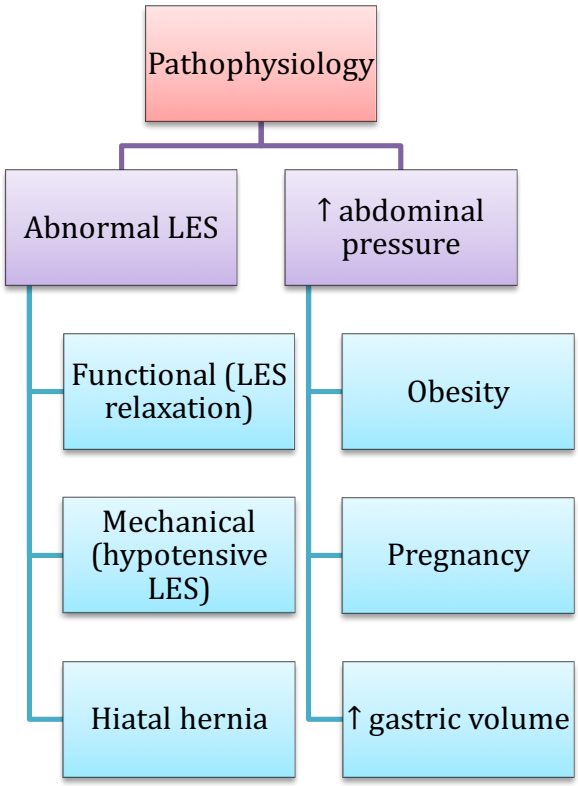
Revision File
SAQs

{ لا أعلم علمًا بعد الحلال والحرام أنبل من الطب }

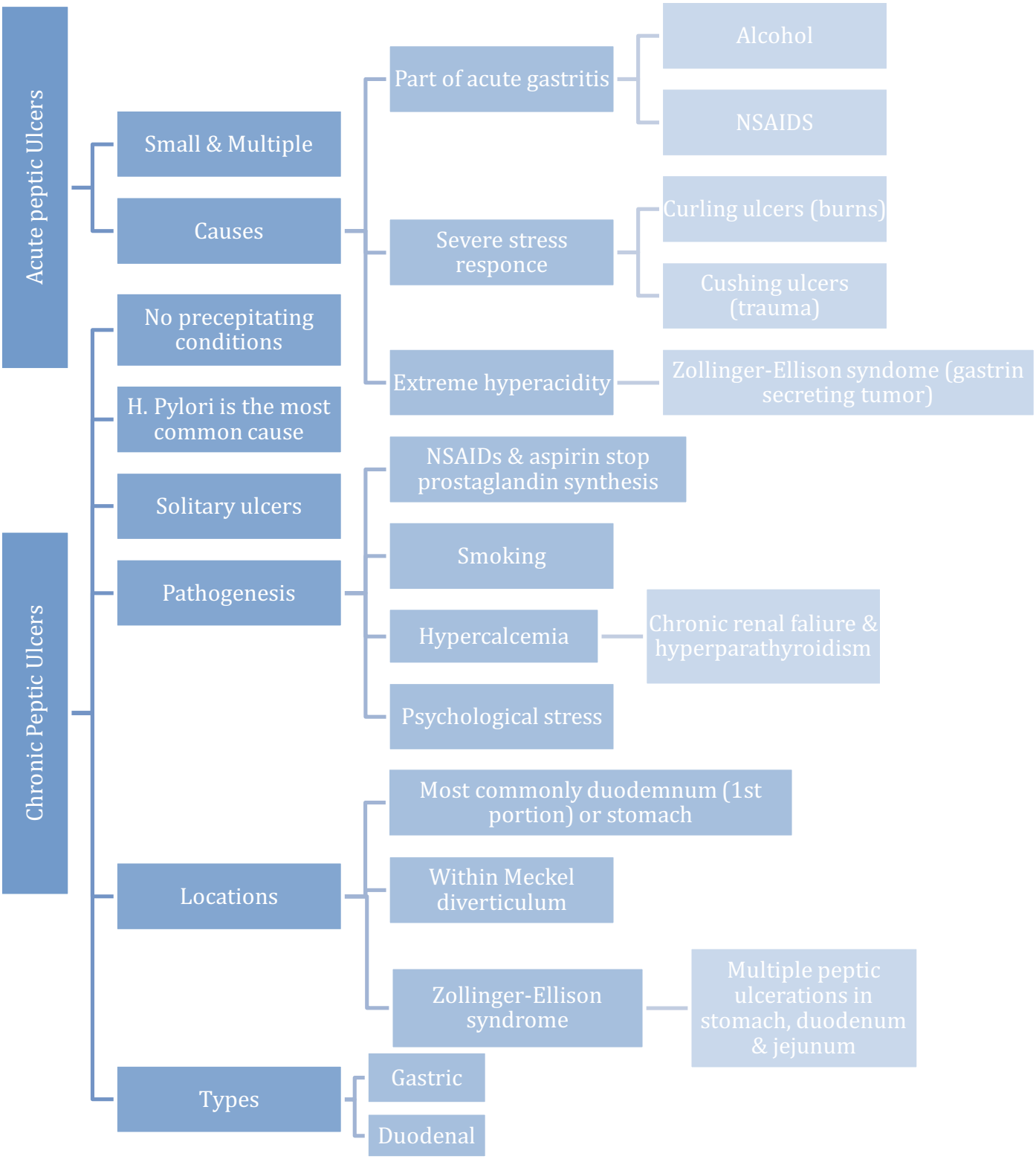
الشافعي

References: Team work, Kaplan Step 1 Pathology, First Aid Step 1 & Pathoma.

- **Gastroesophageal reflux disease (GERD)** occurs when the amount of gastric juice that refluxes into the esophagus exceeds the normal limit, causing symptoms with or without associated esophageal mucosal injury.
  - Most common in 40 year old patients.
  - Commonly present with heartburn, dysphagia & regurgitation.



- **Reflux Esophagitis**: Mucosal damage produced by abnormal reflux of gastric contents into the esophagus.
  - Acute may be caused by:
    - Fungal (Candida) or viral (Herpes & CMV in AIDS) infections, bacterial ones are rare.
    - Irradiation & Chemical ingestion
  - **Severe injury** → Eosinophils, basal zone hyperplasia & elongation of lamina propria papillae.
- **Erosive Esophagitis:**
  - Red mucosa & erosions → Hematemesis & melena.
- **Strictures:**
  - Result of healing of erosive esophagitis.
  - Secondary to fibrosis.
- **Barrett's esophagus:**
  - Metaplasia in the lower esophagus (abnormal columnar cells replace normal squamous ones).
  - Associated with esophageal adenocarcinomas.
  - Most patients **do not** progress to adenocarcinoma.



Ulcer	**Gastric ulcer**	**Duodenal ulcer**
Common cause	Helicobacter pylori (-80%), NSAIDs use.	H pylori (90-95%), NSAIDs use.
Presenting symptoms	Pain with food.	Pain 2-3 hrs. after a meal and relieved by food.
Complications	Perforation, bleeding, malignancy, Gastric outlet obstruction.	Perforation, bleeding, gastric outlet obstruction, pancreatitis.
Malignancy	10%	Rare
Location	Type-dependent; typically lesser curvature	First portion of duodenum.

Pancreatitis	Acute	Chronic
Causes	Caused by activation of pancreatic enzymes, which leads to pancreatic auto- digestion with hemorrhagic fat necrosis.	May present as episodes of acute inflammation in a previously injured pancreas or as chronic damage with persistent pain or malabsorption. The causes are similar to those of acute pancreatitis.
Presentation	Classically presents as sudden-onset epigastric abdominal pain radiating to the back and flanks accompanied by anorexia and nausea. May occur following a large meal or drinking binge.	▪ Epigastric pain radiating to the back is often absent in chronic disease. ▪ Most common type of pain is persistent, deep-seated, and unresponsive to antacids; worsened by ingestion of fatty foods or alcohol. ▪ Symptoms of pancreatic insufficiency include steatorrhea, weight loss, and deficiencies of fat-soluble vitamins (A, D, E, and K).
Diagnosis	Clinical symptoms and imaging: ○ Leukocytosis and elevated serum amylase and lipase. ○ Histology: Fat necrosis with pale basophilic calcium soaps, hemorrhage, necrotic debris, and inflammatory response. ○ Contrast-enhanced CT is recommended for severe pancreatitis in order to rule out pseudocyst and fully visualize the extent of disease.	○ In contrast to acute pancreatitis, serum amylase and lipase are usually not elevated. The classic triad includes progressive parenchymal fibrosis with pancreatic calcification, steatorrhea, and OM. ○ Radiographic hallmark is the presence of scattered calcifications.
Prognosis	Necrosis, organ failure, or both, including disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), diffuse fat necrosis, hypocalcemia, pseudocyst formation, hemorrhage, and infection.	Patients who abstain from alcohol and use vigorous replacement therapy do reasonably well.

Malabsorption

Lactose intolerance:

- Decreased function of the lactase enzyme found in the brush border of **enterocytes**.
- Lactase normally breaks down lactose into **glucose** and **galactose**.
- Presents with abdominal distension and diarrhea upon consumption of **milk products**; undigested lactose is osmotically active.
- Deficiency may be **congenital** (rare autosomal recessive disorder) or acquired (often develops in late childhood); **temporary deficiency** is seen after small bowel infection (lactase is highly susceptible to injury).

Celiac disease:

- Immune-mediated damage of small bowel villi due to gluten exposure; associated with **HLA-DQ2 and DQ8**
- Gluten is present in wheat and grains; its most pathogenic component is gliadin.
  - Once absorbed, gliadin is deamidated by tissue transglutaminase (tTG).
  - Deamidated gliadin is presented by antigen presenting cells via **MHC class II.**
  - **Helper T cells** mediate tissue damage.
- **Clinical presentation:**
  - **Children** classically present with abdominal distension, chronic diarrhea, and failure to thrive.
  - **Adults** classically present with chronic diarrhea and bloating.
  - Small, herpes-like vesicles may arise on skin (**dermatitis herpetiformis).** Due to **IgA** deposition at the tips of dermal papillae; resolves with gluten-free diet.
- **Laboratory findings:**
  - **IgA antibodies** against endomysium, tTG, or gliadin; IgG antibodies are also present and are useful for diagnosis in individuals with IgA deficiency (increased incidence o f IgA deficiency is seen in celiac disease).
  - Duodenal biopsy reveals **flattening of villi**, hyperplasia of crypts, and increased intraepithelial lymphocytes. Damage is most prominent in the duodenum; jejunum and ileum are less involved.
  - Symptoms resolve with **gluten-free diet.**
  - **Small bowel carcinoma and T-cell lymphoma** are late complications that present as refractory disease despite good dietary control.

Tropical sprue:

- Damage to small bowel villi due to an unknown organism resulting in malabsorption.
- Similar to celiac disease **except**:
  - Occurs in tropical regions (e.g., Caribbean)
  - Arises after infectious diarrhea and responds to antibiotics
  - Damage is most prominent in jejunum and ileum (secondary vitamin B12 or folate deficiency may ensue); duodenum is less commonly involved.

Whipple disease:

- Systemic tissue damage characterized by macrophages loaded with **Tropheryma whippelii organisms;** partially destroyed organisms are present in macrophage lysosomes (positive for PAS).
- Classic **site of involvement** is the small bowel lamina propria

Bacterial overgrowth syndrome:

- Malabsorption secondary to excessive bacteria in the small intestine, usually the jejunum.
- **Causes:**
  - Excessive entry of Bacteria.
  - Stagnant region.
  - Disturbed motility.
  - Defective immune-mechanisms.
- **Clinical features:** Weight loss, diarrhea (both secretory & osmotic) , steatorrhea and anaemia (due to vitamin B12 deficiency).

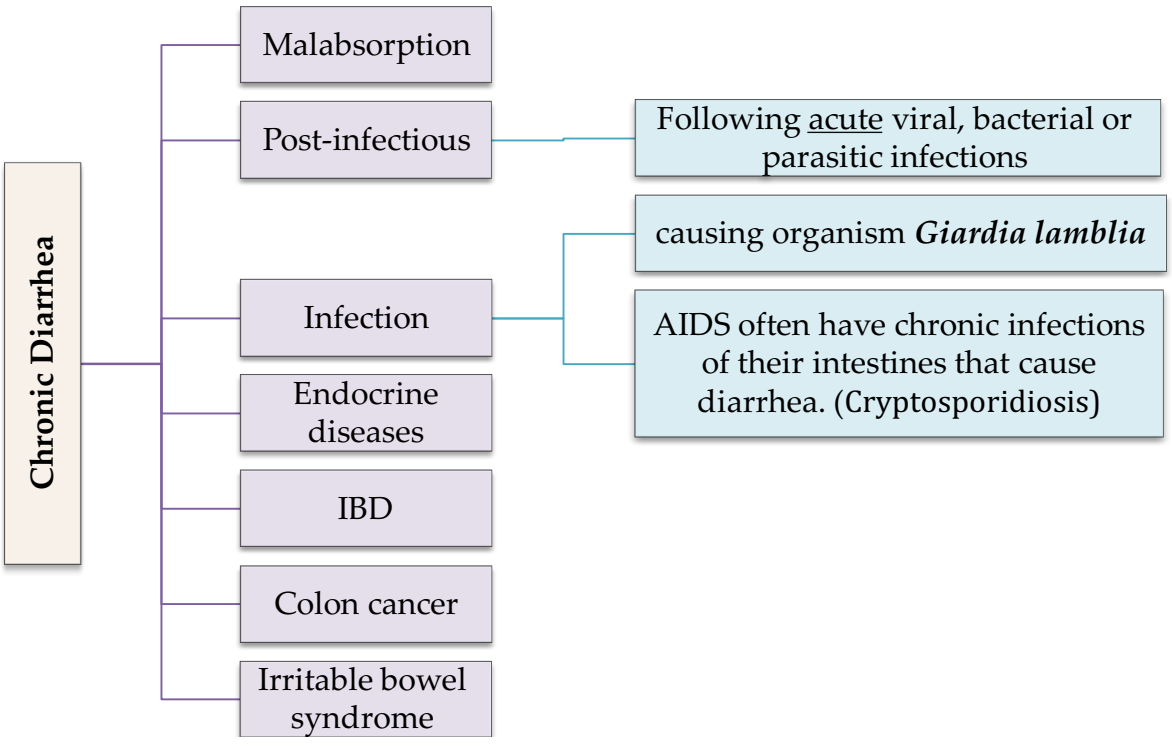
Diarrhea

Acute diarrhea

TYPE	CHARACTERISTICS	CAUSES	SCREENING TESTS
Invasive Inflammatory	Pathogens invade enterocytes Low-volume diarrhea	*Shigella* spp. *Campylobacter jejuni*	Fecal smear for leukocytes: positive in most cases
	Diarrhea with blood and leukocytes (i.e., dysentery)	*Entamoeba histolytica*	Order stool culture & for O&P
Secretory	Loss of isotonic fluid High-volume diarrhea Mechanisms: Laxatives Enterotoxins stimulate Cl^- channels regulated by cAMP and cGMP	Laxatives: melanosis coli with use of phenanthracene laxatives Production of enterotoxins: *Vibrio cholerae* Enterotoxigenic *E. coli*	Stool osmotic gap < 50 mOsm/kg Fecal smear for leukocytes: negative
Osmotic	Osmotically active substance is drawing hypotonic salt solution out of bowel High-volume diarrhea No inflammation in bowel mucosa	Disaccharidase def. Giardiasis, Celiac Dis. Ingestion of poorly absorbable solutes	Fecal smear for leukocytes: negative Stool osmotic gap > 125 mOsm/kg
Motility-related	Rapid movement of food through the Intestines Serotonin increases bowel motility No inflammation in bowel mucosa	Irritable bowel syndrome (IBS) – a motor disorder Increased serotonin: carcinoid syndrome	Increased 5-HIAA

Pathophysiology	
Secretory	- Normal stool osmotic gap. - Bacterial toxin (E. coli, cholera). - Endocrine Tumors.
Osmotic	- Osmotic gab is high. - Malabsorption. - Osmotic Laxatives.
Exudative	- Blood and pus in the stool. - IBD. - Invasive infections.
Motility	- IBS.

Chronic Diarrhea



Colonic tumors & Polyps

Familial adenomatous polyposis (FAP)	Patients develop 500-2500 colonic adenomas that carpet the mucosal surface. Most polyps are tubular adenomas. 1 00% risk of colonic cancer by midlife. Increased risk of duodenal cancer.
Hyperplastic polyp	No malignant potential. Formed as the result of abnormal mucosal maturation, inflammation, or architecture.
Juvenile polyp	Hamartomatous proliferations of the lamina propria enclosing widely spaced, dilated cystic glands. Usually seen in children < 5 y.
Peutz-Jeghers syndrome	Hamartomatous polyps and melanotic mucosal and cutaneous pigmentation.
Gardner's syndrome & Turcot syndrome	Both of these syndromes share the same APC genetic defect as FAP, but differ in one regard: these two syndromes have extraintestinal tumors, whereas FAP does not.
Inflammatory polyp	Longstanding IBD, especially in **chronic ulcerative colitis**. **Pseudopolyps**
Adenomatous polyp	**1. Tubular adenoma: less than 25% villous architecture** ▪ Sigmoid colon most common site. **2. Villous adenoma: villous architecture over 50%** ▪ The least common, largest and most ominous of epithelial polyps ▪ Present with rectal bleeding or anemia, large ones may secrete copious amounts of mucoid material rich in protein and potassium **3. Tubulovillous adenoma: villous architecture between 25 and 50%.** ▪ Intermediate in size, degree of dysplasia and malignant potential between tubular and villous adenomas.

Adenocarcinoma:

- Most common malignancy of the GI tract and is a major cause of morbidity and mortality worldwide.
- Incidence peaks at 60 to 70 years of age.
- Males are affected slightly more often than females.
- Predisposing factors: **IBD, adenomas, polyposis syndrome & Diet.**
- Carcinogenesis:
  - The APC/β-catenin pathway (85%)
    - *TP53* → mutated later.
    - Mutation in *APC* tumor suppressor gene
  - The DNA mismatch repair genes pathway
    - There is accumulation of mutations (as in the *APC/B-catenin schema*)
    - Five DNA mismatch repair genes (**MSH2, MSH6, MLH1,** PMS1 & PMS2)
    - Give rise to the ***hereditary non-polyposis colon carcinoma (HNPCC) syndrome.***

Colorectal Carcinoma:

- Hereditary mutation of the APC gene is the cause of familial adenomatous polyposis (FAP) is a major cause.
- **Morphology:**
  - 70% are in the rectum, rectosigmoid and sigmoid colon.
  - Left-sided carcinomas tend to be annular, encircling lesions with early symptoms of **obstruction**.
  - Right-sided carcinomas tend to grow as polypoid, fungating masses, obstruction is uncommon. (Mostly presents with anemia, most likely to bleed).
  - If located closer to the anus: change in bowel habit, feeling of incomplete defecation, PR bleeding.
- Carcinoembryonic antigen **(CEA) & Carbohydrate antigen (CA19-9)** are **Useful to assess disease recurrence (late stage)**
  - **Elevated in:**

CEA	Some **non-neoplastic** conditions like ulcerative colitis pancreatitis, cirrhosis COPD, Crohn's disease as well as in smokers.
CA19-9	Colon cancer, pancreatic cancer, esophageal cancer and hepatocellular carcinoma. Apart from cancer, pancreatitis, cirrhosis.

- **Tissue inhibitor of metalloproteinases 1 (TIMP1) = Early as well as late stage disease**

Carcinoid tumor:

- Malignant **proliferation of neuroendocrine cells**; low-grade malignancy, polyp-like nodules & neurosecretory granules positive for chromogranin.
- Can arise anywhere along the gut; small bowel is the most common site.
- Often secretes **serotonin**
  - Serotonin is released into the portal circulation and metabolized by liver monoamine oxidase (MAO) into 5-HIAA. 5-HIA A is excreted in the urine.
- **Metastasis** of carcinoid tumor to the liver allows serotonin to **bypass liver metabolism**.
  - Serotonin is released into the hepatic vein and leaks into systemic circulation via hepato-systemic shunts, resulting in carcinoid syndrome.
  - **Carcinoid syndrome** is characterized by bronchospasm, diarrhea, and flushing of skin; symptoms can be triggered by alcohol or emotional stress, which stimulate serotonin release from the tumor.

Table 16-1. Crohn's Disease Versus Ulcerative Colitis

	Crohn's Disease	Ulcerative Colitis
Most common site	Terminal ileum	Rectum
Distribution	Mouth to anus	Rectum → colon "back-wash" ileitis
Spread	Discontinuous/"skip"	Continuous
Gross features	• Focal aphthous ulcers with intervening normal mucosa • Linear fissures • Cobblestone appearance • Thickened bowel wall • "Creeping fat"	Extensive ulceration Pseudopolyps
Micro	Noncaseating granulomas	Crypt abscesses
Inflammation	Transmural	Limited to mucosa and submucosa
Complications	• Strictures • "String sign" on barium studies • Obstruction • Abscesses • Fistulas • Sinus tracts	Toxic megacolon
Genetic association		HLA-B27
Extraintestinal manifestations	Common (e.g., migratory polyarthritis, ankylosing spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, uveitis)	Common (e.g., migratory arthritis, ankylosing spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, uveitis)

Cirrhosis

- Cirrhosis is chronic liver damage, characterized by complete disarray of the hepatic cytoarchitecture, with progressive scarring (generalized fibrosis) and typical "regenerative" nodule formation.
- **Morphologically, it can be divided into:**
  - **Micronodular cirrhosis:** Nodules < 3 mm, uniform in size.
  - **Macronodular cirrhosis:** Nodules > 3 mm, with increased risk of hepatocellular carcinoma (HCC), usually due to significant liver injury leading to hepatic necrosis (postinfectious, or drug-induced).
  - **Mixed:** Macromicronodular form. Many etiologic agents are involved in the development of cirrhosis. They are generally divided into four major groups:

TABLE 3-23. Causes of Cirrhosis

Type of Cirrhosis	Causes
Infectious	**Viral hepatitis,** brucellosis, capillariasis, echinococcosis, schistosomiasis, toxoplasmosis.
Inherited/metabolic disorders	AAT, Alagille syndrome, biliary atresia, Fanconi syndrome, **hemochromatosis, Wilson disease,** glycogen storage diseases.
Drugs/toxins	**Alcohol,** amiodarone, arsenic, oral contraceptive pills.
Other	**Heart failure** with long-standing congestion of the liver, **biliary obstruction,** CF, graft-versus-host disease, nonalcoholic steatohepatitis (NASH), **primary sclerosing cholangitis,** sarcoidosis.

AAT = α_1-antitrypsin; CF = cystic fibrosis.

Cirrhosis has a variety of manifestations:

- **Clinical presentation:** Complex, resulting from severely impaired liver function (hepatocellular damage), consequences of di use hepatic tissue scarring with portal hypertension, or a combination of both.
- **Jaundice and pruritus** → inability of the liver to conjugate bilirubin.
- **Hypoalbuminemia** → impaired albumin synthesis.
- **Hyperestrogenism** causes spider hemangiomas, palmar erythema, gynecomastia (in males), and hypogonadism.
- **Anemia** (multifactorial, folate deficiency can contribute).
- **Coagulopathies** → decreased production of clotting factors.
- **Portal hypertension,** leading to esophageal varices, caput medusae, and hemorrhoids.
- **Splenomegaly** resulting in thrombocytopenia. Additional sequelae include ascites & peripheral edema.
- **Hypoalbuminemia** leads to decreased intravascular oncotic pressure and, along with portal hypertension, contributes to the formation of ascites. Ascitic fluid can become infected, causing spontaneous bacterial peritonitis.
- **Hepatic encephalopathy**: Severe loss of hepatic function leads to shunting of

blood around the liver, leading to accumulation of toxic metabolites in the blood (ammonemia) and causing brain toxicity.

- **Hepatorenal syndrome**: Increased portal venous pressure leads to decreased effective intravascular volume and decreased renal perfusion pressure (due to intrarenal redistribution of blood flow). Renal failure can thus develop in the presence of liver failure without intrinsic renal problems.

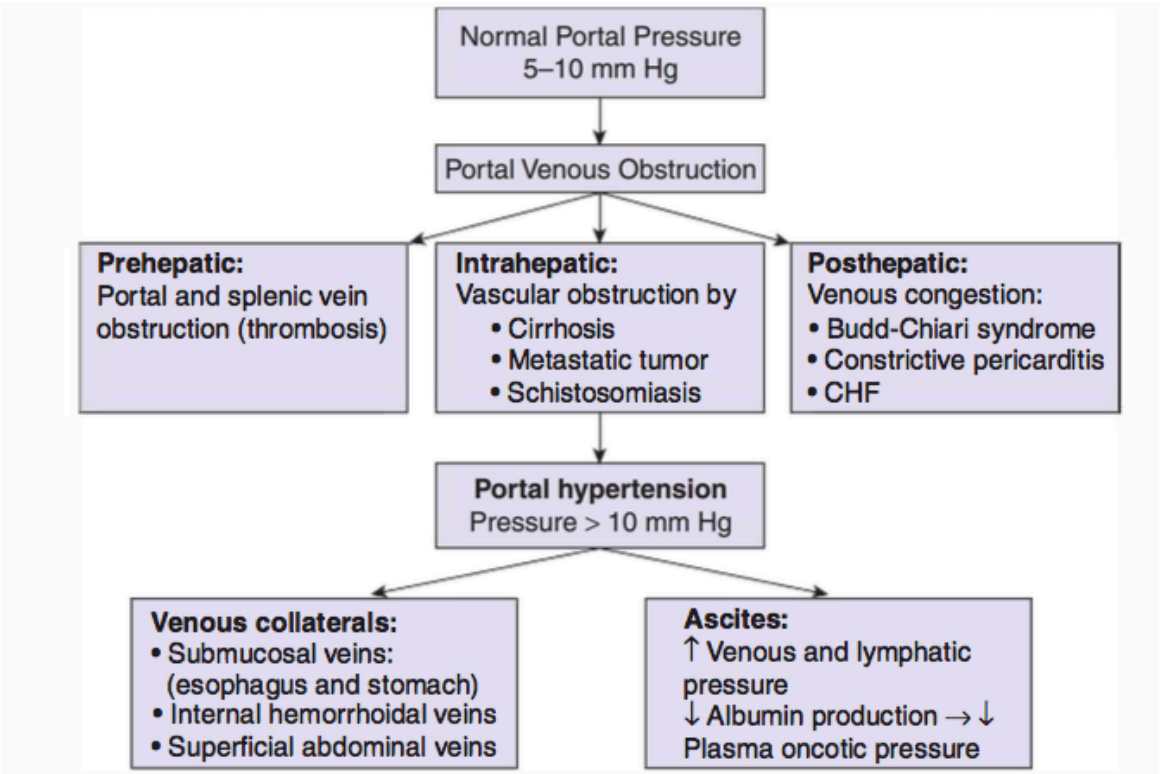


FIGURE 3-54. Pathophysiology of portal hypertension. CHF, congestive heart failure.

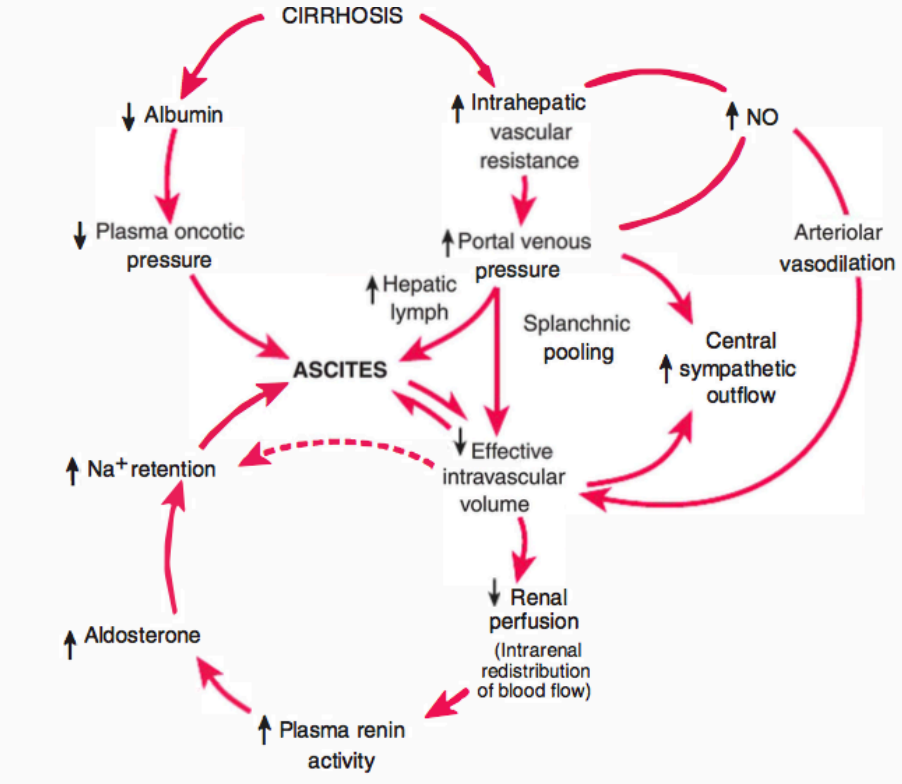


FIGURE 3-55. Multiple factors involved in the development of ascites. NO, nitric oxide. Modified with permission from Kasper DL, Braunwald E, Fauci AS, et al, eds. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1865.)

Cancers of the liver & pancreas

Hepatocellular Carcinomas:

- Male predominance.
- In most cases, HCC develops from **small-cell, high-grade dysplastic nodules** in cirrhotic livers.
- An important criterion for indication of malignancy is **nodule vascularization**.
- **Presence of structural and numeric chromosomal abnormalities** indicative of genomic instability.
- **Positive for alpha-fetoprotein.**
- Ill-defined upper abdominal pain, malaise, fatigue, weight loss, hepatomegaly and feeling of abdominal fullness.
- **Symptomatic cirrhosis of the liver + HCC**: a **rapid ↑ in liver size**, sudden worsening of **ascites**, or the appearance of **bloody ascites**, **fever**, and **pain** call attention to the development of a tumor.

Fibrolamellar carcinoma:

- A distinctive variant of HCC.
- Occurs in young male and female adults (20 to 40 years of age), more in males, has no association with HBV or cirrhosis, and often has a **better prognosis.**
- It usually presents as a **single large, hard "scirrhous" tumor** with fibrous bands coursing through it.
- **Well-differentiated polygonal** cells growing in nests or cords and separated by parallel lamellae of **dense collagen bundles.**

Cholangiocarcinoma:

- Occur mostly in persons of 50 to 70 years of age.
- **Cell origin: Bile duct.**
- Activating mutations in the *KRAS* and *BRAF* oncogenes and loss-of-function mutations in *TP53*
- Risk factors include: exposure to thototrast & infection by Opisthorchis sinensis.
- **Intrahepatic: non-cirrhotic** liver, creates **a treelike tumorous mass** within the liver or a massive tumor nodule. Lymphatic and vascular invasion are **common**.
- **Extrahepatic:** relatively small at the time of diagnosis.
- Alpha-fetoprorein is **not elevated.**
- Elevated serum levels of **alkaline phosphatase and aminotransferases**

Metastatic Tumors:

- Metastatic involvement of the liver is far **more common** than primary neoplasia.
- Most common primaries producing hepatic metastases are those of the breast, lung, and colon.

Angiosarcoma:

- Consists of pleomorphic **endothelial cells** with large hyperchromatic nuclei, giant cells in frequent mitosis and **irregular anastomosing vascular channels.**
- Cells may appear spindle shaped and cirrhosis is present in 20% to 40% of the cases. These have also been linked to vinyl chloride and thorostrast exposure.

Pancreatic Carcinoma:

- Has one of the highest mortality rates
- Arises from ductal epithelial cells.
- 6th to 8th decade, blacks more than whites, males more than females, diabetics more than non-diabetics.
- The strongest environmental influence is **smoking**, which doubles the risk.
- Remain **silent** until their **extension** impinges on some other structure.
- **Migratory thrombophlebitis** (*Trousseau syndrome*) (vein inflammation) occurs in about 10% of patients and is attributable to the elaboration of platelet- aggregating factors and pro-coagulants from the tumor or its necrotic products.
- **Ductal adenocarcinoma: highly invasive &** elicits an intense non-neoplastic host reaction called a **"desmoplastic response".**
- **Head:** Most obstruct the distal common bile duct
- **Body & tail:** Do not impinge on the biliary tract and hence remain silent for some time. Large and widely disseminated by the time they are discovered.
- The most common antecedent lesions of pancreatic cancer arise in small ducts and ductules, and are called **pancreatic intraepithelial neoplasias (PanINs).**
- Four genes are **most commonly** affected by somatic mutations in this neoplasm: **KRAS, CDKNA2A/p16, SMAD4, and TP53.**

Cholecystitis

Acute cholecystitis:

- Acute inflammation of the gallbladder wall.
- Impacted stone in the cystic duct results in dilatation with pressure ischemia,
- Bacterial overgrowth *(E coli),* and inflammation.
- Presents with right upper quadrant pain, often radiating to right scapula, fever with ↑ WBC count, nausea, vomiting, and t serum alkaline phosphatase (from duct damage).
- Risk of rupture if left untreated.

Chronic cholecystitis:

- Chronic inflammation of the gallbladder.
- Due to chemical irritation from longstanding cholelithiasis, with or without superimposed bouts of acute cholecystitis.
- Characterized by herniation of gallbladder mucosa into the muscular wall (Rokitansky-Aschoff sinus).
- Presents with vague right upper quadrant pain, especially after eating.
- Porcelain gallbladder is a late complication.
- Shrunken, hard gallbladder due to chronic inflammation, fibrosis, and dystrophic calcification.
- Increased risk for carcinoma.
- Treatment is cholecystectomy, especially if porcelain gallbladder is present.

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق
