Liver Function Tests

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapters 295 and 296)

Definition

- Biochemical tests useful in evaluation and management of patients with hepatic dysfunction
- Tests that measure detoxification or excretory functions
  - Serum bilirubin
  - Urine bilirubin
  - Blood ammonia
  - Serum enzymes that reflect damage to hepatocytes
    - Aspartate aminotransferase (AST)
    - Alanine aminotransferase (ALT)
  - Serum enzymes that reflect cholestasis
    - Alkaline phosphatase (AP)
    - 5′-nucleotidase
    - Gamma glutamyl transpeptidase (GGT)
- Tests that measure biosynthetic liver function
  - Serum albumin
  - Serum globulins
    - Gamma globulins (immunoglobulins)
    - Alpha globulins
    - Beta globulins
  - Coagulation factors
    - Serum prothrombin time
- Other tests and procedures that may be necessary to make proper diagnosis of liver disease
  - Percutaneous biopsy of the liver
  - Ultrasonography
  - CT scan

Goals

- Detect presence of liver disease.
- Distinguish among different types of liver disorders.
- Gauge extent of known liver damage.
- Follow response to treatment.

Mechanism of Action

Tests of detoxification and excretory functions

- Serum bilirubin
  - Found in blood in two fractions
    - Unconjugated (indirect)
    - Conjugated (direct)

    - In most liver diseases, both conjugated and unconjugated fractions tend to be elevated.
    - Conjugated hyperbilirubinemia almost always implies liver or biliary tract disease.
    - Elevation of unconjugated bilirubin rarely is due to liver disease.
- Urine bilirubin
    - All bilirubin in urine is conjugated.
    - Presence of urine bilirubin implies liver disease.
- Blood ammonia
    - Ammonia is liberated by bacteria in the large intestine or by protein metabolism and is rapidly converted to urea in the liver.
    - In liver disease or portosystemic shunting, the blood ammonia concentration increases.
    - Significant muscle wasting contributes to hyperammonemia in advanced liver disease.
- Aminotransferases
    - Intracellular enzymes involved in amino acid metabolism
    - Released into the blood when there is damage to the liver cell membrane
    - AST is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration.
    - ALT is found primarily in the liver but also in small quantities in kidney, skeletal muscle, and cardiac muscle.
- Alkaline phosphatase, 5′-nucleotidase, and GGT
    - Elevation reflects cholestasis
    - Alkaline phosphatase and 5′-nucleotidase are found in or near the bile canalicular membrane of hepatocytes, while GGT is located in the endoplasmic reticulum and in bile duct epithelial cells.
    - GGT elevation in serum is less specific for cholestasis than are elevations of alkaline phosphatase or 5′-nucleotidase.

Tests that measure biosynthetic liver function

- Serum albumin
    - Synthesized exclusively by hepatocytes
    - Has long half-life: 15–20 days, with approximately 4% degraded per day
    - Because of this slow turnover, the serum albumin is not a good indicator of acute or mild hepatic dysfunction.
- Serum globulins
    - Group of proteins made up of gamma globulins (immunoglobulins) produced by B lymphocytes and alpha and beta globulins produced primarily in hepatocytes
    - Cirrhotic liver fails to clear bacterial antigens that normally reach the liver, causing more antibodies to be made.
- Coagulation factors
    - Made exclusively in hepatocytes (except factor VIII)
    - Serum half-lives are much shorter than albumin, ranging from 6 h for factor VII to 5 days for fibrinogen
    - Because of their rapid turnover, measurement of the clotting factors is the single best acute parameter of hepatic synthetic function
    - Serum prothrombin time
        - Collectively measures factors II, V, VII, and X

Percutaneous biopsy of the liver

- Safe procedure easily performed at bedside with local anesthesia
- Good for disorders causing diffuse changes throughout the liver

- Should not be initial procedure in diagnosis of cholestasis; biliary tree should first be assessed for obstruction.

Ultrasonography

- Used for identification of:
  - Dilated intrahepatic or extrahepatic biliary tree
  - Gallstones
  - Space-occupying lesions within the liver

Indications

- See Figure 1 for workup of chronically abnormal liver tests.

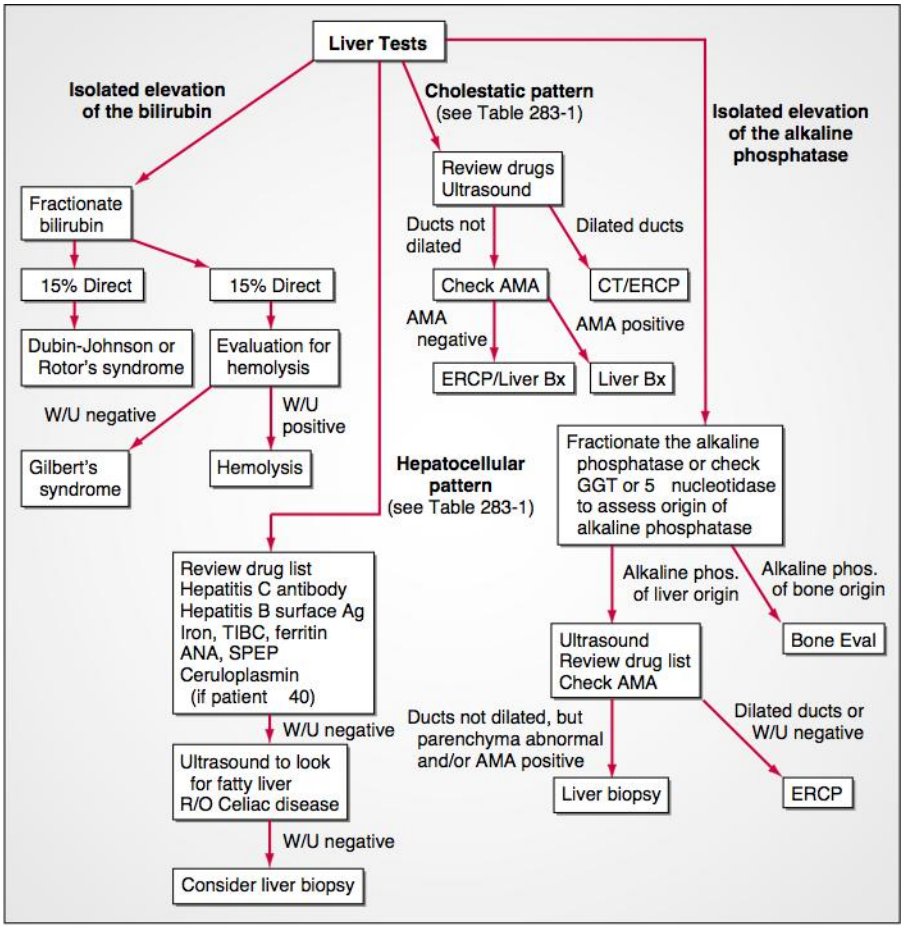

Figure 1: Algorithm for the evaluation of chronically abnormal liver tests. ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; AMA, antimitochondrial antibody; ANA, antinuclear antibody; SPEP, serum protein electrophoresis; TIBC, total iron-binding capacity; GGT, gamma glutamyl transpeptidase.

- Serum bilirubin
  - Normal total serum bilirubin concentration: <17 μmol/L (1 mg/dL)
  - Up to 30%, or 5.1 μmol/L (0.3 mg/dL) of the total is direct-reacting (or conjugated) bilirubin
  - Isolated elevation of unconjugated bilirubin (elevated bilirubin, but <15% direct)
    - Should prompt a workup for hemolysis
    - If otherwise healthy, then Gilbert syndrome; no further workup necessary
- Urine bilirubin
  - Theoretically gives same information as fractionation of serum bilirubin
- Blood ammonia
  - Some physicians use the blood ammonia for detecting encephalopathy or for monitoring hepatic synthetic function; however:
    - There is very poor correlation between either the presence or the degree of acute encephalopathy and elevation of blood ammonia
    - There is poor correlation between the blood serum ammonia and hepatic function.
  - Occasionally useful in identifying occult liver disease in patients with mental status changes
- Aminotransferases (ALT, AST)
  - Most helpful in recognizing acute hepatocellular diseases such as hepatitis
  - Levels ≤300 U/L
    - Nonspecific
  - Levels >1000 U/L exclusive to extensive hepatocellular injury
    - Viral hepatitis
    - Ischemic liver injury (prolonged hypotension or acute heart failure)
    - Toxic or drug-induced liver injury
  - Pattern of elevation helpful diagnostically
  - In most acute hepatocellular disorders
    - Increased ALT more prevalent than increased AST
  - Alcoholic liver disease
    - AST:ALT ratio >2:1 suggestive
    - AST:ALT ratio >3:1 highly suggestive
    - AST rarely >300 U/L
    - Low ALT is due to alcohol-induced deficiency of pyridoxal phosphate
  - Obstructive jaundice
    - AST and ALT usually not greatly elevated
    - Exception: in acute phase of biliary obstruction can be in 1000–2000 U/L range
    - Levels decrease quickly into LFT pattern of cholestasis.
- AP, 5′-nucleotidase, and GGT
  - AP elevations >4×normal in:
    - Cholestatic liver disorders
    - Infiltrative liver diseases (e.g., cancer)
    - Bone conditions characterized by rapid bone turnover (e.g., Paget disease)
  - If elevated AP is only abnormal finding, or if elevation is higher than expected:
    - Measure serum 5′-nucleotidase or GGT (both rarely elevated except in liver disease)
    - Fractionation of AP by electrophoresis
    - Elevated serum AP with a heat-stable fraction strongly suggests placenta or tumor as source
  - Elevated AP of liver origin, in absence of jaundice or elevated aminotransferases suggests:
    - Early cholestasis
    - Hepatic infiltration by tumor or granulomata (less often)

    - Other conditions causing isolated elevations in AP
        - Hodgkin's disease
        - Diabetes
        - Hyperthyroidism
        - Congestive heart failure
        - Inflammatory bowel disease
- Serum albumin
    - <3 g/dL suggests chronic liver disease.
- Serum globulins
    - Gamma globulins are increased in chronic liver disease (e.g., chronic hepatitis, cirrhosis)
        - Increases in concentration of specific isotypes helpful in recognition of certain chronic liver diseases
        - Diffuse polyclonal increases in IgG levels are common in autoimmune hepatitis (increases >100%)
        - Increases in IgM common in primary biliary cirrhosis
        - Increases in IgA occur in alcoholic liver disease
- Coagulation factors
    - Acute assessment of:
        - Hepatic synthetic function
        - Prognosis of acute parenchymal liver disease
    - Serum prothrombin time may be elevated in:
        - Hepatitis
        - Cirrhosis
        - Obstructive jaundice
        - Fat malabsorption of any kind
        - Marked prolongation (>5 sec above control)/not corrected by parenteral vitamin K administration, poor prognostic sign in acute viral hepatitis/other acute and chronic liver diseases
- Percutaneous biopsy of the liver:
    - Should not be initial procedure in diagnosis of cholestasis; first assess biliary tree for obstruction.
    - Of proven value in:
        - Hepatocellular disease of uncertain cause
        - Prolonged hepatitis with the possibility of chronic active hepatitis
        - Unexplained hepatomegaly
        - Unexplained splenomegaly
        - Hepatic filling defects by radiologic imaging
        - Fever of unknown origin
        - Staging of malignant lymphoma
- Ultrasonography
    - First test to use when liver tests suggest cholestasis
    - To look for presence of dilated intrahepatic or extrahepatic biliary tree
    - To identify gallstones
    - To distinguish between cystic and solid masses
    - To help direct cutaneous biopsies
    - First test to order if Budd-Chiari syndrome is suspected

Contraindications

- Percutaneous liver biopsy
    - Uncorrectable coagulopathy

Technique

- Liver function tests
  - Performed on a sample of venous blood
  - Exception is urine bilirubin
- Ultrasound
  - Uses reflections of high-frequency or ultrasonic waves to obtain a 2-dimensional image of a deep structure
- Percutaneous biopsy of the liver
  - Safe procedure easily performed at bedside with local anesthesia

Efficacy

General

- Liver function tests
  - Can be normal in serious liver disease and abnormal in diseases not affecting liver
  - Rarely suggest a specific diagnosis
  - Suggest a general category of disease
    - Hepatocellular
    - Cholestatic
  - No one test enables the clinician to assess the liver's total functional capacity accurately.
  - Usually employed as a battery of tests to improve sensitivity and specificity
    - Bilirubin
    - AST
    - ALT
    - AP
    - Albumin
    - Prothrombin time
  - Probability of liver disease is high when:
    - More than one test provides abnormal findings *or*
    - Findings are persistently abnormal on serial determinations
  - Often necessary to repeat tests on several occasions over days or weeks for a diagnostic pattern to emerge

Specific tests

- Urine dipstick test for bilirubin
  - Almost 100% accurate
  - Phenothiazines may give false-positive reading with Ictotest tablet.
- Blood ammonia
  - Very poor correlation with presence or degree of acute encephalopathy
  - Can be elevated in severe portal hypertension and portal blood shunting around liver even with normal hepatic function
- Serum GGT
  - Elevation is less specific for cholestasis than elevations of AP or 5′-nucleotidase.
  - Questionable for identifying occult alcohol use due to lack of specificity
- Aminotransferases
  - Poor correlation between degree of liver cell damage and level of aminotransferases
  - Absolute elevation is of no prognostic significance in acute hepatocellular disorders.
- AP
  - Elevation is not totally specific for cholestasis.
  - Non-pathologic elevations
    - Mild elevations (1–1.5× normal) over age 60

        - In blood types O and B after eating a fatty meal
        - In children and adolescents undergoing rapid bone growth
        - Late in normal pregnancy
    - Not possible to distinguish between intrahepatic and extrahepatic cholestasis
    - Essentially no difference in values in:
        - Obstructive jaundice due to cancer
        - Common duct stone
        - Sclerosing cholangitis
        - Bile duct stricture
        - Intrahepatic cholestasis due to drug-induced hepatitis
        - Primary biliary cirrhosis
        - Rejection of transplanted livers
        - Alcohol-induced steatonecrosis
        - Hepatobiliary disorders seen in patients with AIDS
            - (e.g., AIDS cholangiopathy due to cytomegalovirus or cryptosporidial infection, tuberculosis with hepatic involvement)
- Albumin levels
    - Not a good indicator of acute or mild hepatic dysfunction
    - Only minimal changes are seen in:
        - Viral hepatitis
        - Drug-related hepatotoxicity
        - Obstructive jaundice
    - Hypoalbuminemia is not specific for liver disease, but may occur in:
        - Protein malnutrition of any cause
        - Protein-losing enteropathies
        - Nephrotic syndrome
        - Chronic infections
- Coagulation factors
    - Levels are single best assessment of acute hepatic synthetic dysfunction
- Percutaneous biopsy of the liver
    - Most accurate in disorders causing diffuse changes throughout the liver
    - Subject to sampling error in focal infiltrative disorders such as hepatic metastases

Complications

- Percutaneous liver biopsy
    - Significant complications in 1–5%
    - Mortality rate of 1:1,000–1:10,000
    - Increased risk with sepsis or coagulopathy
    - Should be done with caution
    - Complications include:
        - Hemorrhage (most common)
        - Pneumothorax
        - Perforation of bowel or gallbladder
        - Hemobilia
        - Peritonitis
        - Seeding needle track with tumor (0.006–1%)

ICD-9-CM

- 794.8 Nonspecific abnormal results of function studies, liver

See Also

- Alcoholic Liver Disease

- Autoimmune Hepatitis
- Cancer of the Biliary Tree
- Cancer of the Liver
- Hepatitis A, Acute
- Hepatitis B, Acute
- Hepatitis B, Chronic
- Hepatitis C, Acute
- Hepatitis C, Chronic
- Hepatitis D, Acute
- Hepatitis D,Chronic
- Hepatitis E, Acute
- Jaundice
- Sclerosing Cholangitis
- Toxic and Drug-Induced Hepatitis

Internet Sites

- Professionals
  - Liver Panel
    Lab Tests Online/American Association for Clinical Chemistry
  - Liver Diseases--Links
    MedlinePlus
- Patients
  - Liver function tests
    MedlinePlus
  - Liver function Tests Factsheet
    American Liver Foundation

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PEARL

- In an otherwise healthy individual with an isolated elevation of serum unconjugated bilirubin, if hemolysis is ruled out, then the diagnosis is almost certainly Gilbert syndrome.