Assessment of Liver Function and Diagnostic Studies

Paul Martin, MD, FRCP, FRCPI ■ Lawrence S. Friedman, MD

KEY POINTS

1 Reflecting the liver’s diverse functions, the colloquial term liver function tests (LFTs) includes true tests of hepatic synthetic function (e.g., serum albumin), tests of excretory function (e.g., serum bilirubin), and tests that reflect hepatic necroinflammatory activity (e.g., serum aminotransferases) or cholestasis (e.g., alkaline phosphatase [ALP]).

2 Abnormal liver biochemical test results are often the first clues to liver disease. The widespread inclusion of these tests in routine blood chemistry panels uncovers many patients with unrecognized hepatic dysfunction.

3 Normal or minimally abnormal liver biochemical test levels do not preclude significant liver disease, even cirrhosis.

4 Laboratory testing can assess the severity of liver disease and its prognosis; sequential testing may allow assessment of the effectiveness of therapy.

5 Although liver biopsy had been the gold standard for assessing the severity of liver disease, as well as for confirming the diagnosis for some causes, fibrosis is increasingly assessed by noninvasive means, most notably by ultrasound elastography, especially in chronic viral hepatitis.

6 Various imaging studies are useful in detecting focal hepatic defects, the presence of portal hypertension, and abnormalities of the biliary tract.

Routine Liver Biochemical Tests

SERUM BILIRUBIN

1. Jaundice
   ■ Often the first evidence of liver disease
   ■ Clinically apparent when serum bilirubin exceeds 3 mg/dL; patient may notice dark urine or pale stool before conjunctival icterus

2. Metabolism
   ■ Bilirubin is a breakdown product of hemoglobin and, to a lesser extent, heme-containing enzymes; 95% of bilirubin is derived from senescent red blood cells.
   ■ After red blood cell breakdown in the reticuloendothelial system, heme is degraded by the enzyme heme oxygenase in the endoplasmic reticulum.
   ■ Bilirubin is released into blood and tightly bound to albumin; free or unconjugated bilirubin is lipid soluble, is not filtered by the glomerulus, and does not appear in urine.
Unconjugated bilirubin is taken up by the liver by a carrier-mediated process, attaches to intracellular storage proteins (ligands), and is conjugated by the enzyme uridine diphosphate (UDP)–glucuronyl transferase to form a diglucuronide and, to a lesser extent, a monoglucuronide.

Conjugated bilirubin is water soluble and thus appears in urine.

When serum levels of bilirubin glucuronides are elevated, some binding to albumin occurs (delta bilirubin), leading to absence of bilirubinuria despite conjugated hyperbilirubinemia; this phenomenon explains delayed resolution of jaundice during recovery from acute liver disease until albumin-bound bilirubin is catabolized.

Conjugated bilirubin is excreted by active transport across the canalicular membrane into bile.

Bilirubin in bile enters the small intestine; in the distal ileum and colon, bilirubin is hydrolyzed by beta-glucuronidases to form unconjugated bilirubin, which is then reduced by intestinal bacteria to colorless urobilinogens; a small amount of urobilinogen is reabsorbed by the enterohepatic circulation and mostly excreted in the bile, with a smaller proportion undergoing urinary excretion.

Urobilinogens or their colored derivatives urobilins are excreted in feces.

3. Measurement of serum bilirubin
   a. van den Bergh reaction
      - Total serum bilirubin represents all bilirubin that reacts with diazotized sulfanilic acid to form chromogenic pyrroles within 30 minutes in the presence of alcohol (an accelerating agent).
      - Direct serum bilirubin is the fraction that reacts with the diazo reagent in an aqueous medium within 1 minute and corresponds to conjugated bilirubin.
      - Indirect serum bilirubin represents unconjugated bilirubin and is determined by subtracting the direct reacting fraction from the total bilirubin level.
   b. More specific methods (e.g., high-pressure liquid chromatography) demonstrate that the van den Bergh reaction often overestimates the amount of conjugated bilirubin; however, the van den Bergh method remains the standard test.

4. Classification of hyperbilirubinemia
   a. Unconjugated (bilirubin nearly always <7 mg/dL)
      - Overproduction (presentation to liver of bilirubin load that exceeds hepatic capacity for uptake and conjugation): Hemolysis, ineffective erythropoiesis, resorption of hematoma
      - Defective uptake and storage of bilirubin: Gilbert syndrome (idiopathic unconjugated hyperbilirubinemia)
   b. Conjugated
      - Hereditary: Dubin-Johnson and Rotor syndromes, bile transport protein defects
      - Cholestasis (Bilirubin is not a sensitive test of hepatic dysfunction.)
        - Intrahepatic: Cirrhosis, hepatitis, primary biliary cholangitis, drug induced
        - Extrahepatic biliary obstruction: Choledocholithiasis, stricture, neoplasm, biliary atresia, sclerosing cholangitis
   c. Very high bilirubin levels
      - >30 mg/dL: Usually signifies hemolysis plus parenchymal liver disease or biliary obstruction; urinary excretion of conjugated bilirubin may help prevent even higher levels of hyperbilirubinemia; renal failure contributes to hyperbilirubinemia.
      - >60 mg/dL: Seen in patients with hemoglobinopathies (e.g., sickle cell disease) in whom obstructive jaundice or acute hepatitis develops.
   d. The diagnostic approach to the evaluation of an isolated serum bilirubin level is shown in Fig. 1.1.
ASSESSMENT OF LIVER FUNCTION AND DIAGNOSTIC STUDIES

5. Urine bilirubin and urobilinogen
   - Bilirubinuria indicates an increase in serum conjugated (direct) bilirubin.
   - Urinary urobilinogen (rarely measured now) is found in patients with hemolysis (increased production of bilirubin), gastrointestinal hemorrhage, or hepatocellular disease (impaired removal of urobilinogen from blood).
   - Absence of urobilinogen from urine suggests interruption of the enterohepatic circulation of bile pigments, as in complete bile duct obstruction.
   - Urobilinogen detection and quantification add little diagnostic information to the evaluation of hepatic dysfunction.

SERUM AMINOTRANSFERASES (Table 1.1)

1. These intracellular enzymes are released from injured hepatocytes and are the most useful marker of hepatic injury (inflammation or cell necrosis).
   - **Aspartate aminotransferase** (AST, serum glutamic oxaloacetic transaminase [SGOT])
     - Found in cytosol and mitochondria
     - Found in liver as well as skeletal muscle, heart, kidney, brain, and pancreas
b. Alanine aminotransferase (ALT, serum glutamic pyruvic transaminase [SGPT])

- Found in cytosol
- Highest concentration in liver (more sensitive and specific than AST for liver inflammation and hepatocyte necrosis)

2. Clinical usefulness

- Normal levels of ALT are up to ~30 U/L in men and up to ~19 U/L in women.
- Levels increase with body mass index (and particularly with trunk fat) and correlate with serum triglyceride, glucose, insulin, and leptin levels and possibly inversely with serum vitamin D levels. There is controversy as to whether levels correlate with the risk of coronary artery disease and mortality.
- Levels may rise acutely with a high caloric meal or ingestion of acetaminophen 4 g/day; coffee appears to lower levels.
- Aminotransferase elevations are often the first biochemical abnormalities detected in patients with viral, autoimmune, or drug-induced hepatitis; the degree of elevation may correlate with the extent of hepatic injury but is generally not of prognostic significance.
- In alcoholic hepatitis, the serum AST is usually no more than 2 to 10 times the upper limit of normal, and the ALT is normal or nearly normal, with an AST:ALT ratio >2; relatively low ALT levels may result from a deficiency of pyridoxal 5-phosphate, a necessary cofactor for hepatic synthesis of ALT. In contrast, in nonalcoholic fatty liver disease, ALT is typically higher than AST until cirrhosis develops.
- Aminotransferase levels may be higher than 3000 U/L in acute or chronic viral hepatitis or drug-induced liver injury; in acute liver failure or ischemic hepatitis (shock liver), even higher values (>5000 U/L) may be found.

---

**TABLE 1.1  Causes of Elevated Serum Aminotransferase Levels**

<table>
<thead>
<tr>
<th>Mild Elevation (&lt;5× normal)</th>
<th>Marked Elevation (&gt;15× normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic: ALT predominant</td>
<td>Acute viral hepatitis (A–E, herpes)</td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td>DILI</td>
</tr>
<tr>
<td>Acute viral hepatitis (A–E, EBV, CMV)</td>
<td>Ischemic hepatitis</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Wilson disease</td>
</tr>
<tr>
<td>DILI</td>
<td>Acute bile duct obstruction</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Acute Budd-Chiari syndrome</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin deficiency</td>
<td>Hepatic artery ligation</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Glycogenic hepatopathy</td>
</tr>
<tr>
<td>Nonhepatic</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related liver injury (AST/ALT &gt;2:1)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

*Almost any liver disease may be associated with ALT levels 5 times to 15 times normal. ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; NAFLD, nonalcoholic fatty liver disease.
Mild-to-moderate elevations of aminotransferase levels are typical of chronic viral hepatitis, autoimmune hepatitis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson disease, and celiac disease.

In obstructive jaundice, aminotransferase values are usually lower than 500 U/L; rarely, values may reach 1000 U/L in acute choledocholithiasis or 3000 U/L in acute cholecystitis, followed by a rapid decline to normal.

The approach to the patient with a persistently elevated ALT level is shown in Fig. 1.2.

Abnormally low aminotransferase levels have been associated with uremia and chronic hemodialysis; chronic viral hepatitis in this population may not result in aminotransferase elevation.

**SERUM ALKALINE PHOSPHATASE**

1. Hepatic ALP is one of several ALP isoenzymes found in humans and is bound to the hepatic canalicular membrane; various laboratory methods are available for its measurement, and comparison of results obtained by different techniques may be misleading.

2. **This test is sensitive for detection of biliary tract obstruction** (a normal value is highly unusual in significant biliary obstruction); interference with bile flow may be intrahepatic or extrahepatic.
An increase in serum ALP results from increased hepatic synthesis of the enzyme, rather than leakage from bile duct cells or failure to clear circulating ALP; because it is synthesized in response to biliary obstruction, the ALP level may be normal early in the course of acute cholangitis when the serum aminotransferases are already elevated.

Increased bile acid concentrations may promote the synthesis of ALP.

Serum ALP has a half-life of 17 days; levels may remain elevated up to 1 week after relief of biliary obstruction and return of the serum bilirubin level to normal.

3. **Isolated elevation of alkaline phosphatase**
   - This may indicate infiltrative liver disease: Tumor, abscess, granulomas, or amyloidosis.
   - High levels are associated with biliary obstruction, sclerosing cholangitis, primary biliary cholangitis, immunoglobulin (Ig) G4-associated cholangitis, acquired immunodeficiency syndrome, cholestatic drug reactions, and other causes of vanishing bile duct syndrome; in critically ill patients with sepsis, high levels may result from secondary sclerosing cholangitis from ischemia with rapid progression to cirrhosis.
   - Nonhepatic sources of ALP are bone, intestine, kidney, and placenta (different isoenzymes); elevations are seen in Paget disease of the bone, osteoblastic bone metastases, small bowel obstruction, and normal pregnancy.
   - A hepatic origin of an elevated ALP level is suggested by simultaneous elevation of either serum gamma-glutamyltranspeptidase (GGTP) or 5'-nucleotidase (5NT).
   - Hepatic ALP is more heat stable than bone ALP. The degree of overlap makes this test less useful than GGTP or 5NT.
   - The diagnostic approach to an isolated elevated ALP level is shown in Fig. 1.3.

4. Mild elevations of serum ALP are often seen in hepatitis and cirrhosis.

5. Low serum levels of ALP may occur in hypothyroidism, pernicious anemia, zinc deficiency, congenital hypophosphatasia, and fulminant Wilson disease.

**GAMMA-GLUTAMYLTRANSPEPTIDASE**

1. Although present in many different organs, GGTP is found in particularly high concentrations in the epithelial cells lining biliary ductules.

2. It is a very sensitive indicator of hepatobiliary disease but is not specific. Levels are elevated in other conditions, including renal failure, myocardial infarction, pancreatic disease, and diabetes mellitus.

3. GGTP is inducible, and thus levels may be elevated by ingestion of phenytoin or alcohol in the absence of other clinical evidence of liver disease.

4. Because of its long half-life of 26 days, GGTP is limited as a marker of surreptitious alcohol consumption.

5. Its major clinical use is to exclude a bone source of an elevated serum ALP level.

6. Many patients with isolated serum GGTP elevation have no other evidence of liver disease; an extensive evaluation is usually not warranted. Patients should be retested after avoiding alcohol and other hepatotoxins for several weeks.

**5'-NUCLEOTIDASE**

1. 5NT is found in the liver in association with canalicular and sinusoidal plasma membranes.

2. Although 5NT is distributed in other organs, serum levels are believed to reflect hepatobiliary release by the detergent action of bile salts on plasma membranes.

3. Serum 5NT levels correlate well with serum ALP levels; an elevated serum 5NT level in association with an elevated ALP level is specific for hepatobiliary dysfunction and is superior to GGTP in this regard.
ASSESSMENT OF LIVER FUNCTION AND DIAGNOSTIC STUDIES

Elevated alkaline phosphatase

History and physical examination (especially pruritus, cholestasis, drugs, pregnancy, renal disease, bony symptoms)

GGTP or 5'-nucleotidase

Elevated

Hepatobiliary disease

Abdominal US

Normal

GGTP or 5'-nucleotidase

Extrahepatic source

AMA, ACE level, serologic tests for hepatitis, alpha fetoprotein

Cholecystectomy and bile duct exploration, if indicated

CT and/or MRI, biopsy

Cholangiography (MRCP, ERCP, THC)

Primary sclerosing cholangitis

Liver biopsy

Colonoscopy

Above negative; elevation persists

Gallstones

Focal lesion(s)

Biliary tract abnormalities

Fig. 1.3 Algorithm for the approach to a patient with isolated serum alkaline phosphatase elevation. ACE, Angiotensin-converting enzyme; AMA, antimitochondrial antibodies; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; GGTP, gamma-glutamyltranspeptidase; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; THC, transhepatic cholangiography; US, ultrasonography.
LACTATE DEHYDROGENASE

Measurement of lactate dehydrogenase (LDH) and the more specific isoenzyme LDH5 adds little to the evaluation of suspected hepatic dysfunction. High levels of LDH are seen in hepatocellular necrosis, ischemic hepatitis, cancer, and hemolysis. The ALT/LDH ratio may help differentiate acute viral hepatitis (≥1.5) from ischemic hepatitis and acetaminophen toxicity (<1.5).

SERUM PROTEINS

Most proteins circulating in plasma are produced by the liver and reflect its synthetic capacity.

1. Albumin
   - Albumin accounts for 75% of serum proteins.
   - Its half-life is approximately 3 weeks.
   - The concentration in blood depends on the albumin synthetic rate (normal, 12 g/day) and plasma volume.
   - Hypoalbuminemia may result from expanded plasma volume or decreased albumin synthesis. It is frequently associated with ascites and expansion of the extravascular albumin pool at the expense of the intravascular albumin pool. Hypoalbuminemia is common in chronic liver disease (an indicator of severity); it is less common in acute liver disease. It is not specific for liver disease and may also reflect glomerular or gastrointestinal losses.

2. Globulins
   - a. Globulins are often increased nonspecifically in chronic liver disease.
   - b. The pattern of elevation may suggest the cause of the underlying liver disease.
      - Elevated IgG: Autoimmune hepatitis
      - Elevated IgM: Primary biliary cholangitis
      - Elevated IgA: Alcoholic liver disease

3. Coagulation factors
   - a. Most coagulation factors are synthesized by the liver, including factors I (fibrinogen), II (prothrombin), V, VII, IX, and X and have much shorter half-lives than that of albumin.
   - Factor VII decreases first in liver disease because of its shortest half-life, followed by factors X and IX.
   - Factor V is not vitamin K dependent, and its measurement can help distinguish vitamin K deficiency from hepatocellular dysfunction in a patient with prolonged prothrombin time. Serial measurement of factor V levels has been used to assess prognosis in acute liver failure; a value <20% of normal portends a poor outcome without liver transplantation.
   - Measurement of factor II (des-gamma-carboxyprothrombin) has also been used to assess liver function. Elevated levels are found in cirrhosis and hepatocellular carcinoma (HCC) and in patients taking warfarin, a vitamin K antagonist. Administration of vitamin K results in normalization of des-gamma-carboxyprothrombin in patients taking warfarin but not in those with cirrhosis.
   - b. The prothrombin time is useful in assessing the severity and prognosis of acute liver disease. The one-stage prothrombin time described by Quick measures the rate of conversion of prothrombin to thrombin after activation of the extrinsic coagulation pathway in the presence of a tissue extract (thromboplastin) and calcium (Ca++) ions. Deficiency of one or more of the liver-produced factors results in a prolonged prothrombin time.
   - c. Prolongation of the prothrombin time in cholestatic liver disease may result from vitamin K deficiency.
      - Explanations for a prolonged prothrombin time apart from hepatocellular disease or vitamin K deficiency include consumptive coagulopathies, inherited deficiencies of a coagulation factor, or medications that antagonize the prothrombin complex.
Vitamin K deficiency as the cause of a prolonged prothrombin time can be excluded by administration of vitamin K 10 mg; intravenous administration can cause severe reactions, and the oral route is preferable, if possible. (Subcutaneous administration is not recommended because of erratic absorption.) Correction or improvement of the prothrombin time by at least 30% within 24 hours implies that hepatic synthetic function is intact.

The international normalized ratio (INR) is used to standardize prothrombin time determinations performed in different laboratories; however, the results are less consistent in patients with liver disease than in those taking warfarin unless liver-disease controls are used.

The prothrombin time and INR correlate with the severity of liver disease but not with the risk of bleeding because of counterbalancing decreases in levels of anticoagulant factors (e.g., proteins C and S, antithrombin) and enhanced fibrinolysis in patients with liver disease.

**Assessment of Hepatic Metabolic Capacity**

Various drugs that undergo purely hepatic metabolism with predictable bioavailability have been used to assess hepatic metabolic capacity. Typically, a metabolite is measured in plasma, urine, or breath following intravenous or oral administration of the parent compound. These tests are not widely used in practice.

**ANTIPYRINE CLEARANCE**

1. Antipyrine is metabolized by cytochrome P-450 oxygenase with good absorption after oral administration and elimination entirely by the liver.
2. In chronic liver disease, good correlation exists between prolongation of the antipyrine half-life and disease severity as assessed by the Child-Turcotte-Pugh score (see Chapter 11).
3. Clearance of antipyrine is less impaired in acute liver disease and obstructive jaundice than in chronic liver disease.
4. Disadvantages of this test include its long half-life in serum, which requires multiple blood sampling, poor correlation with in vitro assessment of hepatic microsomal capacity, and alteration of antipyrine metabolism by increased age, diet, alcohol, smoking, and environmental exposure.

**AMINOPYRINE BREATH TEST**

1. This test is based on detection of $[^{14}\text{C}]\text{O}_2$ in breath 2 hours after an oral dose of $[^{14}\text{C}]\text{dimethyl aminoantipyrine}$ (aminopyrine), which undergoes hepatic metabolism.
2. Excretion is diminished in patients with cirrhosis as well as those with acute liver disease.
3. The test has been used to assess prognosis in patients with alcoholic hepatitis and in cirrhotic patients who are undergoing surgery.
4. A limitation of the aminopyrine breath test is its lack of sensitivity in hepatic dysfunction resulting from cholestasis or extrahepatic obstruction.

**CAFFEINE CLEARANCE**

1. Caffeine clearance after oral ingestion can be assessed by measuring levels in either saliva or serum; the accuracy appears similar to the $[^{14}\text{C}]$aminopyrine breath test, without the need for a radioisotope.
2. Results are clearly abnormal in clinically severe liver disease, but the test is insensitive in mild hepatic dysfunction.

3. Caffeine clearance decreases with age or cimetidine use and increases with cigarette smoking.

**GALACTOSE ELIMINATION CAPACITY**

1. Galactose clearance from blood as a result of hepatic phosphorylation can be determined after either intravenous or oral administration; serial serum levels of galactose are obtained 20 to 50 minutes after an intravenous bolus, with correction for urinary galactose excretion.

2. At plasma concentrations >50 mg/dL, removal of galactose reflects hepatic functional mass, whereas at concentrations lower than this plasma level, clearance reflects hepatic blood flow.

3. [14C]galactose is distributed in extracellular water and is affected by changes in volume.

4. Galactose clearance is impaired in acute and chronic liver disease as well as in patients with metastatic hepatic neoplasms but is typically unaffected in obstructive jaundice.

5. The oral galactose tolerance test incorporates [14C]galactose with measurement of breath [14CO2]; the results of this breath test correlate with [14C]aminopyrine testing.

6. [14C]galactose testing is no more accurate than standard liver biochemical tests in assessing prognosis in patients with chronic liver disease.

**LIDOCAINE METABOLITE**

1. Monoethylglycinexylidide (MEGX), a product of hepatic lidocaine metabolism, is easily measured by a fluorescence polarization immune assay 15 minutes after administration of an intravenous dose of lidocaine.

2. The test may offer prognostic information about the likelihood of life-threatening complications in cirrhotic patients.

3. The test has also been used to assess the viability of donor liver allografts.

4. The test is easy to perform and has few adverse reactions, although it may be unsuitable for some cardiac patients. Test results may be affected by simultaneous use of certain drugs metabolized by cytochrome P-450 3A4 and high bilirubin levels; test results are affected by age and body mass index and are higher in men than in women.

**Other Tests of Liver Function**

**SERUM BILE ACIDS**

1. Bile acids are synthesized from cholesterol in the liver, conjugated to glycine or taurine, and excreted in the bile. Bile acids facilitate fat digestion and absorption within the small intestine. They recycle through the enterohepatic circulation; secondary bile acids form by the action of intestinal bacteria.

2. Detection of elevated serum bile acid levels is a sensitive marker of hepatobiliary dysfunction.

3. Various methods are available to assay individual and total bile acids; assaying an individual bile acid is probably as useful as measuring total bile acid concentration.

4. Numerous different bile acid tests have been described, including fasting and postprandial levels and determination of levels after a bile acid load, either oral or intravenous.

5. Normal bile acid levels in the presence of hyperbilirubinemia suggest hemolysis or Gilbert syndrome.
ASSESSMENT OF LIVER FUNCTION AND DIAGNOSTIC STUDIES

UREA SYNTHESIS
1. Hepatic metabolism of nitrogen from protein results in urea production. Urea is distributed in total body water and is excreted in urine or diffuses into the intestine, where urease-producing bacteria hydrolyze it to CO₂ and ammonia.
2. The rate of urea synthesis can be calculated from the urinary urea excretion and blood urea nitrogen after estimation of body water, with correction for gastrointestinal hydrolysis of urea.
3. The rate of urea synthesis is significantly reduced in cirrhosis and correlates with the Child-Turcotte-Pugh score, although it is insensitive for detection of well-compensated cirrhosis.

BROMSULPHALEIN
Clearance of bromsulphaldehyde (BSP) after an intravenous bolus was formerly used to measure hepatic function. The most accurate information was obtained by the 45-minute retention test and initial fractional rate of disappearance. BSP testing fell out of favor because of reports of severe allergic reactions, lack of accuracy in distinguishing hepatocellular from obstructive jaundice, and the availability of simpler tests of liver function.

INDOCYANINE GREEN
This dye is removed by the liver after intravenous injection. A blood level can be obtained 20 minutes after administration, or levels can be determined by skin sensors. Compared with BSP, the hepatic clearance of indocyanine green is more efficient, and it is nontoxic. Its accuracy in assessing liver dysfunction is no better than standard Child-Turcotte-Pugh scoring. Its major role had been as a measure of hepatic blood flow.

NONINVASIVE SERUM MARKERS OF FIBROSIS
Various tests have been described to determine the extent of fibrosis in patients with chronic liver disease, thereby avoiding the need for liver biopsy.

Direct Markers
These markers include serum hyaluronate, procollagen III N-peptide, and matrix metalloproteinases. They are generally accurate in confirming cirrhosis and excluding severe liver disease in patients with minimal fibrosis.

Indirect Markers
Various formulas have been described that incorporate serum markers of fibrosis or routine laboratory tests, such as platelet count, INR, and serum aminotransferases.
- Examples include FibroSure, Fibrospect, and AST-to-platelet ratio index (APRI).
- **FibroSure is used most commonly in the United States** and includes α₂-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, and GGTP; it is most useful for excluding fibrosis (low score) or suggesting cirrhosis (high score); intermediate scores can reflect a varying degree of fibrosis.

Liver Biopsy
Despite advances in serologic testing and imaging, liver biopsy remains the definitive test in a number of settings: To confirm the diagnosis of specific liver diseases such as Wilson disease,
### Table 1.2: Indications for Liver Biopsy

<table>
<thead>
<tr>
<th>Indications for Liver Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of abnormal liver biochemical test levels and hepatomegaly</td>
</tr>
<tr>
<td>Evaluation and staging of chronic hepatitis</td>
</tr>
<tr>
<td>Identification and staging of alcoholic liver disease</td>
</tr>
<tr>
<td>Recognition of systemic inflammatory or granulomatous disorders</td>
</tr>
<tr>
<td>Evaluation of fever of unknown origin</td>
</tr>
<tr>
<td>Evaluation of the pattern and extent of drug-induced liver injury</td>
</tr>
<tr>
<td>Identification and determination of the nature of intrahepatic masses</td>
</tr>
<tr>
<td>Diagnosis of multisystem infiltrative disorders</td>
</tr>
<tr>
<td>Evaluation and staging of cholestatic liver disease (primary biliary cholangitis, primary sclerosing cholangitis)</td>
</tr>
<tr>
<td>Screening of relatives of patients with familial diseases</td>
</tr>
<tr>
<td>Obtaining tissue to culture infectious agents (e.g., mycobacteria)</td>
</tr>
<tr>
<td>Evaluation of effectiveness of therapies for liver diseases (e.g., Wilson disease, hemochromatosis, autoimmune hepatitis, chronic viral hepatitis)</td>
</tr>
<tr>
<td>Evaluation of liver biochemical test abnormalities following transplantation</td>
</tr>
</tbody>
</table>

### Table 1.3: Contraindications to Liver Biopsy

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of unexplained bleeding</td>
<td>Ascites</td>
</tr>
<tr>
<td>Prothrombin time &gt;3–4 s over control</td>
<td>Infection in right pleural cavity</td>
</tr>
<tr>
<td>Platelets &lt;60,000/mm³</td>
<td>Infection below right diaphragm</td>
</tr>
<tr>
<td>Prolonged bleeding time (&gt;10 min)</td>
<td>Suspected echinococcal disease</td>
</tr>
<tr>
<td>Unavailability of blood transfusion support</td>
<td>Morbid obesity</td>
</tr>
<tr>
<td>Suspected hemangioma</td>
<td>Uncooperative patient</td>
</tr>
</tbody>
</table>

Small-duct primary sclerosing cholangitis, and nonalcoholic fatty liver disease; to assess prognosis in most forms of parenchymal liver disease; and to evaluate allograft dysfunction in liver transplant recipients.

**INDICATIONS**

Indications for liver biopsy are shown in Table 1.2.

**CONTRAINDICATIONS**

Contraindications to liver biopsy are shown in Table 1.3. In patients with renal insufficiency, uremic platelet dysfunction should be corrected by infusion of arginine vasopressin (DDAVP), 0.3 μg/kg in 50 mL N saline intravenously, immediately before biopsy. Aspirin and nonsteroidal antiinflammatory drugs, which may also produce platelet dysfunction, are prohibited for 7 to 10 days before elective liver biopsy.
TECHNIQUE

1. Liver biopsy can be performed safely on an outpatient basis if none of the contraindications noted in Table 1.2 is present and the patient can be adequately observed for 2 to 3 hours after the procedure, with access to hospitalization if necessary (required in up to 5% of patients).
2. A local anesthetic is infiltrated subcutaneously and into the intercostal muscle and peritoneum. A short-acting sedative may be given to allay anxiety. Percussion identifies the point of maximal hepatic dullness.
3. The routine use of ultrasonography to mark the biopsy site or guide the biopsy needle has become standard. In diffuse liver disease, ultrasound-guided liver biopsy results in a higher yield and lower rate of complications than blind biopsy.
4. A transthoracic approach is standard; a subcostal approach should be attempted only with ultrasound guidance.
5. The biopsy is performed at end expiration; various needles (cutting [Tru-Cut, Vim-Silverman] or suction [Menghini, Klatskin, Jamshidi]) are used, including a biopsy “gun.”
6. The biopsy site is tamponaded by having the patient lie on the right side.
7. When the standard approach is contraindicated (e.g., by coagulopathy or ascites), transjugular biopsy may be performed. This technique also allows determination of the hepatic venous wedge pressure gradient (see Chapter 11) to confirm portal hypertension, assess response to therapy with a beta-receptor antagonist, and determine prognosis.
8. Focal hepatic lesions are best sampled for biopsy under imaging guidance.
9. An adequate specimen for histologic interpretation should be at least 1.5 cm long and contains at least six portal triads.

COMPLICATIONS

1. Postbiopsy pain with or without radiation to the right shoulder occurs in up to one third of patients. Vasovagal reactions are also common. Serious complications are uncommon (<3%) and usually manifest within several hours of the biopsy. The fatality rate is 0.03% to 0.32%.
2. Intraperitoneal bleeding is the most serious complication. Increasing age, the presence of hepatic malignancy, and number of passes made are predictors of the likelihood of bleeding, as is the use of a cutting needle rather than a suction needle.
3. Patients who have clinical evidence of hemodynamically significant bleeding, persistent pain unrelieved by analgesia, or other evidence of a serious complication require hospital admission. Pneumothorax may require a chest tube, whereas serious bleeding may be controlled by selective embolization at angiography or, if necessary, surgical ligation of the right hepatic artery or hepatic resection.
4. Biopsy of a malignant neoplasm carries a 1% to 3% risk of seeding of the biopsy tract with tumor.

Hepatic Imaging

Several imaging modalities are available to assess the hepatic parenchyma, vasculature, and biliary tract. A logical sequence of initial and subsequent studies should be determined by the clinical circumstances (Table 1.4). The ready availability of abdominal imaging for unrelated complaints such as vague abdominal pain has led to the frequent detection of hepatic masses that are almost always benign and incidental to the patient’s complaint but that require evaluation.
**TABLE 1.4 Approach to Use of Imaging Studies**

<table>
<thead>
<tr>
<th>Clinical Problem</th>
<th>Initial Imaging</th>
<th>Supplemental Imaging Studies (if necessary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>US</td>
<td>CT, if dilated ducts, an obstructing lesion, or suspicion of a mass in the pancreas or porta hepatis; MRCP to determine site and cause of dilated ducts</td>
</tr>
<tr>
<td>Hepatic parenchymal disease</td>
<td>US CT MRI</td>
<td>Doppler US, color Doppler US, or MRI with flow sequences if a vascular abnormality is suspected and in some instances of portal hypertension</td>
</tr>
<tr>
<td>Screening for liver mass</td>
<td>US CT MRI</td>
<td>CT, MRI</td>
</tr>
<tr>
<td>Characterization of known liver mass</td>
<td>CT MRI</td>
<td>MRI with liver-specific contrast media</td>
</tr>
<tr>
<td>Suspected malignancy</td>
<td>US- or CT-directed biopsy</td>
<td>Intraoperative US, CT portogram</td>
</tr>
<tr>
<td>Suspected benign lesion</td>
<td>US CT MRI; nuclear medicine scan (e.g., $^{99m}$Tc-labeled red blood cell scan) for suspected hemangioma</td>
<td>US- or CT-directed biopsy</td>
</tr>
<tr>
<td>Suspected abscess</td>
<td>US or CT US- or CT-directed aspiration</td>
<td>Nuclear medicine abscess scan (gallium or $^{111}$In-labeled white blood cell scan)</td>
</tr>
<tr>
<td>Suspected biliary tract abnormalities</td>
<td>US to detect dilatation, biliary stones, or mass MRCP, ERCP, or THC to define ductal anatomy</td>
<td>CT or endoscopic US to detect stones or cause of extrinsic compression</td>
</tr>
</tbody>
</table>

CT, Computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; THC, transhepatic cholangiography; US, ultrasonography.

---

**PLAIN ABDOMINAL X-RAY STUDIES AND BARIUM STUDIES**

1. Plain abdominal x-ray studies add little to the evaluation of liver disease. On occasion, calcifications, usually resulting from gallstones, echinococcal cysts, or old lesions of tuberculosis or histoplasmosis, are detected. Tumors or vascular lesions may also be calcified.
2. A barium swallow is significantly less sensitive than endoscopy for detecting esophageal varices.
3. Wireless video capsule endoscopy has been used also to screen for esophageal varices.

**ULTRASONOGRAPHY**

1. Ultrasonography is the initial radiologic study of choice for many hepatobiliary disorders. It is relatively inexpensive, does not require ionizing radiation, and can be used at the bedside.
2. Ultrasound depicts interfaces in tissue of different acoustic properties. Contrast agents have been introduced to enhance the accuracy of ultrasonography; these include a microbubble technique for detection of discrete lesions and galactose-based contrast agents for assessment of vascularity.
3. Ultrasound cannot penetrate gas or bone, a characteristic that may preclude adequate examination of the visceras. Furthermore, increased resolution is generally at the expense of decreased tissue penetration.
4. “Real-time” ultrasonography demonstrates physiologic events such as arterial pulsation.
5. Ultrasonography is better at detecting focal lesions than parenchymal disease and is the initial test of choice to detect biliary dilatation.

6. Hepatic masses as small as 1 cm may be detected by ultrasonography, and cystic lesions may be distinguished from solid ones.

7. Ultrasonography can also facilitate percutaneous biopsy of solid hepatic masses, drainage of hepatic abscesses, or paracentesis of loculated ascites.

8. Doppler ultrasonography is used to assess the patency of hepatic and portal vasculature in liver transplant candidates and recipients.

**COMPUTED TOMOGRAPHY**

1. Computed tomography (CT) is generally more accurate than ultrasonography in defining hepatic anatomy—normal and pathologic.

2. Oral contrast defines the bowel lumen, and intravenous contrast enhances vascular structures and increases anatomic definition.

3. Spiral, or helical, CT is a refinement that allows faster imaging at the peak of intravenous contrast enhancement. A more recent advance is multidetector CT, which permits imaging in a single breath-hold and three-dimensional reconstruction of the hepatic vasculature and biliary tract.

4. **CT with intravenous contrast is an excellent way to identify and characterize hepatic masses.** Cystic and solid masses can be distinguished, as can abscesses. Contrast enhancement after an intravenous bolus may be accurate enough to identify cavernous hemangiomas, which have a characteristic appearance. Neoplastic vascular invasion may also be identified. HCC exhibits arterial enhancement (Fig. 1.4), followed by rapid “washout.”

5. CT can also suggest the presence of cirrhosis and portal hypertension, as well as changes consistent with fatty liver or hemochromatosis.

6. Limitations of CT are cost, radiation exposure, and lack of portability.

**MAGNETIC RESONANCE IMAGING**

1. Magnetic resonance imaging (MRI) can provide images in numerous planes and provides excellent resolution between tissues containing differing amounts of fat and water. Ultrafast sequencing obviates motion artifacts. Unlike CT, MRI does not require ionizing radiation, but there is a risk of nephrogenic systemic fibrosis in patients with impaired renal function after administration of gadolinium contrast.
2. MRI is an excellent method for evaluating blood flow and can detect hepatic iron overload.
3. MRI is not portable, remains expensive, and has a slow imaging time, so physiologic events such as peristalsis can result in blurred images. The magnetic field used precludes imaging in patients with pacemakers or other metallic devices. Claustrophobic patients find the enclosed space in the scanner unpleasant, and many require sedation.
4. MRI is the imaging study of choice in confirming the presence of vascular lesions, notably hemangiomas (Fig. 1.5). It is also useful in differentiating regenerative nodules from HCC; on a T2-weighted image, the signal intensity of a regenerative nodule is equivalent to that of normal hepatic parenchyma, whereas that of a carcinoma is higher.
5. Use of liver-specific contrast media further enhances the accuracy of assessing hepatic mass characteristics by MRI.
6. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive alternative to diagnostic endoscopic cholangiopancreatography.
7. Magnetic resonance angiography, like CT angiography, is a useful method to assess the hepatic vasculature before hepatic resection.

**RADIOISOTOPE SCANNING**

1. Specific isotopes used are preferentially taken up by hepatocytes, Kupffer cells, or neoplastic or inflammatory cells. Radioisotope scanning is particularly helpful in the assessment of suspected acute cholecystitis, although for parenchymal and focal liver disease, ultrasonography and CT have largely superseded nuclear medicine studies.
2. Additional techniques include single-photon emission computed tomography (SPECT), which allows visualization of the cross-sectional distribution of a radioisotope, and positron emission tomography (PET) (see later), which provides information about blood flow and tissue metabolism.

**POSITRON EMISSION TOMOGRAPHY**

1. PET detects increased glucose metabolism characteristic of hepatic neoplasm.
2. Clinical applications include detection and staging of primary hepatic malignant diseases, evaluation of metastatic disease, and differentiation of benign from malignant hepatic tumors.
3. The accuracy of PET in HCC is limited by poor uptake of the most commonly used radiopharmaceutical (\(^{18}\)F-fluoro-2-deoxyglucose [FDG]) by well-differentiated tumors.

ULTRASOUND ELASTOGRAPHY

1. Ultrasound elastography incorporates an ultrasound transducer probe mounted on a vibrator to induce an elastic shear wave to measure hepatic stiffness, which reflects fibrosis. A commonly used technique is transient elastography, in which the results are expressed in kilopascals (kPa) and range from 2.5 to 75 kPa, with upper normal values approximately 5.5 kPa.

2. Ultrasound elastography is most accurate for excluding advanced fibrosis and cirrhosis and for suggesting cirrhosis; considerable overlap in results exists between when the fibrosis stage is intermediate.

3. The procedure is technically difficult in patients with obesity or ascites.

4. It may complement rather than replace liver biopsy.

5. Magnetic elastography is another emerging technique that uses magnetic resonance to measure liver stiffness.

FURTHER READING


