Hepatology Overview: Essential Knowledge for PA/Medical Students

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March 2026

Hepatology Overview: A Student Handout for PA/Medical Students

Learning Objectives

By the end of this session, you should be able to: 1. **Recognize** the major etiologies of chronic liver disease and their distinguishing features 2. **Interpret** liver function tests (LFTs) and hepatic synthetic markers 3. **Use** non-invasive fibrosis assessment tools (FIB-4, VCTE, MRE) to stage liver disease 4. **Explain** the pathophysiology of major complications (portal hypertension, ascites, hepatic encephalopathy) 5. **Discuss** evidence-based management of chronic liver disease 6. **Identify** when to refer patients to specialist hepatology care 7. **Understand** the role of newer medications (e.g., resmetirom for NASH) in modern hepatology

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Why This Matters for You

- **Liver disease prevalence:** ~30% of U.S. adults have hepatic steatosis; ~2% have cirrhosis
- **Growing burden:** Obesity, diabetes, alcohol, viral hepatitis ☐ increasing liver disease rates
- **Your role:** Early recognition, risk stratification, timely referral to hepatology
- **Multidisciplinary care:** Nephrologists manage kidney dysfunction in cirrhosis; cardiologists manage HFpEF in NASH; you need to understand the full context

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The Diagnostic Approach: Laboratory Assessment First

Liver Function Tests (LFTs) — What They Tell You

Marker	Source	Elevation Pattern	Clinical Meaning
ALT (Alanine aminotransferase)	Hepatocyte cytoplasm	Mild-moderate ☐	Hepatocellular injury (viral, autoimmune, toxin)

Marker	Source	Elevation Pattern	Clinical Meaning
AST (Aspartate aminotrans-ferase)	Hepatocyte mitochondria + cytoplasm	Variable	Hepatocellular injury; AST:ALT >2 ☐ alcoholic liver disease
ALP (Alkaline phosphatase)	Bile duct epithelium	☐	Cholestatic or infiltrative disease
GGT (Gamma-glutamyl transferase)	Bile duct epithelium	☐ with ALP	Confirms hepatic origin of ALP elevation
Total Bilirubin	Liver metabolism/excretion	☐	Impaired clearance or cholestasis
Direct Bilirubin	Liver conjugation	☐	Intrahepatic or extrahepatic cholestasis
Albumin	**Synthetic function**	☐	Advanced cirrhosis; poor prognosis
INR/PT	**Synthetic function**	☐ (prolonged)	Impaired clotting factor synthesis; cirrhosis

Key Pattern Recognition

Hepatocellular Pattern (ALT/AST ☐☐, ALP mild ☐): - Viral hepatitis, autoimmune hepatitis, drug-induced injury, alcoholic hepatitis - ALT usually >AST (except in alcoholic hepatitis where AST:ALT >1.5)

Cholestatic Pattern (ALP/GGT ☐☐, ALT/AST mild ☐): - Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), drug toxicity, pregnancy - ALP ☐ confirmed by GGT

Mixed Pattern (Both ☐☐): - Acute hepatitis, infiltrative disease, cirrhosis

Synthetic Dysfunction (☐ Albumin, ☐ INR): - Indicates advanced disease: Cirrhosis or fulminant hepatic failure - Normal LFTs with low albumin/☐ INR = cirrhosis until proven otherwise

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Major Etiologies of Chronic Liver Disease

1. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Formerly NAFLD; new name emphasizes metabolic etiology, not absence of alcohol

Epidemiology: - Most common liver disease globally (~30% of adults) - Linked to obesity (BMI ≥25), diabetes, hypertension, dyslipidemia

Pathophysiology: - Hepatic triglyceride accumulation (>5% of liver weight) - Steatohepatitis (MASH) = steatosis + inflammation + fibrosis - Risk: Progression to cirrhosis in 15-20% over 10 years

Diagnosis: - Imaging (ultrasound, CT, MRI) showing steatosis - ≥1 cardiometabolic risk factor - Exclusion of other liver diseases

Risk Stratification: - **FIB-4 score** = (Age × AST) / (Platelets × √ALT) - FIB-4 <1.3 (or <2.0 if age >65): Low risk - FIB-4 1.3-2.67: Intermediate; needs second-line testing - FIB-4 >2.67: High risk; likely advanced fibrosis - **VCTE (FibroScan):** <8 kPa = low risk; >12 kPa = high risk - **MRE:** Most accurate non-invasive method; thresholds 3.0-5.0 kPa by fibrosis stage

Management: - **Weight loss:** 7-10% for improvement; >10% for regression - **Exercise:** 150 min moderate-intensity weekly - **Diet:** Mediterranean or low-carbohydrate patterns - **Medications:** Resmetirom (recently FDA approved for MASH with F1B-F3 fibrosis)

Resmetirom (Rezdiffra) — New Game-Changer: - **Mechanism:** Selective thyroid hormone receptor-β (THR-β) agonist - **Effect:** Enhances fatty acid oxidation; decreases steatosis; improves fibrosis - **MAESTRO-NASH trial:** 26-30% achieved NASH resolution + fibrosis improvement (vs. 9-14% placebo) - **Side effects:** Diarrhea (30%), nausea (20%), abdominal pain (15%) — mostly mild, transient - **Starting dose:** 80 mg daily; can titrate to 100 mg - **Indication:** F1B-F3 fibrosis (biopsy-confirmed NASH)

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2. Alcoholic Liver Disease (ALD)

Epidemiology: - Second most common cause of cirrhosis (after MASLD) - Requires heavy alcohol use (typically >60 g/day for men, >40 g/day for women, for years) - Risk of cirrhosis: ~10-15% of heavy drinkers

Spectrum: - **Fatty liver:** Usually reversible with abstinence - **Alcoholic hepatitis:** Acute inflammation; mortality 30-40% if severe - **Cirrhosis:** Advanced, often irreversible; high decompensation risk

Key Laboratory Finding: - **AST:ALT ratio >2.0** (AST elevated more than ALT, unlike viral hepatitis) - AST typically <300 U/L (higher values suggest ATN or other cause)

Management: - **Alcohol cessation:** Absolute requirement; brief intervention, counseling, pharmacotherapy - **Nutritional support:** BCAA supplementation for sarcopenia - **Corticosteroids:** Considered in severe acute alcoholic hepatitis (MELD >11 or hepatic encephalopathy) - **Liver transplantation:** Available for carefully selected patients (6 months sobriety usually required)

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3. Viral Hepatitis B and C

Hepatitis B (Chronic)

- **Prevalence:** ~296 million chronically infected globally
- **Transmission:** Sexual, vertical, needle-stick, percutaneous
- **Diagnosis:** HBsAg+; HBeAg/HBeAb; HBV DNA quantification
- **Natural history:** 95% of adults clear acute infection; 5-10% chronic
- **Treatment:** Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) — entecavir, tenofovir
- **Cure:** Not achievable; goal is sustained virological response (undetectable HBV DNA)

Hepatitis C (Chronic)

- **Prevalence:** ~58 million chronically infected
- **Major advance:** Direct-acting antivirals (DAAs) with **>95% cure rate**
- **Treatment:** 8-12 week courses of DAA combinations
- **Post-cure:** Monitor for HCC; fibrosis may regress
- **Special scenario:** HCV + HBV coinfection ☐ higher HCC risk; treat both

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4. Autoimmune Liver Diseases

Autoimmune Hepatitis (AIH)

- **Mechanism:** T-cell mediated hepatocyte destruction
- **Diagnosis:** Elevated transaminases + ☐ immunoglobulins (IgG) + positive autoantibodies (ANA, ASMA, anti-LKM)
- **Treatment:** Corticosteroids + azathioprine
- **Prognosis:** Good with treatment; 80% remission rate

Primary Biliary Cholangitis (PBC)

- **Mechanism:** Autoimmune destruction of small bile ducts
- **Diagnosis:** ☐ ALP + ☐ GGT + anti-mitochondrial antibody (AMA)
- **Treatment:** Ursodeoxycholic acid (UDCA); obeticholic acid if inadequate UDCA response
- **Prognosis:** Slow progression; median transplant-free survival 15-20 years

Primary Sclerosing Cholangitis (PSC)

- **Mechanism:** Progressive fibro-obliteration of bile ducts
- **Association:** 70% have inflammatory bowel disease (IBD)
- **Diagnosis:** MRCP showing “beads on string” appearance
- **Treatment:** Limited; UDCA benefits unclear; monitor for cholangiocarcinoma
- **Prognosis:** Variable; 10-15 year median transplant-free survival from diagnosis

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Non-Invasive Assessment of Fibrosis: The Shift Away From Biopsy

Why Non-Invasive Testing?

- **Liver biopsy:** Invasive, painful, risk of bleeding, sampling error (small sample ≠ whole liver)
- **Non-invasive methods:** Accurate, repeatable, safe, cheaper than biopsy

FIB-4 Index (Calculation & Interpretation)

Formula: FIB-4 = (Age × AST) / (Platelet count × √ALT)

Interpretation (HCV population): - **FIB-4 <1.3:** Low probability advanced fibrosis; NPV 95% (if negative, unlikely F3-F4) - **FIB-4 1.3-2.67:** Intermediate; need second-line test (elastography, biomarkers) - **FIB-4 >2.67:** High probability advanced fibrosis; PPV 65%

Age-Adjusted Thresholds (for age >65): - Use threshold 2.0 (low risk) and 3.25 (high risk) to reduce false positives

Advantages: Free, requires only routine labs, widely validated **Limitations:** Less accurate in cirrhosis; affected by inflammation, hemolysis

Vibration-Controlled Transient Elastography (VCTE / FibroScan)

What It Does: - Measures **liver stiffness** via shear wave propagation - Stiff liver (fibrosis/cirrhosis) = faster wave travel = higher reading

Interpretation (kPa): - **<8 kPa:** No significant fibrosis (F0-F1) - **8-12 kPa:** Intermediate; need additional testing - **>12 kPa:** Likely advanced fibrosis or cirrhosis

Advantages: - Point-of-care; rapid; operator-dependent but reproducible with experience - Can be repeated serially to track progression

Limitations: - Fails in obesity (BMI >30) — XL probe helps but still limited - Affected by inflammation, congestion, ascites - No direct visualization of anatomy

Magnetic Resonance Elastography (MRE)

Advantages: - **Most accurate** non-invasive method for fibrosis - Not affected by obesity, operator, inflammation as much - Measures stiffness over entire liver

Interpretation (Standardized Cutoffs): - **<3.0 kPa:** F0 (no fibrosis) - **3.0-3.5 kPa:** F1 (mild) - **3.5-4.0 kPa:** F2 (significant) - **4.0-5.0 kPa:** F3 (advanced) - **>5.0 kPa:** F4 (cirrhosis)

Limitations: - Expensive; not universally available; requires MRI (contraindications possible) - Longer acquisition time

Biomarker Panels

FIB-4: Discussed above; free **NAFLD Fibrosis Score (NFS):** Age, BMI, diabetes, AST:ALT ratio, platelets, albumin **Enhanced Liver Fibrosis (ELF):** Proprietary blood test measuring hyaluronic acid, TIMP-1, PIIINP **APRI:** AST-to-platelet ratio; simple but lower performance

Combination Algorithms: - **Agile 3+:** VCTE + clinical parameters for F3 detection - **Agile 4:** Optimized for cirrhosis (F4) detection - **MEFIB:** MRE + FIB-4 score for enhanced accuracy

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Portal Hypertension: The Complication Hub

Pathophysiology

- **Cirrhosis ☐ structural resistance to blood flow** through liver
- **Portal pressure rises** (normally <12 mmHg; cirrhosis often >15-20 mmHg)
- **Splanchnic vasodilation ☐ portosystemic shunts form ☐** blood bypasses liver
- **Cascade of complications:** Variceal bleeding, ascites, hepatic encephalopathy, HRS

Non-Invasive Assessment of Portal Hypertension

Baveno VII Criteria: Risk stratify to avoid unnecessary endoscopy

Criteria for LOW variceal bleeding risk (no endoscopy needed): - Platelet count >150,000 - VCTE <20 kPa - If both met: Variceal bleeding risk <5%; can avoid screening endoscopy

Criteria for HIGH risk (endoscopy recommended): - Platelet count ≤150,000 OR VCTE ≥20 kPa - Proceed to upper endoscopy for variceal assessment

Major Complications

1. Variceal Bleeding: - First bleed mortality: 15-20% - Prophylaxis: Beta-blockers reduce bleeding risk by ~40% - Acute treatment: Endoscopic variceal ligation (EVL) >90% success

2. Ascites: - Define as fluid accumulation in peritoneal cavity - Grade 1: Ultrasound only - Grade 2: Mild physical examination findings - Grade 3: Clinically apparent; impairs respiratory function - Management: Sodium restriction (<2 g/day) + diuretics (spironolactone, furosemide)

3. Hepatic Encephalopathy: - Neuropsychiatric dysfunction from portal hypertension + liver failure - Grades 1-4 (subtle confusion ☐ deep coma) - Treatment: Lactulose (osmotic laxative), rifaximin (non-absorbed antibiotic)

4. Spontaneous Bacterial Peritonitis (SBP): - Bacterial infection of ascites without source - Diagnosis: >250 PMN/μL in ascitic fluid culture positive - Treatment: Third-generation cephalosporin (ceftriaxone) - Prophylaxis: Norfloxacin in high-risk patients

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Management Principles: General Approach

Etiology-Specific Therapy

- **Viral hepatitis:** Antivirals (DAA for HCV, NRTIs for HBV)
- **Autoimmune:** Immunosuppression
- **MASLD:** Weight loss, medications (resmetirom)
- **Alcoholic:** Abstinence, nutritional support

Universal Recommendations

- **Lifestyle:** Alcohol cessation, weight loss, exercise, Mediterranean diet
- **Vaccination:** Hepatitis A & B (if non-immune), influenza, pneumococcal, COVID-19
- **Surveillance:** HCC screening (ultrasound ± AFP every 6 months if cirrhosis)
- **Medication safety:** Avoid hepatotoxins (acetaminophen >2 g/day in cirrhosis, NSAIDs)

Monitoring for Decompensation

- Regular assessment for ascites, encephalopathy, bleeding
- Serial albumin, INR, bilirubin (synthetic function)
- MELD score tracking (predicts transplant need)
- FIB-4 or VCTE annually to track fibrosis progression

Referral Criteria: When to Send to Hepatology

Refer immediately if: - **Cirrhosis diagnosed** (any etiology) - **Evidence of portal hypertension** (ascites, varices, splenomegaly, platelet <100) - **Hepatic encephalopathy** present - **Child-Pugh B or C** class cirrhosis - **MELD score >15** (likely transplant candidate)

Refer semi-urgently (weeks) if: - **Advanced fibrosis** (FIB-4 >2.67 or VCTE >12 kPa) without cirrhosis - **Significant ALT/AST elevation** without clear etiology - **Chronic viral hepatitis** needing antiviral therapy - **Autoimmune hepatitis** suspected

Refer electively (routine referral) if: - **MASLD** with obesity/metabolic risk factors requiring risk stratification - **Recent HCV diagnosis** (for DAA therapy evaluation) - **Compensated cirrhosis** for baseline assessment/surveillance planning

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Key Clinical Pearls

1. **AST:ALT ratio is your friend.** >2:1 with AST <300 = alcoholic liver disease. Think alcohol use disorder.
2. **FIB-4 is free and powerful.** Use it as a first-line tool to identify high-risk patients needing further workup.
3. **Liver biopsy is rarely needed today.** Non-invasive tests (FIB-4, VCTE, MRE) are accurate and safe. Biopsy is reserved for diagnostic uncertainty.
4. **MASLD is not benign.** It's the most common liver disease globally and a leading cause of HCC. Risk-stratify appropriately.
5. **Resmetirom changes the game for NASH.** First medication approved specifically for MASH with fibrosis; solid efficacy in trials.
6. **Portal hypertension drives complications.** Once VCTE >20 kPa or platelets drop, expect varices, ascites, encephalopathy. Screen and prevent.
7. **Early recognition saves lives.** Many cirrhotic patients present after variceal bleed or encephalopathy. Earlier referral for endoscopy/imaging could prevent this.
8. **Transplant evaluation is timely intervention.** MELD >15 or decompensation = likely transplant candidate. Don't miss the window.

Summary Table: Major Liver Diseases at a Glance

Disease	Epidemiology	Key Lab Finding	Diagnosis	Treatment Goal
MASLD	30% population; obesity/DM	☐ ALP, normal LFTs early	Imaging + risk factors	Weight loss; resmetirom for MASH

Disease	Epidemiology	Key Lab Finding	Diagnosis	Treatment Goal
Alcoholic LD	2% population; heavy EtOH use	AST:ALT >2, AST <300	Clinical hx; exclude others	Abstinence; transplant if severe
HBV	296M globally; sexual/vertical	HBsAg+; HBV DNA	Serology; HBV DNA quantitation	NRTI therapy; suppress replication
HCV	58M globally; IVDU/transfusion	Anti-HCV+; HCV RNA	Serology; HCV RNA quantitation	DAA therapy; cure (>95%)
AIH	1:100,000; autoimmune	☐☐ ALT/AST; ☐ IgG; ANA+	Serology; biopsy if uncertain	Corticosteroids; remission
PBC	40:100,000; women; autoimmune	☐☐ ALP/GGT; AMA+	Serology; imaging	UDCA; obeticholic acid
PSC	15:100,000; associated IBD	☐☐ ALP/GGT; MRCP	MRCP imaging	Limited; monitor for CCA

Practice Questions

Question 1: Laboratory Interpretation

A 55-year-old man with no prior liver disease presents with ALT 280, AST 140, ALP 95, bilirubin 1.2, albumin 3.8, INR 1.0. Ultrasound shows steatosis without cirrhosis.

Most likely diagnosis?

A. Hepatitis C B. Alcoholic liver disease C. Metabolic dysfunction-associated steatotic liver disease (MASLD) D. Primary biliary cholangitis

Answer: C. **ALT>AST pattern with mild-moderate elevation, normal synthetic markers, steatosis on imaging, no jaundice = MASLD.** In alcoholic liver disease, AST:ALT would be >2. HCV typically causes lower transaminase elevations. PBC would show high ALP. This is straightforward MASLD.

Question 2: Risk Stratification

A 62-year-old woman with MASLD (steatosis on imaging, BMI 32, hypertension) has labs: age 62, AST 48, ALT 65, platelet 240.

Calculate her FIB-4 index and interpret risk:

FIB-4 = (62 × 48) / (240 × √65) = 2976 / (240 × 8.06) = 2976 / 1934 = **1.54**

Interpretation?

A. Low risk; no further workup needed B. Intermediate risk; needs VCTE or MRE C. High risk; likely cirrhosis D. Very high risk; immediate transplant evaluation

Answer: B. FIB-4 = 1.54 = **Intermediate risk (falls between 1.3-2.67).** This patient needs second-line testing (VCTE or MRE) to better characterize her fibrosis stage. She's not high-risk yet, but not low-risk either. Don't stop at FIB-4; continue workup.

Question 3: Clinical Management

A 50-year-old with compensated cirrhosis (VCTE 18 kPa, platelet 160) is found to have esophageal varices (not bleeding). No ascites or encephalopathy.

Best management:

A. Upper endoscopy with variceal ligation (EVL) B. Observe; no intervention needed C. Start beta-blocker (propranolol or carvedilol) D. Immediate hospitalization; prepare for blood transfusion

Answer: C or A (both are correct depending on context). **At minimum, start beta-blocker prophylaxis** (reduces first-bleed risk ~40%). **EVL is also indicated** for documented varices in high-risk patients or as elective prophylaxis. Optimal is both: beta-blocker + EVL. Observation alone is inadequate; this patient needs intervention. No bleeding yet, so hospitalization not needed.

References & Further Reading

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Created for PA/Medical Student Education in Hepatology. Last updated February 2026.