

Liver Diagnostic Tests

Steven K. Herrine, MD

Educational Goals

1. Understand the significance of the following blood tests: total bilirubin, direct bilirubin, alkaline phosphatase, aminotransferases, albumin, prothrombin time
2. Differentiate the test result patterns of hepatocellular, cholestatic and infiltrative liver disorders
3. Using history, physical and laboratory tests, generate a differential diagnosis of a patient's liver disorder

Key Words

- o alanine aminotransferase (ALT)
- o albumin
- o alkaline Phosphatase
- o ascites
- o aspartate aminotransferase (AST)
- o AST/ALT ratio
- o asterixis
- o bilirubin
- o cholestasis
- o conjugated bilirubin
- o Crigler-Najjar syndrome
- o direct bilirubin
- o Dubin-Johnson syndrome
- o Dupuytren's contracture
- o excoriations
- o extrahepatic biliary obstruction
- o fetor hepaticus
- o gamma glutamyltranspeptidase (GGT)
- o Gilbert's syndrome
- o gynecomastia
- o hemolytic anemia
- o hepatic infiltration
- o Indirect bilirubin
- o international normalized ratio (INR)
- o intrahepatic cholestasis
- o palmar erythema
- o petechiae
- o Rotor's syndrome
- o scleral icterus
- o spider angiomas
- o splenomegaly
- o testicular atrophy
- o unconjugated bilirubin
- o vitamin K deficiency

I. Background:

Case Presentation:

A 57 year old woman presents with fatigue and low grade fever. Exam is notable for scleral icterus and right upper quadrant abdominal tenderness.

Liver tests:

- Total bilirubin 4.2 mg/dL
- Direct bilirubin 3.3 mg/dL
- Alkaline phosphatase 160 U/L
- AST 640 U/L
- ALT 880 U/L
- Albumin 3.6 g/dL
- INR 1.1

The goal of this section is to present an approach toward the interpretation of liver tests as it pertains to clinical cases. The function of the liver can not be evaluated with any single test. Because of the organ's many functions, including synthesis of proteins, detoxification, immune modulation and bile metabolism, a battery of tests is necessary to form a complete picture. As always, a thorough history and physical is the basis of further testing. A variety of serologic and biochemical tests are available, which may be supplemented by various specialized serum, radiologic and histologic studies.

II. History:

- A. Acute or chronic symptoms (many patients with abnormal liver tests are asymptomatic)
- B. Symptoms of liver disease such as: jaundice, acholic stool, dark urine, pruritus, abdominal pain, fever, rash, fatigue.
- C. Drug and toxin exposure: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), herbal remedies, mushroom poisoning, any new drug use
- D. Past History: previous biliary surgery, blood transfusions
- E. Family history of liver disease
- F. Social history: travel, IVDU, alcohol abuse, tattoos, STDs, new sexual partners

III. Physical examination:

- A. General appearance: muscle wasting, paucity of body hair (axillary, pubic), parotid enlargement, testicular atrophy, gynecomastia
- B. Skin: excoriations, ecchymoses, petechiae, spider angiomas, palmar erythema, pallor, abnormal pigmentation, needle tracks, scarring from skin abscesses or popping, Dupuytren's contractures, peripheral edema
- C. HEENT: Scleral icterus, Kayser-Fleischer rings
- D. Abdomen: Liver tenderness, enlargement, firmness; ascites; splenomegaly; prominent abdominal collateral vessels
- E. Neuropsychiatric: Confusion, depression, memory loss, inappropriate or unusual behavior, asterixis, fetor hepaticus

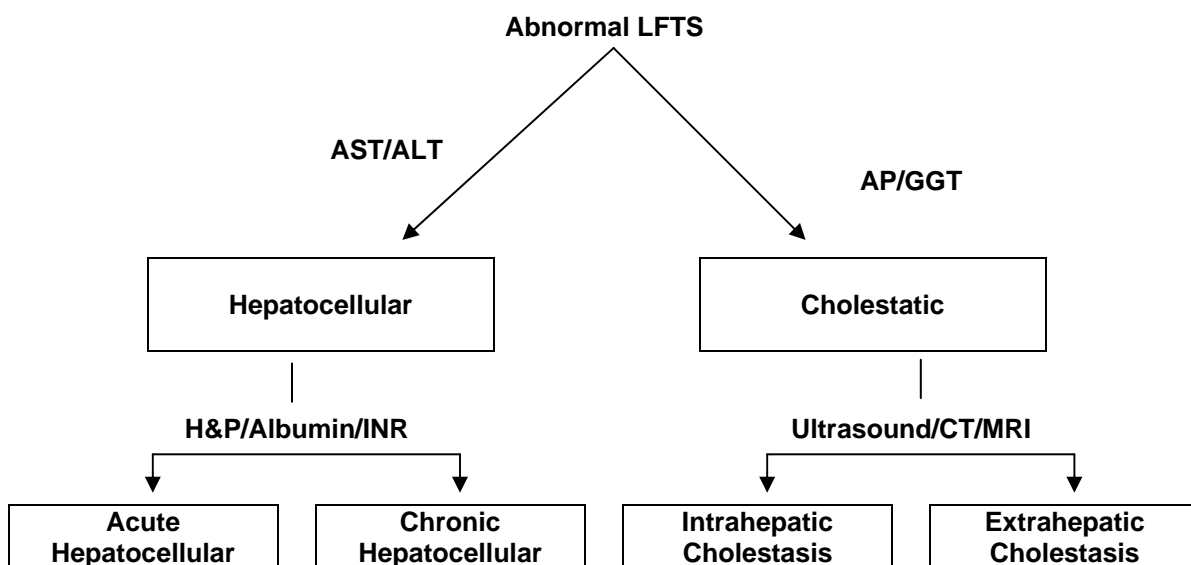
IV. Standard Liver Profile:

- A. Often referred to as "liver function tests," or simply, "LFTs." Interpretation of these tests, especially their pattern, will narrow the differential diagnosis and allow more refined diagnostic procedures.
 1. Total/Direct Bilirubin (TB/DB): These two values are measured directly in the laboratory. The difference between the two values is termed the indirect bilirubin.
 2. Alkaline Phosphatase (AP)
 3. Aspartate Aminotransferase (AST): formerly known as SGOT
 4. Alanine Aminotransferase (ALT): formerly known as SGPT
 5. Gamma Glutamyltransferase (GGT)
 6. Albumin
 7. International Normalized Ratio (INR): a standardized value of prothrombin time
- B. Bilirubin: a relative index of the efficiency of hepatic capacity for transport and metabolism. Jaundice is often the first clinical sign detected in patients with liver disease and becomes clinically apparent when the serum bilirubin exceeds 3 mg/dL (normal 0.2-1.0 mg/dL). A review of bilirubin metabolism is beyond the scope of this lecture, but review of the cycle may add to the students understanding of the disorders to be discussed. Total bilirubin is composed of unconjugated (indirect) bilirubin and conjugated (direct) bilirubin.
 1. Unconjugated hyperbilirubinemia: diagnosed if more than 80% of an elevated total bilirubin is indirect. Elevation results from either increased bilirubin production outstripping the liver capacity to conjugate bilirubin, or reduced hepatic ability to conjugate bilirubin
 - a. Increased bilirubin production
 - Hemolytic anemias (bilirubin rarely > 4 mg/dL)
 - Hematoma
 - Ineffective erythropoiesis (thalassemia, pernicious anemia)
 - Neonatal (physiologic) jaundice
 - b. Reduced or absent glucuronosyltransferase activity

- Gilbert's syndrome: this is common in young men. Often runs in families
 - Crigler-Najjar syndromes (Types I & II): rare syndromes
 - Neonatal (physiologic) jaundice
2. Conjugated hyperbilirubinemia: diagnosed if more than 50% of the elevated bilirubin is direct. Elevation results from either impaired hepatic secretion or decreased hepatic uptake of conjugated bilirubin
 - a. Impaired biliary secretion
 - Extrahepatic obstruction – (e.g. stones, tumors, stricture)
 - Intrahepatic hepatocellular, canalicular, or ductular damage
 - Dubin-Johnson syndrome
 - Rotor's syndrome (rare)
- C. Aminotransferases: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT): These enzymes involved in the transfer of amino groups to ketoglutaric acid. AST and ALT are elevated in syndromes of hepatocellular injury. Aminotransferase elevation is often the first biochemical abnormality detected in a patient with viral, drug-induced or alcoholic hepatitis. Normal range varies by laboratory but is generally 0 - 35 U/L.
1. Aspartate Aminotransferase (AST): Present in liver tissue, but also in heart, skeletal muscle, kidney and brain, pancreas, lungs, leukocytes, and erythrocytes. Not specific for liver disease
 2. Alanine Aminotransferase (ALT): Present almost exclusively in liver tissue: more specific for liver disease
 3. Patterns of transaminase elevation
 - a. ALT > 1000 U/L: a limited differential diagnosis
 - Acute viral hepatitis
 - Drug toxicity (especially acetaminophen)
 - Shock liver (result of hypotensive episode)
 - Autoimmune hepatitis
 - b. AST/ALT ratio > 2: sensitive but not specific for alcoholic hepatitis. It should be noted, however, that aminotransferases are rarely elevated greater than ten times the upper limit of normal in alcoholic liver disease
 - c. ALT predominance
 - Chronic viral hepatitis
 - Nonalcoholic fatty liver disease (NAFLD)
 - Metabolic diseases (Hemochromatosis, Wilson's disease, Alpha-1-antitrypsin deficiency)
 - Medications
 - Autoimmune hepatitis
- D. Alkaline phosphatase (AP): Present in liver, bone, intestine, kidney, placenta. 80% of circulating AP is in liver and bone. If gamma-glutamyltransferase (GGT) is also elevated, the elevation is attributable to liver disease. Measurement of AP isoenzymes is sometimes used to determine the origin of increased serum values. In liver disease, AP elevation connotes cholestasis (intrahepatic or extrahepatic obstruction to the flow of bile) or infiltration of the liver parenchyma.
1. Extrahepatic biliary obstruction: Synthesis of AP by biliary epithelial cells is increased, leading to serum elevation. Imaging by ultrasound, CT or MRI will demonstrate biliary dilatation
 - a. Gallstones
 - b. Tumor (pancreas, ampulla of Vater, bile duct, lymph nodes)
 - c. Stricture, especially primary sclerosing cholangitis (PSC)

- d. Inadvertent surgical ligation of biliary structures
- 2. Intrahepatic cholestasis: Dysfunction of bile transport due to acute or chronic injury
 - a. Primary biliary cirrhosis (PBC: autoimmune destruction of microscopic bile ducts)
 - b. Medication-induced
 - c. Congenital ductopenic syndromes (rare)
- 3. Infiltrative disorders
 - a. Granulomatous hepatitis (sarcoidosis, mycobacterial)
 - b. Malignant infiltration, especially lymphoma
 - c. Amyloidosis
- E. Albumin: major plasma protein, synthesized exclusively by the liver. Albumin can be decreased in any chronic illness, but in the setting of chronic liver disease, decreased serum albumin (normal 3.5-5.5 g/dL) is indicative of severe disease and liver synthetic dysfunction. Other causes of decreased serum albumin include nephrotic syndrome, protein-losing enteropathy and malnutrition.
- F. International Normalized Ratio (INR): A measurement of clotting factor II, prothrombin. An early and sensitive marker of liver synthetic dysfunction
 - 1. Acute liver injury: elevated INR implies a worse prognosis for recovery
 - 2. Chronic liver disease: Elevation of INR, an early sign of liver synthetic dysfunction, implies advanced disease
 - 3. Cholestatic liver disease: INR may be elevated due to malabsorption of fat-soluble Vitamin K.
 - 4. Extensive antibiotic use and malnutrition can lead to Vitamin K deficiency
- G. Approach to the Patient with abnormal liver chemistries
 - 1. History and Physical: Exposures to infectious agents, alcohol use, medications toxicity, complementary remedies, known history of liver disease, family history, etc.
 - 2. Differentiate hepatocellular pattern from cholestatic/infiltrative profile
 - a. If AST/ALT elevation is the predominant abnormality: hepatocellular injury
 - b. If alkaline phosphatase, bilirubin elevation is the predominant abnormality: cholestasis/infiltrative-cross sectional image needed to assess dilatation of biliary system: if non-dilated, intrahepatic cholestasis or infiltrative. If dilated: obstruction
 - c. Further testing as needed to narrow diagnosis. Many of these tests will be discussed later in the course.

Table 1: Interpretation of Abnormal Liver Tests



V. Cases for review:

1. A 42 year old woman presents with RUQ pain, fever and jaundice following a laparoscopic cholecystectomy.

	total bilirubin (mg/dL)	direct bilirubin (mg/dL)	AP (U/L)	AST (U/L)	ALT (U/L)	albumin (g/dL)	INR
normal	0.3-1.0	0.1-0.3	36-92	0-35	0-35	3.5-5.5	0.8-1.2
patient	8.5	5.0	850	75	100	4.0	1.0

Which is the most likely diagnosis?

- A. Acute cholecystitis
- B. Acute viral hepatitis
- C. Ligation of common bile duct
- D. Hemolytic anemia
- E. Pancreatic adenocarcinoma

Which is the best next test?

- A. Exploratory laparotomy
- B. HIDA scan
- C. Liver biopsy
- D. Percutaneous drainage of gallbladder
- E. Ultrasound of the abdomen

2. A 60 year old man with cirrhosis presents with massive ascites and encephalopathy

	total bilirubin (mg/dL)	direct bilirubin (mg/dL)	AP (U/L)	AST (U/L)	ALT (U/L)	albumin (g/dL)	INR
normal	0.3-1.0	0.1-0.3	36-92	0-35	0-35	3.5-5.5	0.8-1.2
patient	1.2	0.5	80	46	58	2.6	1.8

Which is likely cause of his coagulopathy?

- A. Aspirin ingestion
- B. Hepatic synthetic dysfunction
- C. Vitamin K deficiency
- D. Von Willebrand's disease
- E. Warfarin administration

3. A 30 year old graduate student presents with one week of malaise, nausea, RUQ abdominal pain, jaundice and dark urine

	total bilirubin (mg/dL)	direct bilirubin (mg/dL)	AP (U/L)	AST (U/L)	ALT (U/L)	albumin (g/dL)	INR
normal	0.3-1.0	0.1-0.3	36-92	0-35	0-35	3.5-5.5	0.8-1.2
patient	13.6	8.4	250	1783	2135	3.7	1.3

Which is likely diagnosis?

- A. Acute viral hepatitis
- B. Acute cholecystitis
- C. Choledocholithiasis
- D. Hepatic ischemia
- E. Mononucleosis

4. A 65 year old man presents with one month of painless jaundice, back pain and a 30 pound weight loss

	total bilirubin (mg/dL)	direct bilirubin (mg/dL)	AP (U/L)	AST (U/L)	ALT (U/L)	albumin (g/dL)	INR
normal	0.3-1.0	0.1-0.3	36-92	0-35	0-35	3.5-5.5	0.8-1.2
patient	6.8	5.7	1150	56	66	3.3	0.9

Which is the most likely diagnosis?

- Acute cholecystitis
- Acute viral hepatitis
- Ligation of common bile duct
- Hemolytic anemia
- Pancreatic adenocarcinoma

5. A 27 year old man is noted by his family to be jaundiced. Besides fatigue, he feels well.

	total bilirubin (mg/dL)	direct bilirubin (mg/dL)	AP (U/L)	AST (U/L)	ALT (U/L)	albumin (g/dL)	INR
normal	0.3-1.0	0.1-0.3	36-92	0-35	0-35	3.5-5.5	0.8-1.2
patient	4.5	0.4	80	80	25	3.8	0.9

Which is the most likely diagnosis?

- Acute cholecystitis
- Acute viral hepatitis
- Cholelithiasis
- Crigler-Najjar syndrome
- Hemolytic anemia

VI. References

Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ*. 2005;172:367-79.

Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000;342:1266-71.

VII. Answers to practice questions

- C, E. The liver tests are primarily cholestatic, with predominance of alkaline phosphatase and direct bilirubin. Cholestasis may be a result of physical blockage of biliary drainage, intrahepatic bile duct damage or hepatic infiltration. Of the choices, both pancreatic adenocarcinoma (the bile duct traverses the head of the pancreas) and ligation of the bile duct are tenable, but given the history of recent cholecystectomy, inadvertent bile duct ligation is the most likely diagnosis. Cross sectional imaging of the abdomen will be the next test. Choices would include ultrasound, CT or MRI.
- B. The history of advanced liver disease along with the abnormal measures of liver function (albumin, INR) suggest that the coagulopathy seen here is due to liver synthetic dysfunction. Patients in this situation can certainly have otherwise normal liver tests.
- A. Note that although the bilirubin here is quite high, the transaminases are dramatically elevated, indicating hepatocellular injury. The bilirubin elevation and mild increase in alkaline phosphatase do iconnote some cholestasis, but the primary process here is necrosis of hepatocytes. ALT of over 1000 U/L is almost always the product of either (1) viral hepatitis, (2) inchemic injury, or "shock liver", (3) drug hepatotoxicity, most commonly acetaminophen,

and (4) autoimmune hepatitis. Given the lack of history regarding the profound hypotension that could lead to shock liver, the most likely diagnosis is viral hepatitis.

4. E. Note explanation of this liver test pattern for question (1). Given the age of the patient, the weight loss and the lack of information regarding recent bile duct surgery, pancreas cancer is the most likely diagnosis.
5. E. Hyperbilirubinemia is best classified as conjugated (predominance of direct bilirubin) or unconjugated (predominance of indirect bilirubin). In this case, unconjugated bilirubinemia leads to the differential diagnosis of diminished glucuronosyltransferase activity or overproduction of bilirubin breakdown products. This man is too old to present with Crigler-Najjar syndrome, so hemolytic anemia is the most likely diagnosis.