LIVER PATHOLOGY

Complete Master Study Sheet - interconnected, detailed, exam-ready

Source: Liver-1-24.pdf slides uploaded in this conversation.

PART 1 - Understanding the Liver First

Before studying pathology, think of the liver as a metabolic factory, synthetic organ, detoxification center, storage organ, and excretory organ. Most clinical features of liver disease are simply the result of losing one or more of these functions.

Function	What the liver does	What happens if it fails
Metabolic	Glucose, lipid, and protein metabolism	Metabolic disturbance
Synthetic	Albumin and clotting factors	Edema and bleeding
Detoxification	Drugs, hormones, and ammonia (NH_3)	Toxin accumulation and encephalopathy
Storage	Glycogen, triglycerides, iron, copper, vitamins	Storage/metabolic problems
Excretory	Bile production and excretion	Jaundice and cholestasis

PART 2 - Liver Blood Supply and Why It Matters

- Net weight: 1400-1600 g, about 2.5% of body weight.

Blood supply	Percentage	Meaning
Portal vein	60-70%	Nutrient-rich blood from GIT and spleen
Hepatic artery	30-40%	Oxygen-rich arterial blood

This dual supply explains why the liver is relatively resistant to ischemia, but also why injury patterns follow the direction of blood flow.

PART 3 - Microstructure of the Liver

Classical lobule

- Hexagonal unit with a central vein in the center and portal tracts at the corners.
- The parenchyma is organized into plates/cords of hepatocytes.
- Hepatocytes are radially oriented around the terminal hepatic vein, also called the central vein.
- Vascular sinusoids are present between cords of hepatocytes.

Portal triad

- Portal vein branch.
- Hepatic artery branch.
- Bile duct branch.

Blood flow

Portal tract
↓
Sinusoids
↓

Central vein

Acinus and zones

The acinus is the functional unit used to understand zonal injury. The acinus is divided into three zones.

Zone	Location	Oxygen/blood supply	Clinical importance
Zone 1	Periportal, closest to vascular supply	Highest oxygen	First exposed to blood-borne substances
Zone 2	Intermediate	Moderate oxygen	Intermediate injury pattern
Zone 3	Pericentral, near central vein	Lowest oxygen	Most vulnerable to ischemia and many toxins

Memory link: Zone 3 is injured easily because it receives blood last, has the lowest oxygen, and has high CYP450 activity. Therefore alcohol injury, acetaminophen toxicity, and ischemia commonly involve Zone 3.

PART 4 - Normal Histology

Hepatocytes

- Show only minimal variation in overall size normally.
- Nuclei may vary in size, number, and ploidy, especially with advancing age.

Sinusoids

- Special vascular channels between hepatocyte cords.
- They allow exchange between plasma and hepatocytes.

Space of Disse

- Space between sinusoidal endothelial cells and hepatocytes.
- Contains stellate/Ito cells.
- This space is central in cirrhosis because collagen deposition here blocks exchange.

PART 5 - General Response of the Liver to Injury

Injury
↓
Inflammation
↓
Ballooning degeneration
↓
Steatosis / accumulation
↓
Necrosis
↓
Regeneration
↓
Fibrosis
↓
Cirrhosis
↓
Portal hypertension + hepatic failure

PART 6 - Hepatic Injury Patterns

1. Inflammation - Hepatitis

Hepatitis means inflammation of the liver. Causes include viral hepatitis, alcohol, drugs, toxins, and autoimmune disease.

2. Ballooning degeneration

Ballooning degeneration is reversible hepatocyte injury. Water enters damaged hepatocytes, causing swelling and pale/clear cytoplasmic spaces.

- Irregularly clumped cytoplasm.
- Large, clear spaces in the cytoplasm.
- Substances may accumulate in viable hepatocytes: fat, iron, copper, and retained biliary material.

3. Steatosis - fatty change

Steatosis means fat accumulation in hepatocytes. It occurs when fat metabolism, oxidation, or export is disturbed.

Type	Typical causes
Microvesicular	Alcoholic liver disease, Reye syndrome, acute fatty liver of pregnancy
Macrovesicular	Diabetes mellitus, obesity

- Gross fatty liver: enlarged, soft, yellow, and greasy.
- Microscopy: clear fat vacuoles inside hepatocytes.
- Fatty change is reversible if the cause is removed early.

4. Necrosis

Necrosis means irreversible hepatocyte death.

Classification	Types/details
By pattern	Coagulative necrosis around central vein; lytic necrosis
By cause	Ischemic or toxic
By location	Centrilobular, midzonal, periportal/interface hepatitis, focal, piecemeal necrosis, bridging necrosis, diffuse massive/submassive necrosis

- Councilman bodies are apoptotic hepatocytes seen in hepatitis.
- Massive necrosis can lead to fulminant hepatic failure.

5. Regeneration

- Regeneration is evidenced by increased mitosis or cell-cycle markers.
- Cells of the canal of Hering are progenitors for hepatocytes and bile duct cells; these are called oval cells.

6. Fibrosis

Fibrosis is collagen deposition. It is an important feature of chronicity.

Type	Location/meaning
Portal or periportal fibrosis	Fibrosis around portal tracts
Pericentral fibrosis	Fibrosis around central vein
Pericellular fibrosis	Fibrous tissue around single or multiple hepatocytes, often within sinusoids
Bridging fibrosis	Fibrous bands connect vascular/portal structures

7. Cirrhosis

- Cirrhosis is diffuse fibrosis with conversion of liver parenchyma into nodules.
- Types: micronodular and macronodular.

8. Ductular proliferation

- Proliferation of bile ductules, usually a response to chronic injury or regeneration.

PART 7 - Hepatic Failure

Hepatic failure results when hepatic functional capacity is almost totally lost, around 80-90%.

Causes

Cause category	Examples
Massive hepatic necrosis	Fulminant viral hepatitis; drugs and chemicals such as acetaminophen, halothane, anti-TB drugs, CCl4, mushroom poisoning
Chronic liver disease	End-stage chronic injury such as cirrhosis
Hepatic dysfunction without overt cirrhosis	Reye syndrome, tetracycline toxicity, acute fatty liver of pregnancy

Clinical features

Feature	Mechanism/meaning
Jaundice	Failure of bile/bilirubin excretion
Hypoalbuminemia -> edema	Reduced albumin synthesis lowers oncotic pressure
Hyperammonemia	Failure to detoxify ammonia
Fetor hepaticus	Musty or sweet-sour breath odor
Palmar erythema	Hyperestrogenemia
Spider angiomas	Hyperestrogenemia
Hypogonadism and gynecomastia	Hormonal imbalance

Consequences

- Multiple organ failure involving kidneys and lungs.
- Coagulopathy causing bleeding due to deficiency of clotting factors II, VII, IX, and X.
- Hepatic encephalopathy: decreased consciousness, rigidity, hyperreflexia, EEG changes, seizures, and asterixis.
- Hepatorenal syndrome: renal failure in severe liver disease without morphologic or functional primary renal cause.

PART 8 - Massive Hepatic Necrosis and Fulminant Failure

Fulminant hepatic failure progresses from onset of symptoms to hepatic encephalopathy within 2-3 weeks. Subfulminant failure develops within up to 3 months.

Causes

- Viral hepatitis: 50-65% (B, B-D, A, C; HBV more important than HCV in the slide set).
- Drugs and chemicals: 20-30% or 25-50% in the repeated slide list; examples include isoniazid, halothane, methyldopa, acetaminophen.

- Heat stroke.
- Hepatic vein obstruction.
- Wilson disease.
- Acute fatty liver of pregnancy.
- Massive malignant/tumor infiltration.
- Reactivation of chronic HBV or superimposed HDV infection.
- Autoimmune/acute immune hepatitis.

Morphology

- Small liver, around 500-700 g in massive necrosis.
- Necrosis of hepatocytes.
- Collapsed reticulin tissue.
- Inflammatory infiltrate.
- Regenerative activity of hepatocytes.
- Fibrosis may be present.

PART 9 - Alcoholic Liver Disease

Alcohol is a widely abused agent and an important cause of cirrhosis. It contributes to death through accidents and cirrhosis.

Blood alcohol levels and tolerance

- 80-100 mg/dL is the legal definition for driving under the influence of alcohol in the slides.
- About 44 mL ethanol is required to produce this level in a 70 kg person.
- In occasional drinkers, 200 mg/dL may produce coma, and 300-400 mg/dL may cause death and respiratory failure.
- Habitual drinkers can tolerate levels up to 700 mg/dL due to metabolic tolerance.
- Tolerance is explained by 5-10X induction of the cytochrome P450 system, including CYP2E1, which increases metabolism of ethanol and other drugs such as cocaine and acetaminophen.

Forms of alcoholic liver disease

Form	Frequency/details
Hepatic steatosis	90-100% of drinkers
Alcoholic hepatitis	10-35% of drinkers
Cirrhosis	14% of drinkers

Steatosis and hepatitis may develop independently.

Hepatic steatosis

- Can occur following even moderate alcohol intake as microvesicular steatosis.
- Chronic intake produces diffuse steatosis.
- Liver becomes large, 4-6 kg, soft, yellow, and greasy.
- Continued intake leads to fibrosis.
- Fatty change is reversible with complete abstention from further alcohol intake.

Alcoholic hepatitis - characteristic findings

- Hepatocyte swelling and necrosis due to accumulation of fat, water, and proteins.
- Cholestasis.
- Hemosiderin deposition in hepatocytes and Kupffer cells.
- Mallory hyaline bodies: eosinophilic cytoplasmic inclusions in degenerating hepatocytes, made of cytokeratin intermediate filaments and other proteins.
- Neutrophilic reaction.
- Fibrosis: sinusoidal, perivenular, and periportal.

- Mild deposition of hemosiderin in hepatocytes and Kupffer cells.

Mallory hyaline bodies are characteristic but not pathognomonic

- Also seen in primary biliary cirrhosis.
- Wilson disease.
- Chronic cholestatic syndromes.
- Hepatocellular carcinoma.

Alcoholic cirrhosis

- Usually develops slowly.
- Initially the liver is enlarged and yellow.
- Over years it becomes brown, shrunken, non-fatty, and sometimes less than 1 kg in weight.
- Starts micronodular, then becomes mixed micro- and macronodular.
- Laennec cirrhosis means scar tissue pattern associated with alcohol.
- Bile stasis may be present.
- Mallory bodies are only rarely evident at this stage.
- It is irreversible.
- Can develop rapidly in the presence of alcoholic hepatitis, within 1-2 years.

PART 10 - Ethanol Metabolism

Ethanol
↓ alcohol dehydrogenase / CYP450 / catalase
Acetaldehyde
↓ aldehyde dehydrogenase
Acetic acid

- Alcohol dehydrogenase is present in stomach and liver.
- CYP450 and catalase are also involved, especially in liver metabolism.
- After absorption, ethanol is distributed in tissues and fluids in direct proportion to blood level.
- Less than 10% of absorbed ethanol is excreted unchanged in urine, sweat, and breath.

Sex difference

- Women have lower gastric alcohol dehydrogenase activity than men.
- Therefore women may develop higher blood alcohol levels than men after drinking the same quantity and are more susceptible to hepatic injury.

Aldehyde dehydrogenase polymorphism

- About 50% of Chinese, Vietnamese, and Japanese populations have lowered aldehyde dehydrogenase activity due to point mutation.
- This causes acetaldehyde accumulation leading to facial flushing, tachycardia, and hyperventilation.

PART 11 - Pathogenesis of Alcoholic Liver Disease

- Short-term ingestion of 80 g ethanol/day is associated with mild reversible fatty liver.
- Long-term ingestion of 160 g/day for 10-20 years causes severe hepatic injury.
- 50-60 g/day has a borderline effect.
- Only 8-20% of alcoholics develop cirrhosis.

Mechanisms of ethanol toxicity

Mechanism	Explanation
Fatty change	Excess NADH over NAD shifts lipid catabolism toward lipid biosynthesis

Mechanism	Explanation
Acetaldehyde-tubulin adducts	Decreased microtubule function reduces lipoprotein transport from liver
Increased peripheral fat catabolism	Increased free fatty acid delivery to liver
Reduced lipoprotein secretion	Fat remains in hepatocytes
Reduced mitochondrial FFA oxidation	Fat accumulates
CYP450 induction	Enhances metabolism of drugs to toxic metabolites, e.g. acetaminophen
Free radicals	Membrane and protein damage
Direct toxicity	Alcohol affects microtubules, mitochondria, and membrane fluidity
Acetaldehyde immune effects	Lipid peroxidation and antigenic alteration of hepatocytes leading to immune attack
HCV superinfection	Accelerates injury; HCV occurs in about 30% of alcoholics in the slides
Gut endotoxins	Alcohol allows bacterial endotoxins into portal circulation, causing liver inflammation
Regional hypoxia	Endothelins cause vasoconstriction and reduce hepatic sinusoidal perfusion
Cytokine dysregulation	TNF is a major effector; IL-6, IL-8, IL-18 also involved

Clinical features of alcoholic liver disease

Stage	Clinical features
Hepatic steatosis	Reversible; enlarged liver; increased liver enzymes; severe hepatic dysfunction is unusual
Alcoholic hepatitis	After 15-20 years of excessive drinking; malaise, anorexia, weight loss; enlarged liver and spleen; increased LFTs; each bout carries 10-20% risk of death; one-third progress to cirrhosis in a few years
Cirrhosis	Portal hypertension and complications

Causes of death in alcoholic liver disease

- Hepatic failure.
- Massive gastrointestinal bleeding.
- Infections.
- Hepatorenal syndrome.
- Hepatocellular carcinoma in 3-6% of cases.

PART 12 - Cirrhosis

Cirrhosis is a diffuse process characterized by fibrosis and conversion of liver parenchyma into nodules.

Main characteristics

- Bridging fibrous septa.

- Parenchymal nodules encircled by fibrotic bands.
- Diffuse architecture disruption.

Types

Type	Definition
Micronodular cirrhosis	Nodules < 3 mm in diameter
Macronodular cirrhosis	Nodules > 3 mm in diameter

Causes of cirrhosis

- Chronic alcoholism.
- Chronic viral infection: HBV and HCV.
- Biliary disease.
- Hemochromatosis.
- Autoimmune hepatitis.
- Wilson disease.
- Alpha-1 antitrypsin deficiency.
- Rare causes: galactosemia, tyrosinosis, glycogen storage disease III and IV, lipid storage disease, hereditary fructose intolerance, drug-induced cirrhosis such as methyldopa.
- Cryptogenic cirrhosis: about 10%.

Pathogenesis

- Hepatocellular death must occur over a long period and be accompanied by fibrosis.
- Main mechanisms: hepatocellular death, regeneration, progressive fibrosis, and vascular changes.

Normal ECM/collagen distribution

- In normal liver, ECM collagen types I, III, V, and XI are present only in liver capsule, portal tracts, and around central veins.
- A delicate framework of type IV collagen and other proteins lies in the space of Disse.
- In cirrhosis, types I and III collagen and other matrix proteins are deposited in the space of Disse.

Stellate/Ito cells

- Major source of collagen in cirrhosis.
- Located in the space of Disse.
- Normally store vitamin A and fat.
- Upon stimulation, transform into myofibroblast-like cells under the influence of TGF-beta.

Stimuli for stellate cell activation

- Reactive oxygen species.
- Growth factors.
- Cytokines: TNF, IL-1, lymphotoxins.

Vascular changes in cirrhosis

- Loss of sinusoidal endothelial fenestrations.
- Development of vascular shunts: portal vein-hepatic vein and hepatic artery-portal vein.
- Functional defect because blood bypasses hepatocytes.
- Loss of hepatocyte microvilli decreases transport capacity.
- Collagen deposition converts sinusoids from fenestrated exchange channels into higher pressure, fast-flowing vascular channels with poor solute exchange.
- Movement of albumin, clotting factors, and lipoproteins between hepatocytes and plasma becomes markedly impaired.

Clinical features

- May be silent at first.
- Anorexia, weight loss, weakness.
- Major complications: progressive hepatic failure, portal hypertension, hepatocellular carcinoma.

PART 13 - Portal Hypertension

Portal hypertension results from increased resistance to portal blood flow. In cirrhosis this occurs at the sinusoidal level and by compression of central veins due to perivenular fibrosis and parenchymal nodules.

- Arterial-portal anastomoses develop in fibrous bands and impose arterial pressure on the normally low-pressure portal venous system.

Causes

Category	Causes
Prehepatic	Portal vein thrombosis; massive splenomegaly
Posthepatic	Severe right-sided heart failure; constrictive pericarditis; hepatic vein outflow obstruction
Hepatic	Cirrhosis; schistosomiasis; massive fatty change; diffuse granulomatosis such as sarcoidosis or TB; disease of portal microcirculation such as nodular regenerative hyperplasia

Clinical consequences

- Ascites.
- Portosystemic shunts.
- Hepatic encephalopathy.
- Splenomegaly.

PART 14 - Ascites

Ascites is collection of excess fluid in the peritoneal cavity. It becomes clinically detectable when at least 500 mL has accumulated.

Features of ascitic fluid

- Serous fluid.
- Contains as much as 3 g/mL protein, mainly albumin, according to the slide text.
- Same concentration as blood of glucose, Na+, and K+.
- Contains mesothelial cells and lymphocytes.
- Neutrophils suggest infection.
- RBCs suggest disseminated cancer.

Pathogenesis

- Increased sinusoidal blood pressure.
- Hypoalbuminemia.
- Leakage of hepatic lymph into the peritoneal cavity.
- Normal thoracic duct lymph flow is 800-1000 mL/day; in cirrhosis it may reach 20 L/day.
- Renal retention of Na+ and water due to secondary hyperaldosteronism.

PART 15 - Portosystemic Shunts

Because portal pressure increases, bypasses develop wherever systemic and portal circulations share capillary beds.

Site	Clinical manifestation
Around and within rectum	Hemorrhoids

Site	Clinical manifestation
Gastroesophageal junction	Esophageal varices
Retroperitoneum	Retroperitoneal collaterals
Falciform ligament/periumbilical abdominal wall	Caput medusae

- Gastroesophageal varices appear in about 65% of patients with advanced cirrhosis.
- They cause death in about 50% due to upper GI bleeding in the slide set.

PART 16 - Splenomegaly

- Usually 500-1000 g; normal spleen is <300 g.
- Not necessarily correlated with other features of portal hypertension.
- May result in hypersplenism.

PART 17 - Hepatic Encephalopathy

Hepatic encephalopathy is a complication of both acute and chronic hepatic failure.

Clinical spectrum

- Behavioral changes.
- Marked confusion.
- Stupor.
- Deep coma and death.
- Changes may progress over hours or days.

Neurologic signs

- Rigidity.
- Hyperreflexia.
- Nonspecific EEG changes.
- Seizures.
- Asterixis: non-rhythmic rapid extension-flexion movements of head and extremities.
- Brain shows edema and astrocytic reaction.

Pathogenesis

- Severe loss of hepatocellular function.
- Shunting of blood around damaged liver.
- Brain is exposed to toxic metabolic products.
- Increased blood ammonia causes generalized brain edema and impaired neuronal function.
- Alteration in central nervous system amino acid metabolism.

PART 18 - Drug-Induced Liver Disease

Types of drug reactions

Type	Meaning
Predictable / intrinsic	Dose-dependent
Unpredictable / idiosyncratic	Depends on immune response or host rate of metabolism

- Injury may be immediate or take weeks to months.
- Drug-induced chronic hepatitis can be clinically and histologically indistinguishable from chronic viral or autoimmune hepatitis.

Examples

Predictable drugs	Unpredictable drugs
Acetaminophen, tetracycline, antineoplastic agents, CCl4, alcohol	Chlorpromazine, halothane, sulfonamides, methyldopa, allopurinol

Mechanisms

- Direct toxic damage: acetaminophen, CCl4, mushroom toxins.
- Immune-mediated damage.

Patterns of injury

- Hepatocellular necrosis.
- Cholestasis.
- Steatosis.
- Steatohepatitis.
- Fibrosis.
- Vascular lesions.
- Granuloma.
- Benign and malignant neoplasms.

Drugs/toxins that may cause acute liver failure

- Acetaminophen, most common.
- Halothane.
- Antituberculosis drugs: rifampin, isoniazid.
- Antidepressant monoamine oxidase inhibitors.
- Toxins such as CCl4 and mushroom poisoning.

Morphology

- Massive necrosis: liver 500-700 g.
- Submassive necrosis.
- Patchy necrosis.

PART 19 - Chronic Hepatitis

Chronic hepatitis means symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, with histologically documented inflammation and necrosis.

- Can be progressive or non-progressive.
- Important viral causes: HBV, HCV, HBV-HDV.

Morphology

- Ranges from mild to severe.
- Portal inflammation.
- Lymphoid aggregates.
- Necrosis of hepatocytes and Councilman bodies.
- Bile duct damage.
- Steatosis.
- Interface hepatitis.
- Bridging necrosis and fibrosis.
- Fibrosis.
- Ground-glass appearance.
- Sanded nuclei.
- Lobular disarray.

Final Master Flowchart - Never Forget the Story

Alcohol / viruses / drugs / toxins / metabolic disease

↓

Hepatocyte injury

↓

Inflammation = hepatitis

↓

Ballooning degeneration + accumulation of fat/iron/copper/bile

↓

Necrosis

↓

Regeneration attempts through hepatocytes and canal of Hering progenitors

↓

Stellate cell activation in space of Disse

↓

Collagen deposition and fibrosis

↓

Cirrhosis = fibrosis + nodules + distorted architecture

↓

Portal hypertension + vascular shunts

↓

Ascites + varices + splenomegaly + encephalopathy

↓

Hepatic failure: jaundice, edema, bleeding, hyperammonemia, coma

Quick Exam Anchors

- Zone 3: ischemia, toxins, alcohol, acetaminophen vulnerability.
- Ballooning: swollen injured hepatocytes with pale clear spaces.
- Steatosis: reversible fatty change; microvesicular vs macrovesicular.
- Fibrosis: key marker of chronicity; stellate cells make collagen.
- Cirrhosis: diffuse fibrosis + regenerative nodules + architectural distortion.
- Portal hypertension: ascites, varices, splenomegaly, encephalopathy.
- Alcoholic hepatitis: ballooning, necrosis, neutrophils, cholestasis, Mallory bodies, fibrosis.
- Mallory bodies: characteristic but not specific for alcoholic liver disease.
- Hepatic encephalopathy: ammonia + shunting + brain edema.
- Acetaminophen: most common drug causing acute liver failure in the slides.