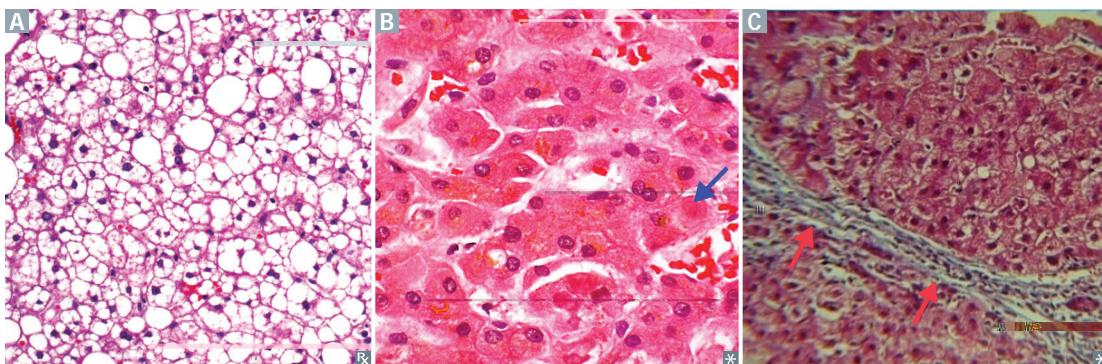
Macrovesicular fatty change **A** that may be reversible with alcohol cessation.

**Alcoholic hepatitis**

Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies **B** (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).

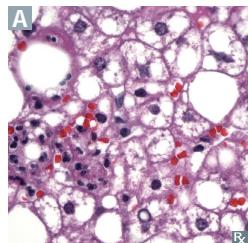
**Alcoholic cirrhosis**

Final and usually irreversible form. Sclerosis around central vein may be seen in early disease. Regenerative nodules surrounded by fibrous bands (red arrows in **C**) in response to chronic liver injury → portal hypertension and end-stage liver disease.

**Nonalcoholic fatty liver disease**

Associated with metabolic syndrome (obesity, insulin resistance, HTN, hypertriglyceridemia, ↓ HDL); obesity → fatty infiltration of hepatocytes **A** → cellular “ballooning” and eventual necrosis. Steatosis present without evidence of significant inflammation or fibrosis. May persist or even regress over time.

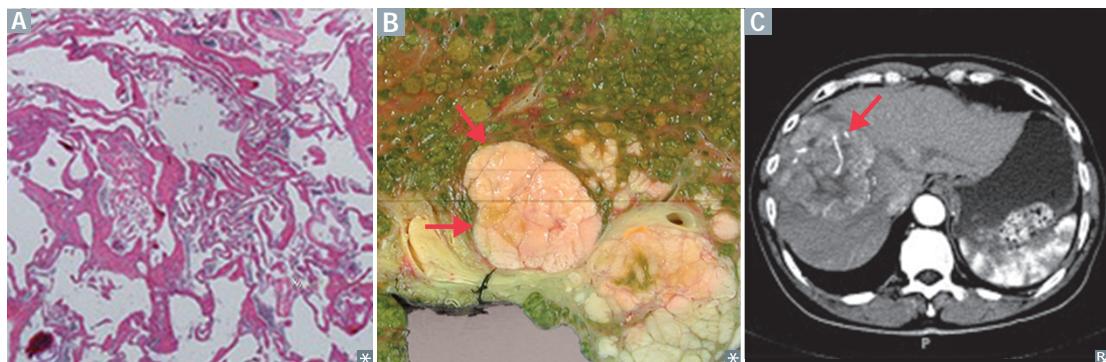
**Nonalcoholic steatohepatitis**—associated with lobular inflammation and hepatocyte ballooning → fibrosis. May progress to cirrhosis and HCC.

**Autoimmune hepatitis**

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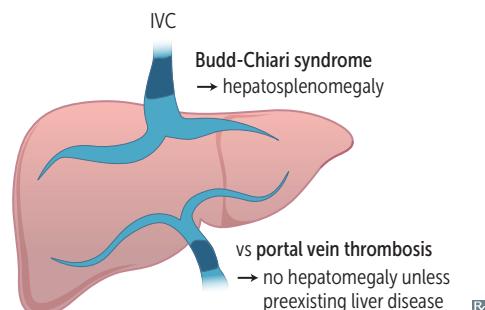
**Liver tumors**

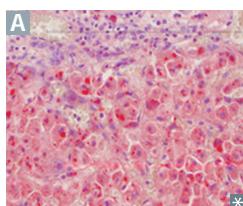
<b>Hepatic hemangioma</b>	Also called cavernous hemangioma. Most common benign liver tumor (venous malformation) <b>A</b> ; typically occurs at age 30–50 years. Biopsy contraindicated because of risk of hemorrhage.
<b>Focal nodular hyperplasia</b>	Second most common benign liver tumor; occurs predominantly in females aged 35–50 years. Hyperplastic reaction of hepatocytes to an aberrant dystrophic artery. Marked by central stellate scar. Usually asymptomatic and detected incidentally.
<b>Hepatic adenoma</b>	Rare, benign tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock).
<b>Hepatocellular carcinoma</b>	Also called hepatoma. Most common 1° malignant liver tumor in adults <b>B</b> . Associated with HBV (+/- cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and nonalcoholic fatty liver disease, autoimmune disease, hemochromatosis, Wilson disease, $\alpha_1$ -antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from <i>Aspergillus</i> ). Findings: anorexia, jaundice, tender hepatomegaly. May lead to decompensation of previously stable cirrhosis (eg, ascites) and portal vein thrombosis. Spreads hematogenously. Diagnosis: ultrasound (screening) or contrast CT/MRI <b>C</b> (confirmation); biopsy if diagnosis is uncertain.
<b>Hepatic angiosarcoma</b>	Rare, malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.
<b>Metastases</b>	Most common malignant liver tumors overall; 1° sources include GI, breast, lung cancers. Metastases are rarely solitary.

**Budd-Chiari syndrome**

Hepatic venous outflow tract obstruction (eg, due to thrombosis, compression) with centrilobular congestion and necrosis  
→ congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure). Absence of JVD. Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC. May cause nutmeg liver (mottled appearance).

**Portal vein thrombosis**—thrombosis in portal vein proximal to liver. Usually asymptomatic in the majority of patients, but associated with portal hypertension, abdominal pain, fever. May lead to bowel ischemia if extension to superior mesenteric vein. Etiologies include cirrhosis, malignancy, pancreatitis, and sepsis.



**$\alpha_1$ -antitrypsin deficiency**

Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS + globules **A** in liver. Codominant trait. Often presents in young patients with liver damage and dyspnea without a history of tobacco smoking.

In lungs, ↓  $\alpha_1$ -antitrypsin → uninhibited elastase in alveoli → ↓ elastic tissue → panacinar emphysema.

**Jaundice**

Abnormal yellowing of the skin and/or sclera **A** due to bilirubin deposition. Hyperbilirubinemia 2° to ↑ production or ↓ clearance (impaired hepatic uptake, conjugation, excretion).

**HOT Liver**—common causes of ↑ bilirubin level:  
**H**emolysis  
**O**bturbation  
**T**umor  
**L**iver disease

**Conjugated (direct) hyperbilirubinemia**

Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke. Biliary tract disease: 1° sclerosing cholangitis, 1° biliary cholangitis. Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.

**Unconjugated (indirect) hyperbilirubinemia**

Hemolytic, benign (neonates), Crigler-Najjar, Gilbert syndrome.

**Mixed hyperbilirubinemia**

Both direct and indirect hyperbilirubinemia.  
Hepatitis, cirrhosis.

**Benign neonatal hyperbilirubinemia**

Formerly called physiologic neonatal jaundice. Mild unconjugated hyperbilirubinemia caused by:

- ↑ fetal RBC turnover (↑ hematocrit and ↓ fetal RBC lifespan).
- Immature newborn liver (↓ UDP-glucuronyltransferase activity).
- Sterile newborn gut (↓ conversion to urobilinogen → ↑ deconjugation by intestinal brush border β-glucuronidase → ↑ enterohepatic circulation).

**β-glucuronidase**—lysosomal enzyme for direct bilirubin deconjugation. Also found in breast milk.

May lead to pigment stone formation.

Occurs in nearly all newborns after first 24 hours of life and usually resolves without treatment in 1–2 weeks. Exaggerated forms:

**Breastfeeding failure jaundice**—insufficient breast milk intake → ↓ bilirubin elimination in stool → ↑ enterohepatic circulation.

**Breast milk jaundice**—↑ β-glucuronidase in breast milk → ↑ deconjugation → ↑ enterohepatic circulation.

Severe cases may lead to kernicterus (deposition of unconjugated, lipid-soluble bilirubin in the brain, particularly basal ganglia).

Treatment: phototherapy (non-UV) isomerizes unconjugated bilirubin to water-soluble form.

**Biliary atresia**

Most common reason for pediatric liver transplantation. Fibro-obliterative destruction of bile ducts → cholestasis. Associated with absent/abnormal gallbladder on ultrasonogram. Often presents as a newborn with persistent jaundice after 2 weeks of life, darkening 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 with stress, illness, or fasting. ↑ unconjugated bilirubin without overt hemolysis.  
Relatively common, benign condition.

**② Crigler-Najjar syndrome, type I**

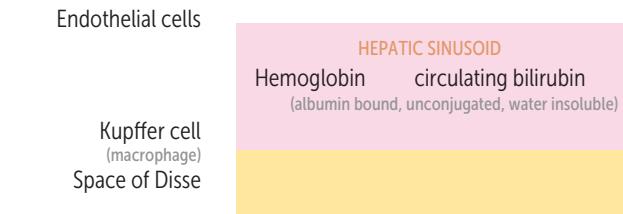
Absent UDP-glucuronosyltransferase. Presents early in life, but some patients may not have neurologic signs until later in life.  
Findings: jaundice, kernicterus (unconjugated bilirubin deposition in brain), ↑ unconjugated bilirubin.  
Treatment: plasmapheresis and phototherapy (does not conjugate UCB; but does ↑ polarity and ↑ water solubility to allow excretion). Liver transplant is curative.  
Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.

**③ Dubin-Johnson syndrome**

Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black (**Dark**) liver due to impaired excretion of epinephrine metabolites. Benign.

**④ Rotor syndrome**

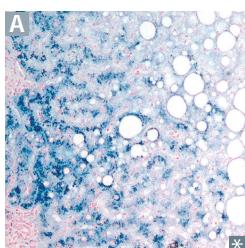
Phenotypically similar to Dubin-Johnson, but milder in presentation without black (**Regular**) liver.  
Due to impaired hepatic storage of conjugated bilirubin.



Obstructive jaundice  
(downstream)

**Wilson disease**

Also called hepatolenticular degeneration. Autosomal recessive mutations in hepatocyte copper-transporting ATPase (*ATP7B* gene; chromosome 13) → ↓ copper incorporation into apoceruloplasmin and excretion into bile → ↓ serum ceruloplasmin. Copper accumulates, especially in liver, brain (eg, basal ganglia), cornea, kidneys; ↑ urine copper. Presents before age 40 with liver disease (eg, hepatitis, acute liver failure, cirrhosis), neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism), psychiatric disease, Kayser-Fleischer rings (deposits in Descemet membrane of cornea) **A**, hemolytic anemia, renal disease (eg, Fanconi syndrome). Treatment: chelation with penicillamine or trientine, oral zinc. Liver transplant in acute liver failure related to Wilson disease.

**Hemochromatosis**

Autosomal recessive. Mutation in *HFE* gene, located on chromosome 6. Leads to abnormal (low) hepcidin production, ↑ intestinal iron absorption. Iron overload can also be 2° to chronic transfusion therapy (eg, β-thalassemia major). Iron accumulates, especially in liver, pancreas, skin, heart, pituitary, joints. Hemosiderin (iron) can be identified on liver MRI or biopsy with Prussian blue stain **A**. Presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in females. Classic triad of cirrhosis, diabetes mellitus, skin pigmentation (“bronze diabetes”). Also causes restrictive cardiomyopathy (classic) or dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death. Treatment: repeated phlebotomy, iron (**Fe**) chelation with deferasirox, deferoxamine, deferiprone.

**Biliary tract disease**

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP, ↑ GGT).

	PATHOLOGY	EPIDEMIOLOGY	ADDITIONAL FEATURES
<b>Primary sclerosing cholangitis</b>	Unknown cause of concentric “onion skin” bile duct fibrosis → alternating strictures and dilation with “beading” of intra- and extrahepatic bile ducts on ERCP <b>A</b> , magnetic resonance cholangiopancreatography (MRCP).	Classically in middle-aged males with ulcerative colitis.	Associated with ulcerative colitis. MPO-ANCA/p-ANCA +. ↑ IgM. Can lead to 2° biliary cirrhosis. ↑ risk of cholangiocarcinoma and gallbladder cancer.
<b>Primary biliary cholangitis</b>	Autoimmune reaction → lymphocytic infiltrate +/- granulomas → destruction of lobular bile ducts.	Classically in middle-aged females.	Antimitochondrial antibody +, ↑ IgM. Associated with other autoimmune conditions (eg, Hashimoto thyroiditis, rheumatoid arthritis, celiac disease). Treatment: ursodiol.
<b>Secondary biliary cirrhosis</b>	Extrahepatic biliary obstruction → ↑ pressure in intrahepatic ducts → injury/ fibrosis and bile stasis.	Patients with known obstructive lesions (gallstones, biliary strictures, pancreatic carcinoma).	May be complicated by acute cholangitis.

### Cholelithiasis and related pathologies



↑ cholesterol and/or bilirubin, ↓ bile salts, and gallbladder stasis all cause sludge or stones.

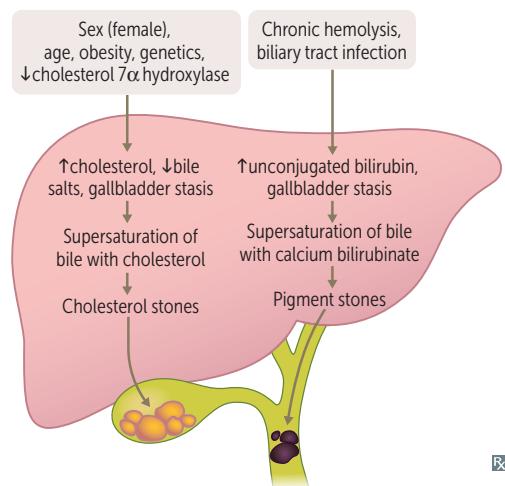
2 types of stones:

- Cholesterol stones **A** (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, medications (eg, fibrates), race (↑ incidence in White and Native American populations).
- Pigment stones (black = radiopaque,  $\text{Ca}^{2+}$  bilirubinate, hemolysis; brown = radiolucent, infection). Associated with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

Most common complication is cholecystitis; can also cause acute pancreatitis, acute cholangitis.

Diagnose with ultrasound. Treat with elective cholecystectomy if symptomatic.

Risk factors (**5 F's**): female, fat (obesity), fertile (multiparity), forty, fair.



#### RELATED PATHOLOGIES

##### Biliary colic

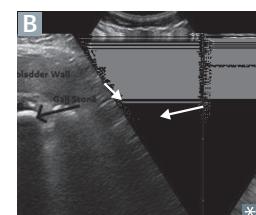
#### CHARACTERISTICS

Associated with nausea/vomiting and dull RUQ pain. Neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing stone into cystic duct. Labs are normal, ultrasound shows cholelithiasis.

##### Choledocholithiasis

Presence of gallstone(s) in common bile duct, often leading to elevated ALP, GGT, direct bilirubin, and/or AST/ALT.

##### Cholecystitis



Acute or chronic inflammation of gallbladder.

**Calculus cholecystitis**—most common type; due to gallstone impaction in the cystic duct resulting in inflammation and gallbladder wall thickening (arrows in **B**); can produce 2° infection.

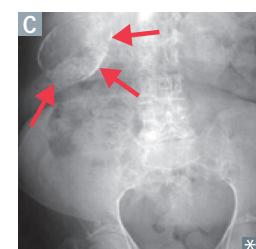
**Acalculus cholecystitis**—due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients.

Murphy sign: inspiratory arrest on RUQ palpation due to pain. Pain may radiate to right shoulder (due to irritation of phrenic nerve). ↑ ALP if bile duct becomes involved (eg, acute cholangitis).

Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction.

**Gallstone ileus**—fistula between gallbladder and GI tract → stone enters GI lumen → obstructs at ileocecal valve (narrowest point); can see air in biliary tree (pneumobilia). Rigler triad: radiographic findings of pneumobilia, small bowel obstruction, gallstone (usually in iliac fossa).

##### Porcelain gallbladder



Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging **C**.

Treatment: prophylactic cholecystectomy generally recommended due to ↑ risk of gallbladder cancer (mostly adenocarcinoma).

##### Acute cholangitis

Also called ascending cholangitis. Infection of biliary tree usually due to obstruction that leads to stasis/bacterial overgrowth.

Charcot triad of cholangitis includes jaundice, fever, RUQ pain.

Reynolds pentad is Charcot triad plus altered mental status and shock (hypotension).

**Cholangiocarcinoma**

Malignant tumor of bile duct epithelium. Most common location is convergence of right and left hepatic ducts. Risk factors include 1° sclerosing cholangitis, liver fluke infections. Usually presents late with fatigue, weight loss, abdominal pain, jaundice. Imaging may show biliary tract obstruction. Histology: infiltrating neoplastic glands associated with desmoplastic stroma.

**Pancreatitis**

Refers to inflammation of the pancreas. Usually sterile.

**Acute pancreatitis**

Autodigestion of pancreas by pancreatic enzymes (**A** shows pancreas [yellow arrows] surrounded by edema [red arrows]).

Causes: **I**диopathic, **G**allstones, **E**thanol, **T**rauma, **S**teroids, **M**umps, **A**utoimmune disease, **S**corpion sting, **H**ypercalcemia/**H**ypertriglyceridemia (> 1000 mg/dL), **ERCP**, **D**rugs (eg, sulfa drugs, NRTIs, protease inhibitors). **I GET SMASHED.**

Diagnosis by 2 of 3 criteria: acute epigastric pain often radiating to the back, serum amylase or lipase (more specific) to 3× upper limit of normal, or characteristic imaging findings.

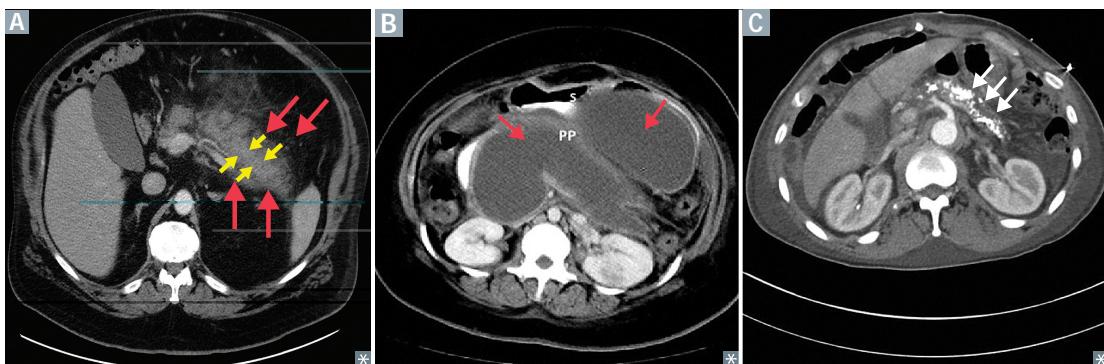
Complications: pancreatic pseudocyst **B** (lined by granulation tissue, not epithelium), abscess, necrosis, hemorrhage, infection, organ failure (ALI/ARDS, shock, renal failure), hypocalcemia (precipitation of  $\text{Ca}^{2+}$  soaps).

**Chronic pancreatitis**

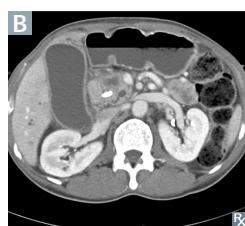
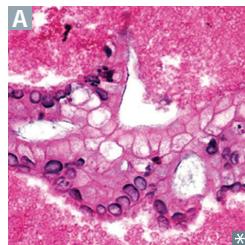
Chronic inflammation, atrophy, calcification of the pancreas **C**. Major risk factors include alcohol use disorder and genetic predisposition (eg, cystic fibrosis, SPINK1 mutations); can be idiopathic. Complications include pancreatic insufficiency and pseudocysts.

Pancreatic insufficiency (typically when <10% pancreatic function) may manifest with steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus.

Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).



### Pancreatic adenocarcinoma



Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration **A**); often metastatic at presentation, with average survival ~1 year after diagnosis. Tumors more common in pancreatic head **B** (lead to obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).

#### Risk factors:

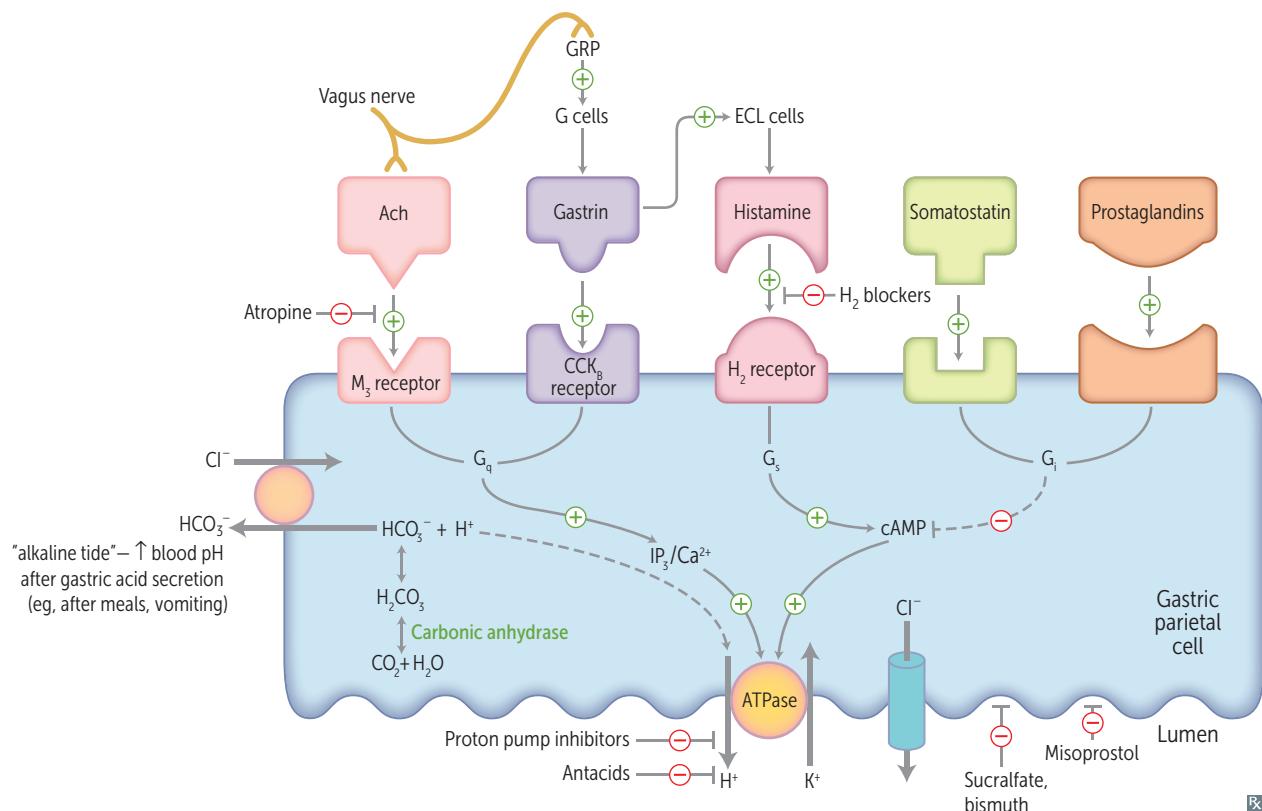
- Tobacco smoking (strongest risk factor)
- Chronic pancreatitis (especially > 20 years)
- Diabetes
- Age > 50 years

#### Often presents with:

- Abdominal pain radiating to back
- Weight loss (due to malabsorption and anorexia)
- Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome)
- Obstructive jaundice with palpable, nontender gallbladder (Courvoisier sign)

## ► GASTROINTESTINAL—PHARMACOLOGY

### Acid suppression therapy



<b>H<sub>2</sub>-blockers</b>	Cimetidine, famotidine, nizatidine. Take H <sub>2</sub> blockers before you <b>dine</b> . Think “table for 2” to remember H <sub>2</sub> .
MECHANISM	Reversible block of histamine H <sub>2</sub> -receptors → ↓ H <sup>+</sup> secretion by parietal cells.
CLINICAL USE	Peptic ulcer, gastritis, mild esophageal reflux.
ADVERSE EFFECTS	Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions); it also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males); can cross blood-brain barrier (confusion, dizziness, headaches) and placenta. Cimetidine ↓ renal excretion of creatinine. Other H <sub>2</sub> blockers are relatively free of these effects.

<b>Proton pump inhibitors</b>	Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.
MECHANISM	Irreversibly inhibit H <sup>+</sup> /K <sup>+</sup> -ATPase in stomach parietal cells.
CLINICAL USE	Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome, component of therapy for <i>H pylori</i> , stress ulcer prophylaxis.
ADVERSE EFFECTS	↑ risk of <i>C difficile</i> infection, pneumonia, acute interstitial nephritis. Vitamin B <sub>12</sub> malabsorption; ↓ serum Mg <sup>2+</sup> /Ca <sup>2+</sup> absorption (potentially leading to increased fracture risk in older adults).

<b>Antacids</b>	Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying. All can cause hypokalemia.
<b>Aluminum hydroxide</b>	Constipation, Hypophosphatemia, Osteodystrophy, Proximal muscle weakness, Seizures
<b>Calcium carbonate</b>	Hypercalcemia (milk-alkali syndrome), rebound acid ↑
<b>Magnesium hydroxide</b>	Diarrhea, hyporeflexia, hypotension, cardiac arrest

<b>Bismuth, sucralfate</b>	
MECHANISM	Bind to ulcer base, providing physical protection and allowing HCO <sub>3</sub> <sup>-</sup> secretion to reestablish pH gradient in the mucous layer. Sucralfate requires acidic environment, not given with PPIs/H <sub>2</sub> blockers.
CLINICAL USE	↑ ulcer healing, travelers' diarrhea (bismuth). Bismuth also used in quadruple therapy for <i>H pylori</i> .

<b>Misoprostol</b>	
MECHANISM	PGE <sub>1</sub> analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.
CLINICAL USE	Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE <sub>1</sub> production). Also used off-label for induction of labor (ripen cervix).
ADVERSE EFFECTS	Diarrhea. Contraindicated in patients of childbearing potential (abortifacient).

**Octreotide**

MECHANISM	Long-acting somatostatin analog; inhibits secretion of various splanchnic vasodilatory hormones.
CLINICAL USE	Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors.
ADVERSE EFFECTS	Nausea, cramps, steatorrhea. ↑ risk of cholelithiasis due to CCK inhibition.

**Sulfasalazine**

MECHANISM	A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria.
CLINICAL USE	Ulcerative colitis, Crohn disease (colitis component).
ADVERSE EFFECTS	Malaise, nausea, sulfonamide toxicity, reversible oligospermia.

**Loperamide, diphenoxylate**

MECHANISM	Agonists at $\mu$ -opioid receptors → ↓ gut motility. Poor CNS penetration (low addictive potential).
CLINICAL USE	Diarrhea.
ADVERSE EFFECTS	Constipation, nausea.

**Antiemetics** All act centrally in chemoreceptor trigger zone of area postrema.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Ondansetron, granisetron	5-HT <sub>3</sub> -receptor antagonists Also act peripherally (↓ vagal stimulation)	Nausea and vomiting after chemotherapy, radiotherapy, or surgery	Headache, constipation, QT interval prolongation, serotonin syndrome
Prochlorperazine, metoclopramide	D <sub>2</sub> -receptor antagonists Metoclopramide also causes ↑ gastric emptying and ↑ LES tone	Nausea and vomiting Metoclopramide is also used in gastroparesis (eg, diabetic), persistent GERD	Extrapyramidal symptoms, hyperprolactinemia, anxiety, drowsiness, restlessness, depression, GI distress
Aprepitant, fosaprepitant	NK <sub>1</sub> (neurokinin-1) receptor antagonists NK <sub>1</sub> receptor = substance P receptor	Chemotherapy-induced nausea and vomiting	Fatigue, GI distress

**Orlistat**

MECHANISM	Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats. Taken with fat-containing meals.
CLINICAL USE	Weight loss.
ADVERSE EFFECTS	Abdominal pain, flatulence, bowel urgency/frequent bowel movements, steatorrhea; ↓ absorption of fat-soluble vitamins.

**Anticonstipation drugs**

DRUG	MECHANISM	ADVERSE EFFECTS
<b>Bulk-forming laxatives</b> Methylcellulose, psyllium	Soluble fibers that draw water into gut lumen, forming viscous liquid that promotes peristalsis	Bloating
<b>Osmotic laxatives</b> Lactulose, magnesium citrate, magnesium hydroxide, polyethylene glycol	Provide osmotic load to draw water into GI lumen Lactulose also treats hepatic encephalopathy: gut microbiota degrades lactulose into metabolites (lactic acid, acetic acid) that promote nitrogen excretion as $\text{NH}_4^+$ by trapping it in colon	Diarrhea, dehydration; may be misused by patients with bulimia
<b>Stimulant laxatives</b> Bisacodyl, senna	Enteric nerve stimulation → colonic contraction	Diarrhea
<b>Emollient laxatives</b> Docusate	Surfactants that ↓ stool surface tension, promoting water entry into stool	Diarrhea
<b>Lubiprostone</b>	Chloride channel activator → ↑ intestinal fluid secretion	Diarrhea, nausea
<b>Guanylate cyclase-C agonists</b> Linaclotide, plecanatide	Activate intracellular cGMP signaling → ↑ fluid and electrolyte secretion in the intestinal lumen	Diarrhea, bloating, abdominal discomfort, flatulence
<b>Serotonergic agonists</b> Prucalopride	5HT <sub>4</sub> agonism → enteric nerve stimulation → ↑ peristalsis, intestinal secretion	Diarrhea, abdominal pain, nausea, headache
<b>NHE<sub>3</sub> inhibitor</b> Tenapanor	Inhibits Na <sup>+</sup> /H <sup>+</sup> exchanger → ↓ Na <sup>+</sup> absorption → ↑ H <sub>2</sub> O secretion in lumen	Diarrhea, abdominal pain, nausea