Chapter 19
Approach to Abnormal Liver Blood Tests

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Learning Objectives

1. Implement a systematic approach to the interpretation of abnormal liver blood tests.
2. Describe the workup of liver test abnormalities, including indications for liver biopsy.
3. Describe worrisome liver blood test results that require urgent evaluation.

Clinical Vignette: An asymptomatic 50-year-old woman presents to clinic for a new patient evaluation. She brings in laboratory results obtained a few months ago from another provider, including liver blood tests notable for elevated aspartate aminotransferase (AST) of 45 international units (IU)/L (reference range 9–38 U/L) and an alanine aminotransferase (ALT) of 60 international units/L (reference range 7–33 U/L). Alkaline phosphatase (alk phos) is within the normal range at 100 international units/L (reference range 34–121 U/L). Total bilirubin and gamma-glutamyltransferase (GGT) are normal.

A. **To understand the significance of her abnormal liver blood test results, it is useful to review the important functional units of the liver: the liver lobule and portal triad. What are the components of each?**

Draw the schematic of the liver lobule and the portal triad, labeling the components as they are named.

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Teaching points

- Venous blood from the gut flows to the liver from the portal vein.
- Oxygenated blood flows to the liver through the hepatic artery.
- These two sources of blood mix in the sinusoid and drain to the central vein, which drains to the IVC.
- Conjugated bilirubin travels from the hepatocytes toward the portal triad and exits the liver via the bile ducts.

B. **What is the source of the "liver function test (LFT)" results given above (AST, ALT, alkaline phosphatase, bilirubin, GGT)?**

List the lab values to the right and draw arrows to indicate their source. Key teaching points are tabulated below for reference (the table does not need to be reproduced on the white board). Add albumin and INR to the list of labs if they are not mentioned by the learners.

Teaching points

Lab	Notes		Significance
AST	Also called "transaminases," "aminotransferases," or "liver enzymes" Intracellular enzymes that convert amino acids into high-energy molecules	90% from liver Also found in skeletal muscle, heart, brain, gastric mucosa, kidney, pancreas, spleen, lung, red blood cells	Released from injured hepatocytes
ALT		Almost 100% from liver Very small amounts come from kidney and muscle	
Alk Phos	Found in liver, bone, gut, and placenta In the liver, it is produced by the canalicular membrane (hepatocytes next to bile canaliculi). Alk phos production is induced by high levels of bile acids.		Bile duct obstruction or hepatocyte injury
GGT	Active in biliary epithelial cells. More specific to the liver than alk phos. Supports a hepatic source of the elevated alk phos (as opposed to bone or other source).		Bile duct dysfunction
Bilirubin	Produced by the breakdown of hemoglobin. Conjugated in the hepatocyte. After conjugation, bilirubin is called "direct bilirubin".		Bile duct obstruction or hepatocyte injury
Albumin, INR	Albumin and clotting factors are proteins synthesized in the liver. Albumin production is inhibited by physiologic stress and advanced liver disease. Most of the body's clotting factors (II, V, VII, IX, X, XI, and XII) are made by the liver. A rise in INR reflects deficient production of at least one of the extrinsic cofactors (or vitamin K deficiency).		Decreased hepatic synthetic ability

C. **While we often refer to "liver function tests," not all of these labs actually reflect liver function. Which of these labs actually reflect liver function?**

Put a box around albumin and INR.

D. **It is useful to think of liver blood test abnormalities as being "cholestatic" (primarily a bile duct problem) or "hepatocellular" (primarily a hepatocyte problem). Our patient has a mild elevation in AST and ALT—how would you categorize her liver test abnormalities? What is your differential diagnosis?**

Complete the "hepatocellular" side of abnormal liver tests.

Teaching points

- There are many causes of drug-induced liver injury; Livertox.nih.gov is a useful resource for both hepatocellular and cholestatic causes.
- Common drugs include trimethoprim-sulfamethoxazole, isoniazid, methotrexate, valproic acid, herbal supplements (e.g., body-building products, green tea extract)
- Iron overload = hemochromatosis, copper overload = Wilson disease
- A few etiologies can cause severe elevations in transaminases with ALT and AST >1000. Examples include:
  - Hypotension/shock
  - Toxic ingestion (e.g., acetaminophen overdose, amanita phalloides ["death cap"] mushroom poisoning)
  - Acute infection
  - Acute Budd–Chiari syndrome
  - Flares of autoimmune hepatitis
  - HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome

E. **An elevated bilirubin and alkaline phosphatase would be more characteristic of cholestatic injury. What are some of the main causes of cholestatic liver injury?**

Complete the "cholestatic" side of abnormal liver tests.

Teaching points

- There are many causes of drug-induced liver injury. A few classic culprits include amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, and amiodarone.
- PBC = primary biliary cholangitis, PSC = primary sclerosing cholangitis.
- Cholelithiasis may cause isolated elevated alkaline phosphatase unless also associated with bile duct obstruction.

F. **Our patient is asymptomatic, does not take any medications or supplements, and does not drink alcohol. Her liver tests are repeated and the results are unchanged from previous. What labs or diagnostic studies should we send to work up her mild aminotransferase elevation?**

Add check marks next to the items on the differential diagnosis that you're are going to test the patient for.

- Viral hepatitis (hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody), hemochromatosis (iron, ferritin, transferrin saturation).
- If these are normal: ultrasound to look for fatty infiltration, masses, or obstruction.
- In a patient with suggestive risk factors or symptoms, consider selective workup for rarer causes such as autoimmune hepatitis (antinuclear antibody, antismooth muscle antibody, serum immunoglobulin levels), Wilson disease (ceruloplasmin level), alpha-1 antitrypsin deficiency (alapha-1-antitrypsin level), thyroid dysfunction (thyroid-stimulating hormone), or celiac disease (tissue transglutaminase).

G. **If our patient had an isolated elevated alkaline phosphatase on labs, what labs or studies should we send?**

Write out the algorithm shown in Fig. 19.1.

Teaching points

- First, check GGT to confirm hepatic source of alkaline phosphatase.
- If GGT is elevated, evaluate for hepatic sources with an ultrasound. If biliary obstruction or mass is seen:
  - Obtain additional imaging with computed tomography (CT) or magnetic resonance imaging (MRI).
  - Consider endoscopic retrograde cholangiopancreatogram (ERCP) or magnetic resonance cholangiopancreatography (MRCP) if signs of biliary tract disease.
  - For masses without obvious source, check alpha-fetoprotein (AFP), CA 19-9, carcinoembryonic antigen (CEA), and consider biopsy of the mass.
- If no evidence of biliary obstruction:
  - Exclude primary biliary cholangitis (check antimitochondrial antibody).
  - Exclude hepatocellular carcinoma (check liver protocol CT or MRI, and AFP).
  - Consider liver biopsy if suspicion for infiltrative disease persists.
  - Consider need for MRCP if clinical suspicion for ductal abnormality persists.

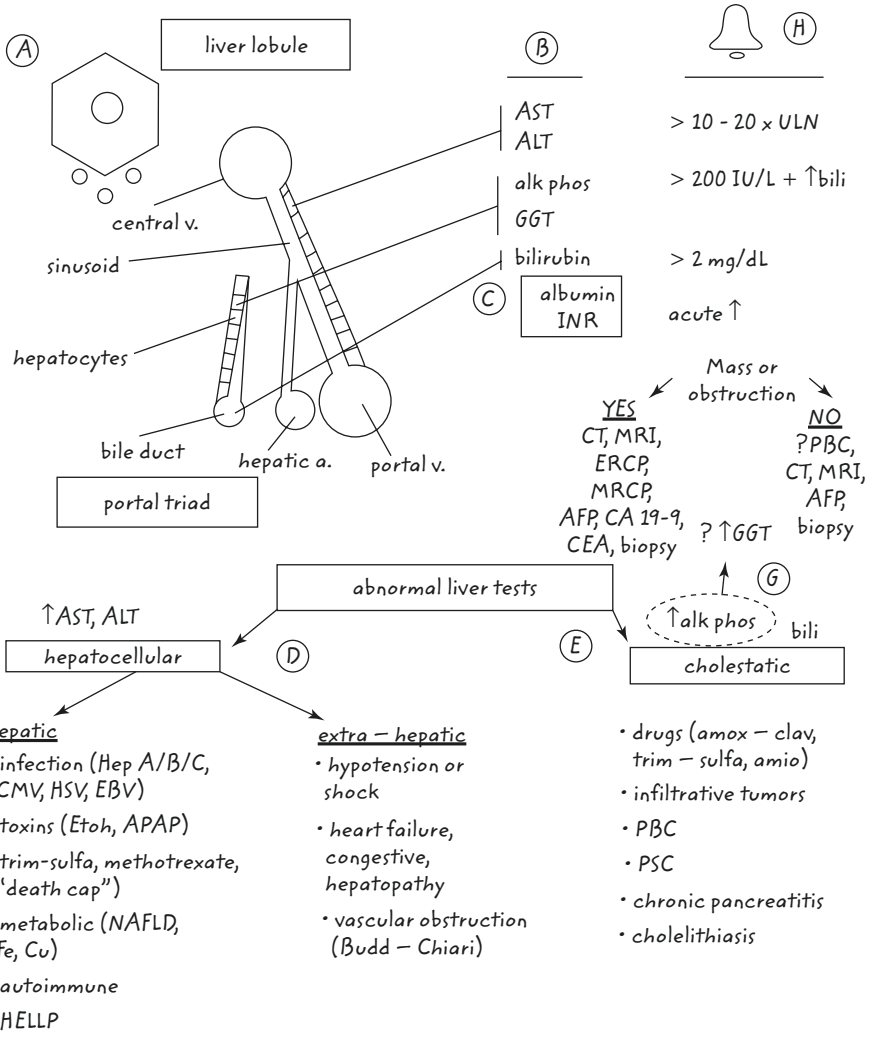

Fig. 19.1 Approach to abnormal liver blood tests, A–H

H. **Keeping in mind that acute changes in labs or symptoms are generally more worrisome than chronic laboratory abnormalities, what lab abnormalities should prompt an urgent evaluation?**

Fill out the alarming lab levels as shown in Fig. 19.1.

Teaching points

- Patients with severe liver test abnormalities often require hospitalization, especially if there are also clinical signs of decompensation (e.g., new encephalopathy, new ascites, gastrointestinal bleeding).
- Examples of situations where you would likely monitor closely with serial labs:
  - AST, ALT >10–20 times the upper limit of normal but no other liver test abnormalities, and no concerning symptoms
  - Total bilirubin >2 mg/dL in the setting of new medications, and no concerning symptoms
- Examples of situations where you would almost always hospitalize the patient:
  - Alk phos >200 IU/L with newly elevated total bilirubin, +/− fever or chills (i.e., acute cholangitis)
  - AST, ALT >10–20 times the upper limited of normal, plus newly elevated INR or total bilirubin
  - INR >1.5, newly elevated total bilirubin, new encephalopathy (i.e., acute liver failure). Patients like this ideally should be transferred to a facility capable of performing liver transplantation.

Return to objectives and emphasize key points

1. Identify which LFT abnormalities reflect liver injury rather than true dysfunction
   - Liver injury—AST, ALT, bilirubin, alk phos
   - Liver dysfunction—albumin and clotting factors
2. Distinguish between hepatocellular and cholestatic patterns of injury and highlight some of the common causes of each
   - Hepatocellular—Hepatitis A/B/C, alcohol, fatty infiltration, iron overload
   - Cholestatic—cholelithiasis, infiltrative tumors, PBC
3. Highlight worrisome liver blood test results that require urgent evaluation
   - Liver test abnormalities in the setting of new symptoms of hepatic decompensation
   - AST, ALT >10–20 times the upper limit of normal
   - Acute increase in total bilirubin >2 mg/dL, especially in the setting of new medications or additional symptoms
   - Alk phos >200 IU/L with elevated total bilirubin, +/− fever or chills (i.e., acute cholangitis)
   - INR >1.5, acutely elevated total bilirubin, new encephalopathy (i.e., acute liver failure)

Resources

1. American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of liver chemistry tests. Gastroenterology. 2002;123(4):1364–6.
2. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112(1):18–35.
3. Livertox.nih.gov.