

Cirrhosis and Its Complications

Chapter 355 | Part 10: Disorders of the Gastrointestinal System

KEY CLINICAL POINTS

- 1 Cirrhosis is defined histopathologically by architectural distortion with regenerative nodules and fibrosis.
- 2 Alcohol-associated cirrhosis typically presents with an AST:ALT ratio >2:1 and AST <400 IU/mL.
- 3 Primary Biliary Cholangitis (PBC) is characterized by AMA positivity in ~95% of cases and treated with UDCA (13–15 mg/kg/day).
- 4 Primary Sclerosing Cholangitis (PSC) diagnosis requires cholangiographic imaging showing multifocal stricturing and beading.
- 5 Portal hypertension is defined by a hepatic venous pressure gradient (HVPG) >5 mmHg; clinically significant portal hypertension (CSPH) is HVPG ≥ 10 mmHg.
- 6 Variceal bleeding has a 20–30% mortality rate per episode; screening endoscopy is recommended for known cirrhotics.
- 7 Hepatic encephalopathy is caused by portosystemic shunting and ammonia accumulation.
- 8 Spontaneous bacterial peritonitis (SBP) is a major complication requiring empiric antibiotics in patients with ascites.
- 9 Liver transplantation is the treatment of choice for decompensated cirrhosis due to PBC or PSC.
- 10 Ascites pathophysiology involves both increased hydrostatic pressure (portal hypertension/splanchnic vasodilation) and decreased effective arterial blood volume (RAAS/sympathetic activation).

DEFINITION & OVERVIEW

• **Definition:** *Cirrhosis is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening.*

• **Pathologic Features:**

- Fibrosis to the point of architectural distortion with the formation of regenerative nodules.
- Result: Decrease in hepatocellular mass/function and alteration of blood flow.
- Mechanism: Activation of hepatic stellate cells → increased collagen and extracellular matrix production.
- Progression: Connective tissue in periportal and pericentral zones connects portal triads with central veins.
- Physical Change: Liver contracts and shrinks due to hepatocyte loss and collagen deposition.
- Timeline: Typically takes years to decades; requires repeated insults.

Classification by Etiology

• **Categories (Table 355-1):**

- Alcohol: Alcohol-associated fatty liver, Alcoholic hepatitis, Alcohol-associated cirrhosis.

- Chronic viral hepatitis: Hepatitis B, Hepatitis C.
- Autoimmune: Autoimmune hepatitis, Autoimmune cholangiopathy.
- Metabolic: Metabolic dysfunction–associated steatohepatitis (MASH).
- Biliary: Primary biliary cholangitis (PBC), Primary sclerosing cholangitis (PSC), Autoimmune cholangiopathy.
- Inherited: Hemochromatosis, Wilson’s disease, α Antitrypsin deficiency, Cystic fibrosis.
- Cardiac: Cardiac cirrhosis.
- Other: Cryptogenic cirrhosis.

EPIDEMIOLOGY

- **General Statistics:**
 - Chronic liver disease is the 10th most common cause of death in US adults.
 - Alcohol-associated cirrhosis accounts for ~48% of deaths due to cirrhosis.
- **Alcohol Use (US):**
 - >70% of adults drink alcohol annually.
 - >14 million adults meet criteria for alcohol use disorder.
- **Hepatitis C (HCV):**
 - ~80% of exposed individuals develop chronic hepatitis C.
 - ~20–30% of those with chronic infection develop cirrhosis over 20–30 years.
 - ~170 million individuals worldwide have HCV.
- **Hepatitis B (HBV):**
 - ~5% of exposed individuals develop chronic HBV.
 - ~20% of those with chronic HBV develop cirrhosis.
 - ~300–400 million individuals have HBV worldwide; ~25% may develop cirrhosis.
- **Other Conditions:**
 - Hemochromatosis: 1 in 250 have genetic susceptibility, but <5% of these develop severe liver disease.
 - Wilson’s disease: Affects 1 in 30,000 individuals.
 - PBC: 100–200 per million; strong female predominance; median age ~50 at diagnosis.

ETIOLOGY & PATHOPHYSIOLOGY

- **General Pathophysiology:**
 - Fibrosis → Architectural distortion → Regenerative nodules.
 - Stellate cell activation → Collagen production → Liver shrinkage.

Alcohol-Associated Liver Disease Pathogenesis

- **Metabolism:**
 - Absorption: Small intestine and stomach.
 - Enzymes: Cytosolic ADH, MEOS (CYP2E1), Peroxisomal catalase.
 - Pathway: Alcohol → Acetaldehyde (via ADH) → Acetate (via ALDH).
 - MEOS Induction: Chronic use → CYP2E1 induction → Reactive oxygen species + more acetaldehyde.
- **Cellular Damage:**
 - Triglyceride accumulation → increased fatty acid uptake, decreased oxidation/secretion.

- Acetaldehyde effects: Forms adducts with proteins/nucleic acids; impairs enzyme activity and protein trafficking.
- Kupffer cell activation → release of profibrogenic cytokines → stellate cell activation.

Viral Hepatitis Pathogenesis

- **HCV:**
 - Noncytopathic virus; damage is immune-mediated.
 - Progression: Portal-based fibrosis → bridging fibrosis → nodularity → cirrhosis.
 - Morphology: Small, shrunken liver; mixed micro- and macronodular cirrhosis; interface hepatitis.
- **HBV:**
 - Similar findings to HCV.
 - Markers: HBsAg (ground-glass hepatocytes), HBc, and HBs antigens.

Biliary Cirrhosis Pathogenesis

- **Mechanism:** Result of chronic cholestasis.
 - Features: Cholate stasis; copper deposition; xanthomatous transformation of hepatocytes; irregular, so-called biliary fibrosis.
 - Distinction: Intrahepatic (no benefit from decompression) vs. Extrahepatic (may benefit from surgery/endoscopy).

Cardiac Cirrhosis Pathogenesis

- **Mechanism:** Right-sided congestive heart failure → increased venous pressure → dilated/engorged sinusoids.
 - Result: Centrilobular hepatocyte necrosis → pericentral fibrosis → expansion to periphery.

Wilson's Disease Pathogenesis

- **Mechanism:** Inherited disorder of copper homeostasis; failure to excrete copper → liver accumulation.
 - Prevalence: 1 in 30,000; affects adolescents/young adults.

Alpha-1 Antitrypsin Deficiency Pathogenesis

- **Mechanism:** Inherited defect → abnormal folding of α AT protein → failure of secretion from liver.
 - Risk: ZZ phenotype (only 10–20% develop liver disease).
 - Pathology: PAS-positive, diastase-resistant globules.

CLINICAL FEATURES

- **General Clinical Presentation:**
 - Severity reflects pathology.
 - Distinction: Stable/Compensated vs. Decompensated (Ascites, Hepatic Encephalopathy, Variceal Bleeding).
 - Portal Hypertension: Drives ascites and variceal bleeding.
 - Loss of Function: Jaundice, coagulopathy, hypoalbuminemia.

Alcohol-Associated Liver Disease Clinical Features

- **Diagnosis Criteria:**

- History: >2 drinks/day (women) or >3 drinks/day (men) for >12 months.
- **Symptoms:** Vague RUQ pain, fever, nausea, vomiting, diarrhea, anorexia, malaise.
- **Physical Exam:**
 - Liver/Spleen: Enlarged, firm, nodular.
 - Skin: Scleral icterus, palmar erythema (Fig. 355-1), spider angioma (Fig. 355-2).
 - Other: Parotid enlargement, digital clubbing, muscle wasting, edema, ascites.
 - Male specific: Decreased body hair, gynecomastia, testicular atrophy.
- **Laboratory Findings:**
 - Anemia: Chronic blood loss, nutritional deficiency, or hypersplenism.
 - Zieve's Syndrome: Hemolytic anemia (spur cells/acanthocytes) in severe alcoholic hepatitis.
 - Platelets: Reduced early due to portal hypertension/hypersplenism.
 - Bilirubin: Normal or elevated in advanced disease.
 - Coagulation: Prothrombin times prolonged; no response to Vitamin K.
 - Sodium: Low if ascites present (free water ingestion).
 - Enzymes: AST & ALT elevated; AST >1 ALT (usually 2:1 ratio); AST <400 IU/mL.

Primary Biliary Cholangitis (PBC) Clinical Features

- **Presentation:** Often asymptomatic until late.
 - Fatigue: Significant, out of proportion to disease severity.
 - Pruritus: ~50% at diagnosis; debilitating; worse in evening.
 - Prognosis: Pruritus before jaundice indicates severe disease/poor prognosis.
 - Unique features: Hyperpigmentation (trunk/arms), xanthelasma, xanthomata (altered cholesterol metabolism).
 - Bone: Osteopenia or osteoporosis.

Primary Sclerosing Cholangitis (PSC) Clinical Features

- **Symptoms:** Fatigue, pruritus, steatorrhea, fat-soluble vitamin deficiencies.
 - Physical: Signs of CHF; enlarged firm liver.
 - Labs: ALP characteristically elevated; AST >1 ALT.
 - Note: Variceal hemorrhage and encephalopathy are unlikely.

Other Types of Cirrhosis Clinical Features

- **Cardiac:** Signs of CHF, enlarged firm liver, elevated ALP.
 - Wilson's: Low ceruloplasmin, high 24-h urine copper, Kayser-Fleischer rings.
 - Hemochromatosis: High transferrin saturation, high ferritin, HFE mutation.
 - Cystic Fibrosis: Biliary-type cirrhosis; may benefit from UDCA.

DIFFERENTIAL DIAGNOSIS

- **General Approach:**
 - Alcohol use → consider alcohol-associated liver disease.
 - Rule out/identify other causes (viral, metabolic, autoimmune).
 - Role of Biopsy: Helpful to confirm diagnosis but not performed unless alternative suspected.
- **Prognosis Factors:**
 - Continued drinking with complications → <50% 5-year survival.

- Abstinence → significantly improved prognosis.

Distinguishing Features by Etiology

- **Alcohol-associated:** AST:ALT >2:1; AST <400; history of >2/3 drinks for >12 months.
 - **Viral Hepatitis:** Positive serologies (HBsAg, HCV RNA); ground-glass hepatocytes (HBV); portal-based fibrosis.
 - **Autoimmune Hepatitis:** Positive ANA or ASMA; elevated IgG; interface hepatitis.
 - **MASH:** Steatosis on biopsy.
 - **PBC:** AMA positive (~95%); elevated IgM; cholestatic enzymes.
 - **PSC:** pANCA positive (~65%); IBD association (60-80%); cholangiographic beading.
 - **Cardiac:** Signs of heart failure, enlarged liver, elevated ALP, no variceal hemorrhage risk.
 - **Wilson's:** Low ceruloplasmin, high urine copper, Kayser-Fleischer rings.

DIAGNOSTIC APPROACH

1. **Initial Assessment:** History and Physical Examination (Alcohol use, symptoms, signs).
2. **Laboratory Evaluation:** LFTs, Viral Serologies (HBsAg, HBeAg, anti-HBe, HCV RNA/Genotype), Iron Studies (Transferrin saturation, Ferritin), Autoantibodies.
3. **Specific Diagnostic Pathways:**
 - **PBC:** If cholestatic enzymes abnormal → AMA test.
 - If AMA negative (5–10%) → other antibodies (sp100, gp210) → Liver biopsy.
 - **PSC:** If AMA negative with cholestatic enzymes → Cholangiography (MRCP preferred; ERCP if MRCP is suboptimal or bilirubin rises).
 - Criteria: Multifocal stricturing and beading of intra- and extrahepatic bile ducts.
 - **Hemochromatosis:** Serum iron studies (high transferrin saturation, high ferritin) + HFE mutation analysis.
 - **Alpha-1 Antitrypsin:** Determine α AT levels and phenotype.
 - **Wilson's Disease:** Ceruloplasmin (low), 24-h urine copper (high), Kayser-Fleischer rings, biopsy.

MANAGEMENT & TREATMENT

1. **Variceal Hemorrhage Management (Flowchart 1):**
 - Step 1: Recurrent acute bleeding → Endoscopic therapy + Pharmacologic therapy.
 - Step 2: Control of bleeding achieved.
 - Step 3: Assess Child-Pugh score.
 - Step 4: If Child's class A (Compensated) → Perform TIPS → Consider liver transplantation evaluation.
 - Step 5: If Child's class B or C (Decompensated) → Transplant evaluation → Endoscopic therapy or beta blockers → Consider TIPS → Liver transplantation.
2. **Ascites Management (Flowchart 2):**
 - Step 1: Highly symptomatic ascites → Large-volume paracentesis (LVP) + albumin.
 - Step 2: Maintenance → Dietary sodium restriction + diuretics.
 - Step 3: If Ascites reaccumulation occurs → Decision based on clinical status:
 - Option A: Consider TIPS.
 - Option B: Continue LVP with albumin as needed.

- Option C: Consider liver transplantation (especially if azotemia develops during diuretic treatment).

3. Pharmacologic Therapy:

- **PBC:** Treatment with Ursodeoxycholic acid (UDCA) at 13–15 mg/kg/day.

4. Surgical/Procedural Therapy:

- **TIPS:** Used for variceal bleeding or refractory ascites.
- **Transplantation:** Preferred for decompensated cirrhosis due to PBC or PSC.

COMPLICATIONS & PROGNOSIS

• Portal Hypertension (Table 3):

- Prehepatic: Portal vein thrombosis, Splenic vein thrombosis, Massive splenomegaly (Banti's syndrome).
- Hepatic: Presinusoidal (Schistosomiasis, Congenital hepatic fibrosis).
- Sinusoidal: Cirrhosis (many causes), Alcoholic hepatitis.
- Postsinusoidal: Hepatic sinusoidal obstruction (venoocclusive syndrome), Budd-Chiari syndrome, Inferior vena caval webs, Cardiac causes (Restrictive cardiomyopathy, Constrictive pericarditis, Severe congestive heart failure).

• General Complications (Table 2):

- Portal hypertension related: Gastroesophageal varices, Portal hypertensive gastropathy, Splenomegaly/hypersplenism, Ascites, Spontaneous bacterial peritonitis (SBP), Acute kidney injury-hepatorenal syndrome (HRS), Chronic kidney disease-hepatorenal syndrome.
- Coagulopathy: Factor deficiency, Fibrinolysis, Thrombocytopenia.
- Bone disease: Osteopenia, Osteoporosis, Osteomalacia.
- Hematologic: Anemia, Hemolysis, Neutropenia.

• Other Complications:

- Hepatic encephalopathy.
- Hepatopulmonary syndrome.
- Portopulmonary hypertension.
- Malnutrition.

Classification of Portal Hypertension

- **Prehepatic:** Portal vein thrombosis, Splenic vein thrombosis, Massive splenomegaly (Banti's syndrome).
- **Hepatic:** Presinusoidal (Schistosomiasis, Congenital hepatic fibrosis).
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- **Postsinusoidal:** Hepatic sinusoidal obstruction (venoocclusive syndrome), Budd-Chiari syndrome, Inferior vena caval webs, Cardiac causes (Restrictive cardiomyopathy, Constrictive pericarditis, Severe congestive heart failure).

KEY PEARLS & HIGH-YIELD POINTS

- **Variceal Hemorrhage:** Mortality 20–30% per episode; screening endoscopy for all known cirrhotics.
- **Ascites Pathophysiology:** Dual mechanism: ↑ Hydrostatic pressure (Portal HTN) + ↓ Effective arterial volume (RAAS/Sympathetic activation).
- **Alcoholic Cirrhosis:** AST:ALT >2:1; AST <400; Zieve's syndrome (hemolytic anemia).

- **PBC vs. PSC:** PBC is AMA+ (~95%); PSC is pANCA+ and associated with IBD.
- **TIPS Decision:** Used for variceal bleeding or refractory ascites; choice of timing depends on Child-Pugh class.
- **Symptom Alert:** Pruritus before jaundice in PBC indicates severe disease/poor prognosis.

REFERENCE TABLES

TABLE 355-1

Causes of Cirrhosis Alcohol Chronic viral hepatitis

Alcohol	Cardiac cirrhosis
Chronic viral hepatitis	Inherited metabolic liver disease
Hepatitis B	Hemochromatosis
Hepatitis C	Wilson's disease
Autoimmune hepatitis	α Antitrypsin deficiency 1
Metabolic dysfunction-associated steatohepatitis	Cystic fibrosis
Biliary cirrhosis	Cryptogenic cirrhosis
Primary biliary cholangitis	
Primary sclerosing cholangitis	
Autoimmune cholangiopathy	
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TABLE 355-3

Classification of Portal Hypertension Prehepatic

Portal hypertension	Coagulopathy
Gastroesophageal varices	Factor deficiency
Portal hypertensive gastropathy	Fibrinolysis
Splenomegaly, hypersplenism	Thrombocytopenia
Ascites	Bone disease
Spontaneous bacterial peritonitis	Osteopenia
Acute kidney injury-hepatorenal syndrome	Osteoporosis
Chronic kidney disease-hepatorenal syndrome	Osteomalacia
Hematologic abnormalities	

Portal hypertension	Coagulopathy
Hepatic encephalopathy	Anemia
Hepatopulmonary syndrome	Hemolysis
Portopulmonary hypertension	Thrombocytopenia
Malnutrition	Neutropenia

TABLE 355-3

Classification of Portal Hypertension

- Prehepatic
 - Portal vein thrombosis
 - Splenic vein thrombosis
 - Massive splenomegaly (Banti's syndrome)
- Hepatic
 - Presinusoidal
 - Schistosomiasis
 - Congenital hepatic fibrosis
 - Sinusoidal
 - Cirrhosis—many causes
 - Alcoholic hepatitis
- Postsinusoidal
 - Hepatic sinusoidal obstruction (venoocclusive syndrome)
- Posthepatic
 - Budd-Chiari syndrome
 - Inferior vena caval webs
- Cardiac causes
 - Restrictive cardiomyopathy
 - Constrictive pericarditis
 - Severe congestive heart failure