CHAPTER

73

Liver Chemistry and Function Tests

DANIEL S. PRATT

CHAPTER OUTLINE

When appropriately ordered and interpreted, serum biochemical tests, the so-called "liver function tests" or "liver chemistries," can be useful in the evaluation and management of patients with liver disorders. The term *liver biochemical tests* is preferable to *liver function tests* because the most commonly used tests—the aminotransferases and alkaline phosphatase—do not measure a known function of the liver. These tests have the potential to identify liver disease, distinguish among types of liver disorders, gauge the severity and progression of liver dysfunction, and monitor response to therapy. Understanding the shortcomings of these tests, however, is important. No test can accurately assess the liver's total functional capacity; biochemical tests measure only a few of the thousands of biochemical functions performed by the liver. Furthermore, considered individually, these tests lack sensitivity and specificity for liver injury; a battery of tests must be used to evaluate the liver. The standard battery of tests that is most helpful in assessing liver disease includes total and direct bilirubin, albumin, prothrombin time, and the serum enzymes: ALT, AST, alkaline phosphatase (ALP), and occasionally GGTP and 5′ nucleotidase (5′NT). Interpretation of these results in concert with careful history taking and a physical examination may suggest a specific type of liver injury, thereby allowing a directed evaluation, risk assessment for surgical procedures, and estimation of prognosis. Other more specialized tests include quantitative tests of liver function and a growing number of options to assess the degree of hepatic fibrosis.

BILIRUBIN (See Chapter 21)

Metabolism

Bilirubin is a breakdown product of heme (ferroprotoporphyrin IX). About 4 mg/kg body weight of bilirubin is produced each day, nearly 80% from the breakdown of hemoglobin in senescent red blood cells and prematurely destroyed erythroid cells in the bone marrow and the remainder from the turnover of hemoproteins such as myoglobin and cytochromes distributed throughout the body.[1] The initial steps of bilirubin metabolism occur in reticuloendothelial cells, predominantly in the spleen. Heme is converted to biliverdin by the microsomal enzyme heme oxygenase. Biliverdin is then converted to bilirubin by the cytosolic enzyme biliverdin reductase.

Bilirubin formed in the reticuloendothelium is lipid soluble and virtually insoluble in water. In order to be transported in blood, unconjugated bilirubin must be solubilized. The process is initiated by reversible, noncovalent binding to albumin, which has both high-affinity and lower-affinity binding sites for unconjugated bilirubin. The unconjugated bilirubin-albumin complex passes readily through the fenestrations in the endothelium lining the hepatic sinusoids into the space of Disse, where the bilirubin dissociates from albumin and is taken up by hepatocytes via a protein-mediated, facilitated process, possibly mediated by a liver-specific organic anion transport protein.

After entering the hepatocyte, unconjugated bilirubin is bound in the cytosol to a number of proteins, including proteins in the glutathione *S*-transferase superfamily.[2] These proteins serve to reduce efflux of bilirubin back into the serum and present the bilirubin for conjugation. The enzyme uridine-5′-diphosphate (UDP) glucuronyl transferase found in the endoplasmic reticulum solubilizes bilirubin by conjugating it to glucuronic acid to produce bilirubin monoglucuronide and diglucuronide.[3] The now hydrophilic bilirubin diffuses to the canalicular membrane for excretion into the bile canaliculi. Conjugated bilirubin is transported across the canalicular membrane by the multidrug resistance-associated protein 2 (MRP2) via an ATP-dependent process.[4] This is the only

energy-dependent step in bilirubin metabolism and explains why even patients with fulminant hepatic failure have a predominantly conjugated hyperbilirubinemia. Once in the bile, conjugated bilirubin passes undisturbed until it reaches the distal ileum and colon, where bacteria containing β-glucuronidases hydrolyze conjugated bilirubin to unconjugated bilirubin, which is further reduced by bacteria to colorless urobilinogen.[5] The urobilinogen is either excreted unchanged, oxidized and excreted as urobilin (which has an orange color), or absorbed passively by the intestine into the portal system. The majority of the absorbed urobilinogen is re-excreted by the liver. A small percentage filters across the renal glomerulus and is excreted in urine. Unconjugated bilirubin is never found in urine because in the serum it is bound to albumin and not filtered by the glomerulus. The presence of bilirubin in urine indicates conjugated hyperbilirubinemia and hepatobiliary disease.

Measurement

The terms *direct* and *indirect bilirubin*, which correspond roughly to conjugated and unconjugated bilirubin, respectively, derive from the original van den Bergh reaction.[6] Serum bilirubin is still measured in clinical laboratories by some modification of this method.[7] In this assay, bilirubin is exposed to diazotized sulfanilic acid. The conjugated fraction of bilirubin reacts promptly, or "directly," with the diazo reagent without the need for an accelerant and thereby allows measurement of the conjugated bilirubin fraction by photometric analysis within 30 to 60 seconds. The total bilirubin is measured 30 to 60 minutes after the addition of an accelerant such as alcohol or caffeine. The unconjugated, or indirect, fraction is then determined by subtracting the direct component from the total bilirubin.

Newer and more accurate methods of measuring bilirubin, such as high-performance liquid chromatography, have been developed but are not generally available because they are more difficult to perform and do not add additional information beyond that provided by the diazo method in most clinical situations. These newer methods allow the identification of delta bilirubin—conjugated bilirubin tightly linked to albumin through covalent binding. Delta bilirubin is found in cases of prolonged and severe elevation of serum conjugated bilirubin levels, and because of the strength of the covalent binding, delta bilirubin has the half-life of albumin, 14 to 21 days, which far exceeds the usual serum half-life of bilirubin of 4 hours. The identification of delta bilirubin explains why the decline in serum bilirubin in some patients with prolonged jaundice seems to lag behind clinical recovery and why some patients with conjugated hyperbilirubinemia do not have bilirubinuria.

Using the diazo method, normal values of total serum bilirubin are between 1.0 and 1.5 mg/dL, with 95% of a normal population falling between 0.2 and 0.9 mg/dL.[8] Normal values for the indirect component are between 0.8 and 1.2 mg/dL. The diazo method, however, tends to overestimate the amount of conjugated bilirubin, particularly within the normal range. As a result, "normal" ranges for conjugated bilirubin have crept upward over time. In general, if the direct acting fraction is less than 15% of the total, the bilirubin can be considered to be entirely indirect. The most frequently reported upper limit of normal for conjugated bilirubin is 0.3 mg/dL. The presence of even a mild increase in conjugated bilirubin in the serum should raise the possibility of liver injury. The measurement and fractionation of serum bilirubin in patients with jaundice does not allow differentiation between parenchymal (hepatocellular) and obstructive (cholestatic) jaundice.

The magnitude and duration of hyperbilirubinemia have not been critically assessed as prognostic markers. In general, the higher the serum bilirubin level in patients with viral hepatitis, the greater the hepatocellular damage and the longer the course of disease. Patients may die, however, of acute liver failure with only a modest elevation of serum bilirubin. Total serum bilirubin correlates with poor outcomes in alcoholic hepatitis and is a critical component of the MELD score, which is used to estimate survival of patients with end-stage liver disease (see later and Chapter 97).

Approach to the Patient with an Elevated Level

Hyperbilirubinemia may be the result of overproduction of bilirubin through excessive breakdown of hemoglobin; impaired hepatocellular uptake, conjugation, or excretion of bilirubin; or regurgitation of unconjugated and conjugated bilirubin from damaged hepatocytes or bile ducts. The presence of conjunctival icterus suggests a total serum bilirubin level of at least 3.0 mg/dL but does not allow differentiation between conjugated and unconjugated hyperbilirubinemia. Tea- or cola-colored urine may indicate the presence of bilirubinuria and thus conjugated hyperbilirubinemia.

The evaluation of the patient with an isolated elevation of the serum bilirubin level is quite different from that of the patient with an elevated bilirubin associated with elevated liver enzyme levels; the latter suggests either a hepatocellular or cholestatic process, as discussed later. The first step in the evaluation of a patient with an isolated elevation of the serum bilirubin level is to fractionate the bilirubin to determine if it is conjugated or unconjugated (Fig. 73-1). If less than 15% of the total is conjugated, one can be assured that virtually all the serum bilirubin is unconjugated. Overproduction of bilirubin as a result of excessive breakdown of hemoglobin can occur

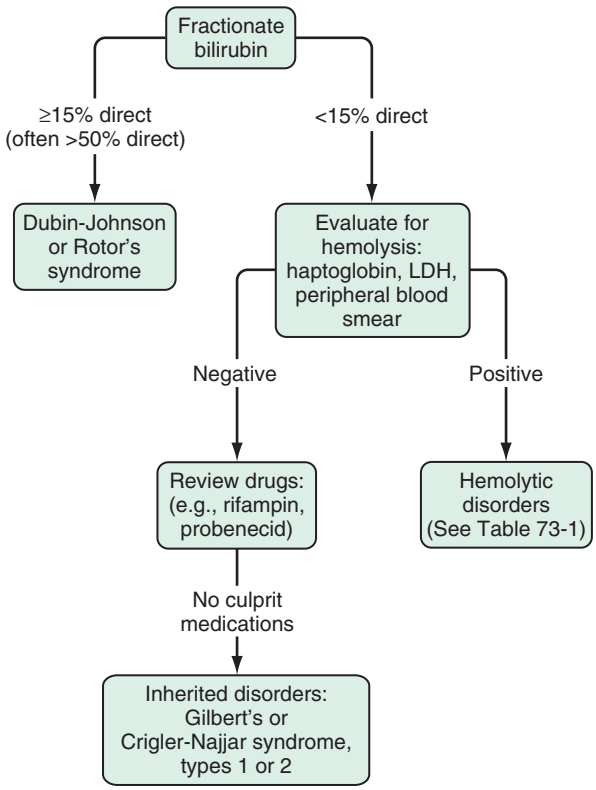

FIGURE 73-1. Evaluation of an isolated elevation of the serum bilirubin level.

TABLE 73-1 Causes and Mechanisms of Isolated Hyperbilirubinemia in Adults

Cause	Mechanism
Indirect Hyperbilirubinemia	
Hemolytic Disorders	Overproduction of bilirubin
Inherited Red cell enzyme defects (e.g., glucose-6-phosphate dehydrogenase deficiency) Sickle cell disease Spherocytosis and elliptocytosis Acquired Drugs and toxins Hypersplenism Immune mediated Paroxysmal nocturnal hemoglobinuria Traumatic: macro- or microvascular injury	
Ineffective Erythropoiesis	Overproduction of bilirubin
Cobalamin deficiency Folate deficiency Profound iron deficiency Thalassemia	
Drugs: Rifampin, Probenecid	Impaired hepatocellular uptake of bilirubin
Inherited Conditions	Impaired conjugation of bilirubin
Crigler-Najjar syndrome types I and II Gilbert's syndrome	
Other	
Hematoma and massive blood transfusion	Overproduction of bilirubin
Direct Hyperbilirubinemia	
Inherited Conditions	
Dubin-Johnson syndrome Rotor's syndrome	Impaired excretion of conjugated bilirubin

with any of a number of inherited or acquired disorders (Table 73-1). The patient's medication history should be reviewed for drugs that can cause impaired hepatocellular uptake of bilirubin. If no cause is identified, a genetic enzyme deficiency that results in impaired conjugation of bilirubin, the most common of which is Gilbert's syndrome, is likely.

As discussed in Chapter 21, Gilbert's syndrome is common, with a reported frequency of 6% to 12% (see Table 21-2). A mutation in the TATAA element in the 5′ promoter region of the UDP glucuronyl transferase gene results in a reduction in enzyme activity to approximately one third of normal. The mildly elevated indirect serum hyperbilirubinemia seen in Gilbert's syndrome is of no clinical consequence. This benign clinical course contrasts with those of much rarer conditions, Crigler-Najjar syndrome types I and II (see Table 21-2). The mutations in these conditions result in significantly reduced UDP glucuronyl transferase activity: less than 10% in Crigler-Najjar type II and complete absence of enzyme activity in Crigler-Najjar type I, leading to much greater elevations of unconjugated serum bilirubin to levels that carry an increased risk of kernicterus.

When isolated hyperbilirubinemia is associated with a conjugated fraction of over 15%, and typically over 50%, the diagnosis is either the uncommon Dubin-Johnson syndrome or the even rarer Rotor's syndrome (see Fig. 73-1, Table 21-2, and Table 64-5). The defect in Dubin-Johnson syndrome is in the gene that encodes MRP2. A 2012 study has suggested that the defect in Rotor's syndrome is due to coexisting deficiencies of the organic anion transporting polypeptides OATP1B1 and OATP1B3 (see Chapter 64).[9] In both syndromes, excretion of conjugated bilirubin across the bile canalicular membrane is reduced, resulting in an increase in the conjugated serum bilirubin level. Neither syndrome is associated with adverse clinical outcomes. Additional genetic disorders of bile acid transport that may be associated with hyperbilirubinemia are discussed in Chapters 64 and 77.

AMINOTRANSFERASES

The serum aminotransferases (also called *transaminases*), the most sensitive markers of acute hepatocellular injury, have been used to identify liver disease since the 1950s.[10] ALT (formerly serum glutamic pyruvic transaminase, or SGPT) and AST (formerly serum glutamic oxaloacetic transaminase, or SGOT) catalyze the transfer of the α-amino groups of alanine and L-aspartic acid, respectively, to the α-keto group of ketoglutaric acid. AST, found in cytosol and mitochondria, is widely distributed throughout the body; it is found, in order of decreasing concentration, in liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, and erythrocytes. ALT, a cytosolic enzyme also found in many organs, is present in greatest concentration by far in the liver and is, therefore, a more specific indicator than AST of liver injury. Increases in serum values of the aminotransferases reflect either damage to tissues rich in these enzymes or changes in cell membrane permeability that allow ALT and AST to leak into serum; hepatocyte necrosis is not required for the release of aminotransferases, and the degree of elevation of the aminotransferases does not correlate with the extent of liver injury.[11]

Aminotransferases have no function in serum and act like other serum proteins. They are distributed in plasma and interstitial fluid and have half-lives measured in days. The activity of ALT and AST at any moment reflects the relative rate at which they enter and leave the circulation. They are probably cleared by cells of the reticuloendothelial system, with AST cleared more rapidly than ALT.

Normal values for aminotransferases in serum vary widely among laboratories, but values gaining general acceptance are equal to or below 30 U/L for men and 19 U/L for women. The inter-laboratory variation in the normal range is the result of technical issues; no reference standards exist to establish the upper limits of normal for serum ALT and AST levels. Therefore, each reference laboratory is responsible for identifying a locally defined reference population or for using a normal range first established in the 1950s.[10] The normal range is defined as the mean of the reference population plus 2 standard deviations; approximately 95% of a uniformly distributed population will fall within this "normal" range. Some investigators have recommended revisions of normal values for the aminotransferases with adjustments for sex and BMI, but others have raised concern about the potential costs and unclear benefits of implementing such a change.[12-16] A longitudinal analysis observed that serum levels of ALT decrease with age, independent of sex, alcohol use, BMI, diabetes mellitus, serum TG levels, and other factors known to affect ALT

levels, thereby prompting the investigators to suggest that clinicians consider a patient's age, especially in older adults, when interpreting serum ALT levels.[17] A serum aminotransferase level below the lower limit of normal is of no clinical importance; it has been reported in patients with chronic kidney disease on hemodialysis and is believed to be caused in part by vitamin B_6 deficiency.

Approach to the Patient with an Elevated Level

Serum aminotransferase levels are typically elevated in all forms of liver injury; levels up to 300 U/L are nonspecific. In certain circumstances the degree and pattern of elevation of the aminotransferases, evaluated in the context of a patient's characteristics, symptoms, and physical examination findings, can suggest particular diagnoses and direct the subsequent evaluation (Box 73-1). The differential diagnosis of marked elevations of aminotransferase levels (>1000 U/L) includes viral hepatitis (A to E), toxin or drug-induced liver injury, ischemic hepatitis, and less commonly, autoimmune hepatitis, acute Budd-Chiari syndrome, fulminant Wilson disease, and acute obstruction of the biliary tract.

The ratio of AST to ALT in serum is helpful in a few specific circumstances—perhaps most importantly in the recognition of alcoholic liver disease. If the AST level is less than 300 U/L, a ratio of AST to ALT of more than 2 suggests alcoholic liver disease, and a ratio of more than 3 is highly suggestive of alcoholic liver disease.[18] The ratio results from a deficiency of pyridoxal 5′-phosphate in patients with alcoholic liver disease; ALT synthesis in the liver requires pyridoxal phosphate more than does AST synthesis.[19] When a patient with chronic alcoholic liver disease sustains a superimposed liver injury, particularly acetaminophen hepatotoxicity, the aminotransferase levels can be strikingly elevated, yet the AST/ALT ratio is maintained.

An increased ratio of AST to ALT may also be seen in muscle disorders. The degree of elevation is typically less than 300 U/L, but in rare cases, such as rhabdomyolysis, levels typically observed in patients with acute hepatocellular disease can be reached. In cases of acute muscle injury, the AST/ALT ratio may initially be greater than 3:1, but the ratio quickly declines toward 1:1 because of the shorter serum half-life of AST.[20] The ratio typically is close to 1:1 in patients with chronic muscle diseases.

Although the AST/ALT ratio is typically less than 1 in patients with chronic viral hepatitis and nonalcoholic fatty liver disease (NAFLD), a number of investigators have observed that, as cirrhosis develops, the ratio rises and may become greater than 1. Studies have shown that an AST/ALT ratio of greater than 1 as an indicator of cirrhosis in patients with chronic hepatitis C has a high specificity (94% to 100%) but a relatively low sensitivity (44% to 75%).[21] The increase in AST/ALT ratio with the development of cirrhosis is believed to result from impaired functional hepatic blood flow, with a consequent decrease in hepatic sinusoidal uptake of AST.[22]

The majority of patients evaluated for elevated serum aminotransferase levels are asymptomatic and have mild elevations (≤5-fold) identified during routine screening. The first step in the evaluation of mildly elevated serum aminotransferase levels is to repeat the test to confirm persistence of the elevated value. If the aminotransferase level remains elevated, the recommended evaluation is illustrated in Figure 73-2. The next step is to take a careful history focused on identifying all of the patient's medications, including over-the-counter (OTC) medications, complementary and alternative medications (CAM), and substances of abuse. Correlating the use of medications temporally with the laboratory abnormalities will sometimes reveal a specific culprit. Almost any medication, including OTC medications, CAM, and substances of abuse, has the potential to elevate serum aminotransferase levels. Relatively common offending agents include NSAIDs, antibiotics, hydroxymethylglutaryl-coenzyme A reductase inhibitors, antiepileptics, and antituberculous medications (see Chapter 88). The association between use of a medication and liver enzyme elevations is readily established by stopping the medication and observing return of the enzyme levels to normal. Rechallenge with the suspect medication followed by a rise in serum aminotransferase levels is confirmatory but often not undertaken. Muscle disease should also be excluded by obtaining serum creatine kinase and aldolase levels.

The next step in the evaluation is to assess the patient for the more common and treatable causes of liver disease, including chronic hepatitis B and C, hemochromatosis, autoimmune hepatitis, Wilson disease, and NAFLD. Although autoimmune hepatitis is commonly considered a disease of young to

BOX 73-1 Causes of Elevated Serum Aminotransferase Levels*

Chronic, Mild Elevations, ALT > AST (<150 U/L or 5 × normal)

Hepatic Causes
α_1-Antitrypsin deficiency
Autoimmune hepatitis
Chronic viral hepatitis (B, C, and D)
Hemochromatosis
Medications and toxins
Steatosis and steatohepatitis
Wilson disease

Nonhepatic Causes
Celiac disease
Hyperthyroidism

Severe, Acute Elevations, ALT > AST (>1000 U/L or >20-25 × normal)

Hepatic Causes
Acute bile duct obstruction
Acute Budd-Chiari syndrome
Acute viral hepatitis
Autoimmune hepatitis
Drugs and toxins
Hepatic artery ligation
Ischemic hepatitis
Wilson disease

Severe, Acute Elevations, AST > ALT (>1000 U/L or >20-25 × normal)

Hepatic Cause
Medications or toxins in a patient with underlying alcoholic liver injury

Nonhepatic Cause
Acute rhabdomyolysis

Chronic, Mild Elevations, AST > ALT (<150 U/L, <5 × normal)

Hepatic Causes
Alcohol-related liver injury (AST/ALT > 2:1, AST nearly always <300 U/L)
Cirrhosis

Nonhepatic Causes
Hypothyroidism
Macro-AST
Myopathy
Strenuous exercise

*Virtually any liver disease can cause moderate aminotransferase elevations (5-15 × normal).

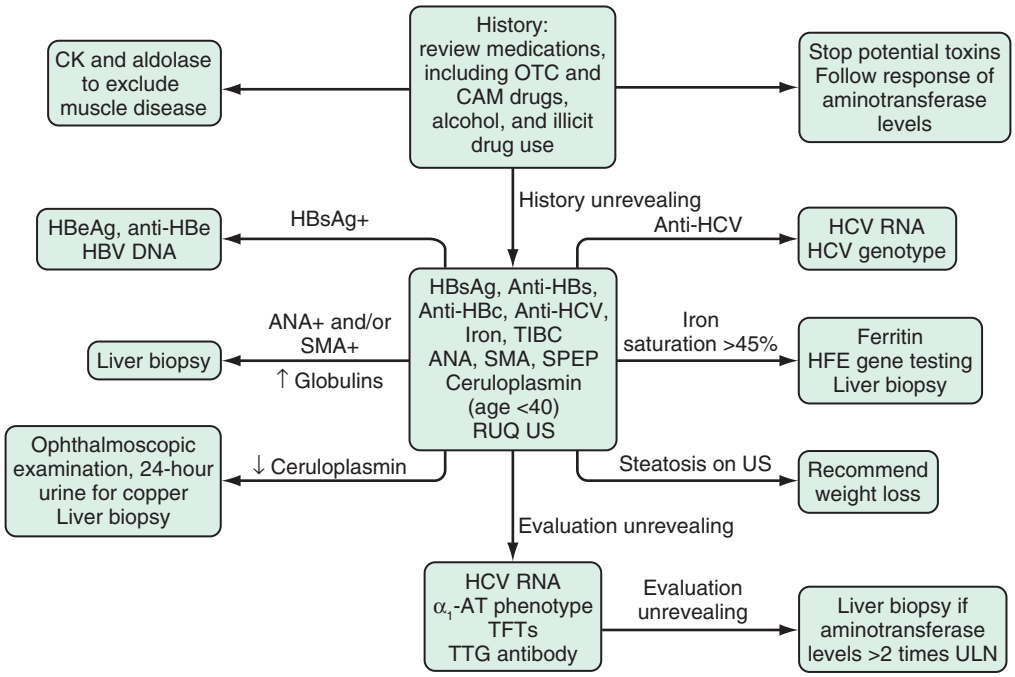

FIGURE 73-2. Evaluation of asymptomatic elevation of serum aminotransferase levels. a_1-AT, a_1-antitrypsin; ANA, antinuclear antibodies; Anti-HBc, antibody to hepatitis B core antigen; Anti-HBe, antibody to hepatitis B e antigen; Anti-HBs, antibody to hepatitis B surface antigen; Anti-HCV, antibody to HCV; CAM, complementary and alternative medicines; CK, creatine kinase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HFE, hemochromatosis; OTC, over-the-counter; RUQ, right upper quadrant; SMA, smooth muscle antibodies; SPEP, serum protein electrophoresis; TIBC, total iron binding capacity, TFTs, thyroid function tests; TTG, tissue transglutaminase; ULN, upper limit of normal.

middle-aged women, it also is seen in men and has been reported in all ethnic groups (see Chapter 90). The clinical onset of Wilson disease is usually between 5 and 25 years of age; the diagnosis should be considered initially in all patients age 40 or younger and those older than age 40 with aminotransferase elevations that remain unexplained after other causes are excluded (see Chapter 76). NAFLD is the most common cause of elevated serum aminotransferase levels in the United States (see Chapter 87), but there is no specific laboratory test for NAFLD.

If testing for the more common causes fails to provide a diagnosis, the less common causes of liver disease, such as α_1-antitrypsin deficiency, and extrahepatic causes of persistently elevated liver enzyme levels, such as thyroid disease and celiac disease, should be sought. A meta-analysis of 11 studies has shown that undetected celiac disease is a potential cause of otherwise unexplained elevated serum aminotransferase levels in 3% to 4% of cases.[23] If testing for these disorders is negative, the decision to perform a liver biopsy is determined by the degree of aminotransferase elevation, with the recognition that the results of the biopsy are unlikely to alter management.

ALKALINE PHOSPHATASE

The term *alkaline phosphatase* applies generally to a group of isoenzymes distributed widely throughout the body.[24] The isoenzymes of greatest clinical importance in adults are in the liver and bone because these organs are the major sources of serum ALP. Other isoenzymes originate from the placenta, small intestine, and kidneys. In the liver, ALP is found on the canalicular membrane of hepatocytes; its precise function is undefined. ALP has a serum half-life of approximately 7 days, and although the sites of degradation are unknown, clearance of ALP from serum is independent of either patency of the biliary tract or functional capacity of the liver. Hepatobiliary disease leads to increased serum ALP levels through induced synthesis of the enzyme and leakage into the serum, a process mediated by bile acids.[25]

A number of individual physiologic variations in serum ALP levels have been identified. Patients with blood groups O and B have elevations in serum ALP levels caused by release of intestinal ALP after a fatty meal.[26] This observation is the basis for the recommendation by some authorities that the serum ALP level be checked in the fasting state. An increased serum ALP level of intestinal origin is seen in benign familial elevation of the serum ALP. Serum ALP values vary with age. Male and female adolescents have serum ALP levels twice the level seen in adults; the level correlates with bone growth, and the increase in serum is in bone ALP. Although the level of serum ALP increases after 30 years of age in both men and women, the increase is more pronounced in women than in men; a healthy 65-year-old woman has a serum ALP level 50% higher than that of a healthy 30-year-old woman.[27] The reason for this difference is not known. In a person with isolated elevation of the serum ALP level, the serum GGTP or 5′NT are used to distinguish a liver origin from bone origin of the ALP elevation (see later). A low serum ALP level may occur in patients with Wilson disease, especially those presenting with fulminant hepatitis and hemolysis, possibly because of reduced activity of the enzyme owing to displacement of the cofactor zinc by copper (see Chapter 76).

GGTP

GGTP is found in the cell membranes of a wide distribution of tissues including liver (both hepatocytes and

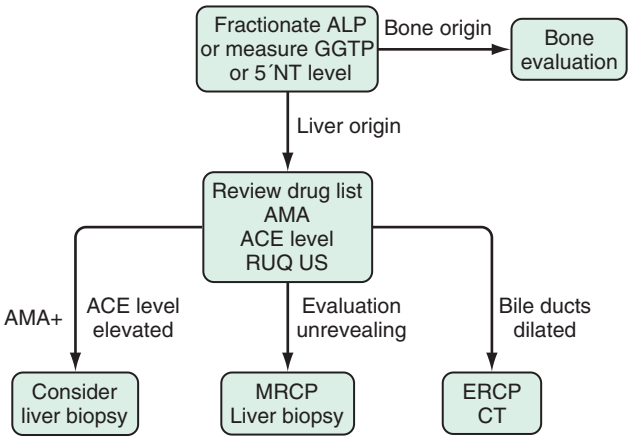

FIGURE 73-3. Evaluation of an isolated elevation of the serum alkaline phosphatase level. ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; 5′NT, 5′ nucleotidase; RUQ, right upper quadrant.

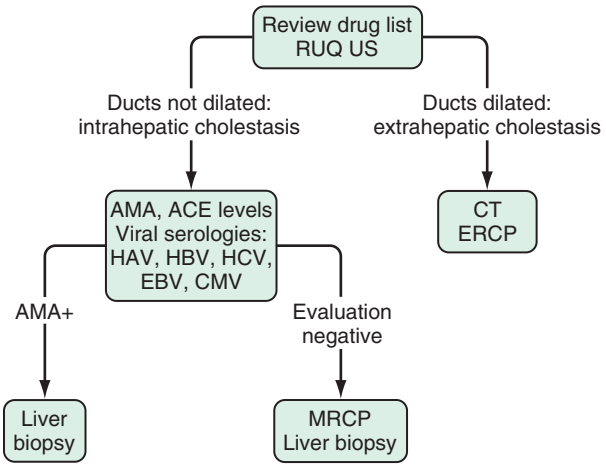

FIGURE 73-4. Evaluation of cholestatic liver enzyme elevations. ACE, angiotensin-converting enzyme; AMA, antimitochondrial antibodies; CMV, cytomegalovirus; RUQ, right upper quadrant.

cholangiocytes), kidney, pancreas, spleen, heart, brain, and seminal vesicles. It is present in the serum of healthy persons. Serum levels are not different between men and women and do not rise in pregnancy. Although an elevated serum GGTP level has high sensitivity for hepatobiliary disease, its lack of specificity limits its clinical utility. The primary use of serum GGTP levels is to identify the source of an isolated elevation in the serum ALP level; GGTP is not elevated in bone disease (Fig. 73-3).[28] GGTP is elevated in patients taking phenytoin, barbiturates, and some drugs used in HAART, including nonnucleoside reverse transcriptase inhibitors and the protease inhibitor abacavir.[29,30]

Serum GGTP levels are also elevated in patients who drink alcohol, and some experts have advocated use of the GGTP level for identifying unreported alcohol use (see Chapter 86). The sensitivity of an elevated serum GGTP level for alcohol use ranges from 52% to 94%, but a low specificity limits its usefulness for this purpose.[31] One study has suggested an association between high serum GGTP levels and the risk of hepatocellular carcinoma.[32] The GGTP level had a negative predictive value of 97.9%—higher than that for ALP, total bilirubin, ALT, and AST—for detecting bile duct stones in patients undergoing laparoscopic cholecystectomy.[33] An isolated GGTP level was associated with an elevated mortality risk in 560,000 insurance applicants and with metabolic syndrome, diabetes mellitus, and cardiovascular disease.[34]

5′-Nucleotidase

5′NT is associated with the canalicular and sinusoidal plasma membranes; its function is undefined. 5′NT is also found in the intestine, brain, heart, blood vessels, and endocrine pancreas. Serum levels of 5′NT are unaffected by sex or race, but age affects the level; values are lowest in children and increase gradually, reaching a plateau at approximately 50 years of age. As with GGTP, the primary role of the serum 5′NT level is to identify the organ source of an isolated serum ALP elevation (see Fig. 73-3). The 5′NT level is not increased in bone disease and is primarily increased in hepatobiliary disease.

Approach to the Patient with an Elevated Level

The first step in the evaluation of a patient with an isolated and asymptomatic elevation of the serum ALP is to identify the tissue source (see Fig. 73-3). The most precise way of doing this is via fractionation through electrophoresis; each isoenzyme of ALP has different electrophoretic mobilities.[35] Tests used in the past that involved heat and urea denaturation of ALP are neither sensitive nor specific. An acceptable alternative method is to check either the serum GGTP or 5′NT level; elevation of either verifies that the elevated ALP is the result of hepatobiliary disease. A normal 5′NT level, however, does not rule out the possibility of hepatobiliary disease, because the 5′NT and ALP do not necessarily increase in parallel in early or mild hepatic injury, thus making GGTP the preferred test.

The primary value of an elevated serum level of ALP of liver origin is to allow the recognition of a cholestatic disorder (i.e., a disorder associated with impaired bile flow, often with jaundice). In general, a serum ALP elevation out of proportion to the level of the aminotransferases suggests a cholestatic disorder (see Chapter 21). A 4-fold elevation of the serum ALP is seen in approximately 75% of patients with chronic cholestasis, both intrahepatic or extrahepatic, whereas lesser elevations are nonspecific and can occur in a wide range of conditions. Figures 73-3 and 73-4 illustrate the recommended evaluation of cholestatic liver enzymes—either an isolated ALP elevation (see Fig. 73-3) or a disproportionate elevation of the ALP compared with the aminotransferases (Fig. 73-4).

Central to the evaluation of an elevated ALP level is imaging of the biliary tract. Absence of dilated intrahepatic bile ducts focuses the search on intrahepatic causes of cholestasis (Box 73-2), whereas dilated ducts should lead to an evaluation of extrahepatic causes of cholestasis (Box 73-3). As with elevated aminotransferase levels, the evaluation of intrahepatic causes of cholestatic liver enzymes begins with a carefully taken history of medication use, including OTC medications, CAM, and drugs of abuse, and temporal correlation of their use with elevation of the liver enzyme levels. Withdrawal of the offending agent and resolution of the liver enzymes is sufficient to confirm the diagnosis, and a liver biopsy is generally not required. The rate of improvement can be slow, and if bile duct destruction has developed ("vanishing bile duct syndrome"), the changes may be irreversible.

PBC is a classic autoimmune disease. The immunologic injury is characterized by T cell–mediated destruction of the intrahepatic bile ducts. Although predominantly a disease of middle-aged women, with a median age at diagnosis of

BOX 73-2 Intrahepatic Causes of Cholestatic Liver Enzyme Elevations in Adults

Drugs*
Bland cholestasis
- Anabolic steroids
- Estrogens

Cholestatic hepatitis
- Angiotensin-converting enzyme inhibitors: captopril, enalapril
- Antimicrobials: amoxicillin-clavulanic acid, ketoconazole
- Azathioprine
- Chlorpromazine
- NSAIDs: sulindac, piroxicam

Granulomatous hepatitis
- Allopurinol
- Antibiotics: sulfonamides
- Antiepileptics: carbamazepine, phenytoin
- Cardiovascular agents: hydralazine, procainamide, quinidine
- Phenylbutazone

Vanishing bile duct syndrome
- Amoxicillin-clavulanic acid
- Chlorpromazine
- Dicloxacillin
- Flucloxacillin
- Macrolides

PBC

PSC

Granulomatous Liver Disease
Infections
- Brucellosis
- Fungal: histoplasmosis, coccidioidomycosis
- Leprosy
- Q fever
- Schistosomiasis
- TB, *Mycobacterium avium* complex, bacillus Calmette-Guérin

Sarcoidosis
Idiopathic granulomatous hepatitis
Other
- Crohn's disease
- Heavy metal exposure: beryllium, copper
- Hodgkin's disease

Viral Hepatitis
HAV and HEV
HBV and HCV, including fibrosing cholestatic hepatitis
EBV
Cytomegalovirus

Idiopathic Adulthood Ductopenia

Genetic Conditions
Progressive familial intrahepatic cholestasis
- Type 1 (formerly Byler's disease)
- Type 2
- Type 3

Benign recurrent intrahepatic cholestasis
- Type 1
- Type 2

CF

Malignancy
Hepatocellular carcinoma
Metastatic disease
Paraneoplastic syndrome
- Non-Hodgkin's lymphoma
- Prostate cancer
- Renal cell cancer

Infiltrative Liver Disease
Amyloidosis
Lymphoma

Intrahepatic Cholestasis of Pregnancy

TPN

Graft-versus-Host Disease

Sepsis

*Categorized by histologic pattern. Drug lists are not meant to be comprehensive.

approximately 50 years, 5% to 10% of affected patients are men. The reported age range is 22 to 93 years. Antimitochondrial antibodies (AMA) are found in serum in 95% of patients and are diagnostic; a liver biopsy that demonstrates characteristic histologic findings is confirmatory (see Chapter 91).

PSC is a disease of altered immunity marked by inflammation and fibrosis of the intra- or extrahepatic bile ducts, or both. The disorder is strongly associated with IBD and is found most commonly in younger men. The diagnosis is confirmed by cholangiography, either MRCP or ERCP (see Chapter 68).

Granulomatous liver disease can be caused by a number of disorders (see Box 73-2). Infectious etiologies must be excluded because treatment for many of the other causes of granulomatous liver disease is immunosuppressive therapy. Sarcoidosis is the most common etiology. The diagnosis is based on an elevated angiotensin-converting enzyme (ACE) level and typical extrahepatic manifestations. Hepatic involvement, however, is uncommonly the impetus for initiating therapy for sarcoidosis (see Chapter 36).

Viral hepatitis, particularly cases caused by EBV and cytomegalovirus (CMV), can manifest with a prominent cholestatic liver enzyme pattern (see Chapter 83). A number of familial conditions produce intrahepatic cholestasis (see Table 64-5). Progressive forms of these disorders manifest in childhood, whereas the benign forms—benign recurrent intrahepatic cholestasis types 1 and 2—can manifest for the first time in adulthood. Other intrahepatic causes of cholestatic liver enzymes are listed in Box 73-2.

If imaging shows intrahepatic ductal dilatation, the evaluation focuses on the extrahepatic biliary tract to identify an intrinsic or extrinsic cause of biliary obstruction (see Box 73-3). The evaluation often includes an ERCP for tissue acquisition and placement of a biliary stent if obstruction is present (see Chapter 70). CT provides assessment for an extrinsic process, and tissue acquisition can be performed with CT or EUS guidance.

TESTS OF HEPATIC SYNTHETIC FUNCTION

Albumin

Quantitatively, the most important plasma protein, albumin, accounts for 75% of the plasma colloid oncotic pressure and is synthesized exclusively by hepatocytes. The average adult

BOX 73-3 Extrahepatic Causes of Cholestatic Liver Enzymes in Adults

Intrinsic
Choledocholithiasis

Immune-Mediated Duct Injury
Autoimmune pancreatitis
PSC

Malignancy
Ampullary cancer
Cholangiocarcinoma

Infections
AIDS cholangiopathy
- Cytomegalovirus
- Cryptosporidiosis
- Microsporidiosis

Parasitic infections
- Ascariasis

Extrinsic
Malignancy
Gallbladder cancer
Metastases, including portal adenopathy from metastases
Pancreatic cancer

Mirizzi's Syndrome*

Pancreatitis

Pancreatic Pseudocyst

*See Chapters 65 and 66.

produces approximately 15 g/day and has 300 to 500 g of albumin distributed in body fluids. The liver has the ability to double the rate of synthesis in the setting of rapid albumin loss or a dilutional decrease in the serum albumin concentration.[36] The half-life of albumin is 14 to 21 days; the site of degradation is not known. Albumin synthesis is regulated by changes in nutritional status, osmotic pressure, systemic inflammation, and hormone levels.[37] Therefore, the differential diagnosis of serum hypoalbuminemia, in addition to hepatocellular dysfunction, includes malnutrition, excessive loss from protein-losing enteropathy or nephrotic syndrome, chronic systemic inflammatory conditions, and hormonal imbalances.

The long half-life of albumin in serum accounts for its unreliability as a marker of hepatic synthetic function in acute liver injury. Serum albumin levels less than 3 g/dL in a patient with newly diagnosed hepatitis should raise suspicion of a chronic process. Serum albumin is an excellent marker of hepatic synthetic function in patients with chronic liver disease and cirrhosis, with the exception of patients with cirrhosis and ascites, who may have normal or increased albumin production but an increased volume of distribution that results in a low serum albumin level. Albumin has no utility as a screening test in patients for whom there is low suspicion of liver disease; a study in which the serum albumin level was measured in 449 consecutive patients yielded 56 abnormal results, of which only 2 (0.4%) were of clinical importance.[38]

Prothrombin Time

Clotting is the end result of a complex series of enzymatic reactions involving clotting factors, all of which are produced in the liver except factor VIII, which is produced by vascular endothelial cells. The prothrombin time is a measure of the rate at which prothrombin is converted to thrombin, reflecting the extrinsic pathway of coagulation. Factors involved in the synthesis of prothrombin include II, V, VII, and X. The INR is used to express the degree of anticoagulation on warfarin therapy. The INR standardizes prothrombin time measurement according to the characteristics of the thromboplastin reagent used in a particular laboratory; the initial measurement is expressed as an international sensitivity index (ISI), which is then used in calculating the INR. Because the ISI is validated only for patients taking a vitamin K antagonist, concern has been raised about the validity of using the ISI (and INR) in patients with chronic liver disease.[39] Two studies have demonstrated, in fact, that the ISI, as currently determined, is not accurate for calculating the INR in patients with cirrhosis, and the investigators have proposed that specific ISI and INR determinations using control patients with liver disease be used to eliminate inter-laboratory variability in calculating the INR in patients with cirrhosis.[40,41]

A prolonged prothrombin time can be caused by a number of conditions besides reduced hepatic synthetic function: congenital deficiency of clotting factors, vitamin K deficiency (vitamin K is required for normal functioning of factors II, VII, IX, and X), and DIC. DIC can be identified by measuring a factor VIII level in serum; the level is decreased in DIC and normal or increased in liver disease. Vitamin K deficiency is identified by demonstrating that IV administration of vitamin K (e.g., 10 mg) leads to improvement in the prothrombin time; a 30% or more improvement in the prothrombin time is consistent with hypovitaminosis K. Oral vitamin K may not be absorbed by the intestine in patients with jaundice (see Chapter 94).

Measurement of the prothrombin time in patients with liver disease is most useful in cases of acute liver disease. Unlike the serum albumin, the prothrombin time allows an assessment of current hepatic synthetic function; factor VII has the shortest serum half-life (6 hours) of all the clotting factors. The prothrombin time has prognostic value in patients with acute acetaminophen- and nonacetaminophen-related liver failure (see Chapter 95), as well as alcoholic hepatitis (see Chapter 86). The INR, along with total serum bilirubin and creatinine levels, are components of the MELD score, which is used to allocate donor organs for liver transplantation (see Chapter 97). The MELD score accurately predicts survival in patients with decompensated cirrhosis (see later).

The prothrombin time is not an accurate measure of bleeding risk in patients with cirrhosis, because it assesses only the activity of procoagulant clotting factors, not anticoagulants such as protein C and antithrombin, the production of which is also reduced in cirrhosis. The partial thromboplastin time (PTT) assesses the intrinsic pathway of the coagulation cascade. The PTT can be prolonged in patients with advanced cirrhosis, but prolongation of the PTT is less sensitive than the PT for detecting coagulopathy.

TESTS TO DETECT HEPATIC FIBROSIS

Although liver biopsy is the standard for the assessment of hepatic fibrosis, noninvasive measures of hepatic fibrosis have been developed and show promise (see Chapter 74).[42] These measures include single serum biochemical markers that potentially reflect the activity level of hepatic fibrogenesis (hyaluronan is the best to date) and multiparameter tests aimed at detecting and staging the degree of hepatic fibrosis (>20 such tests are described in the literature).

Hyaluronan is a glucosaminoglycan produced in mesenchymal cells and widely distributed in the extracellular

space. Typically degraded by hepatic sinusoidal cells, serum levels of hyaluronan are elevated in patients with cirrhosis as a result of sinusoidal capillarization (see Chapter 92). A fasting hyaluronan level greater than 100 mg/L had a sensitivity of 83% and specificity of 78% for the detection of cirrhosis in patients with a variety of chronic liver diseases.[43] Hyaluronan has been shown to be useful for identifying advanced fibrosis in patients with chronic hepatitis C, chronic hepatitis B, alcoholic liver disease, and nonalcoholic steatohepatitis.[44] Preoperative serum hyaluronan levels also have been shown to correlate with the development of hepatic dysfunction after hepatectomy.[45]

FibroTest (marketed as FibroSure in the United States) is the best evaluated of the multiparameter blood tests. The test incorporates haptoglobin, bilirubin, GGTP, apolipoprotein A-1, and α_2-macroglobulin and has been found to have high positive and negative predictive values for diagnosing advanced fibrosis in patients with chronic hepatitis C (see Chapter 80). One study showed that use of a more sensitive index cut-off had a sensitivity of 90%, specificity of 36%, positive predictive value of 88%, and negative predictive value of 40% for the diagnosis of bridging fibrosis in patients with chronic hepatitis C.[46] The test has similar performance characteristics in patients with chronic hepatitis B and alcoholic liver disease and has been shown to predict advanced fibrosis in patients taking methotrexate for psoriasis.[47] The newer FIBROSpect II assay incorporates hyaluronate, tissue inhibitor of metalloproteinase 1, and α_2-macroglobulin. In a group of patients with chronic hepatitis C, FIBROSpect II had a sensitivity of 72% and a specificity of 74% for identifying advanced fibrosis.[48]

Transient elastography, marketed as FibroScan, as well as acoustic force radiation impulse elastography, uses US waves to measure hepatic stiffness noninvasively (see Chapter 74). Central to the development of this technique were the principles that fibrosis leads to increased stiffness of hepatic tissue and that a shear wave will propagate faster through stiff material than through elastic material.[49] The US transducer emits a low-frequency (50 Hz) shear wave, and the amount of time required for the wave to go through a set "window" of tissue is measured.[50] The window of tissue is 1 cm by 4 cm—100 times the area of an average liver biopsy. A meta-analysis showed that transient elastography performed best at differentiating cirrhosis from absence of cirrhosis but was less accurate for the estimation of lesser degrees of fibrosis.[51] Transient elastography has been shown to be accurate for identifying advanced fibrosis in patients with chronic hepatitis C, PBC, hemochromatosis, NAFLD, and recurrent chronic hepatitis after liver transplantation[52-55] and was approved by the FDA in 2013 for use in patients with liver disease.

Magnetic resonance elastography (MRE) is another noninvasive technique that has been approved by the FDA. The shear elasticity of the liver is measured after low-frequency (65 Hz) waves are transmitted into the right lobe of the liver. In one study,[56] MRE was found to be superior to transient elastography for staging liver fibrosis in patients with a variety of chronic liver diseases.

QUANTITATIVE LIVER FUNCTION TESTS

Quantitative function tests have been developed in the hope of evaluating the excretory or detoxification capacity of the liver more specifically than the serum bilirubin level. Unfortunately, although these tests lead to improved sensitivity, their lack of specificity and often cumbersome methodology have limited their widespread acceptance, except in research settings.

Indocyanine Green Clearance

Indocyanine green (ICG) is a nontoxic dye that is cleared exclusively by the liver; 97% of an administered dose (0.64 to 6.4 mol/kg given as an IV bolus) is excreted unchanged into bile. ICG can be measured directly by spectrophotometry. Noninvasive methods (dichromatic earlobe densitometry and fingertip optical sensors) generate data that appear to correlate well with levels determined by blood sampling. Possible uses of ICG include the assessment of hepatic dysfunction, measurement of hepatic blood flow, and prediction of clinical outcomes in patients with liver disease. Unfortunately, measurement of ICG has proved to be insensitive for detecting hepatic dysfunction and is inaccurate for measuring blood flow in patients with cirrhosis because of decreased ICG extraction by the diseased liver. Although ICG measurement has shown some promise for predicting outcomes in certain clinical situations such as burn patients, it has not been employed widely outside of research protocols.[57]

Galactose Elimination Capacity

The galactose elimination capacity (GEC) has been studied as a measure of functional hepatic mass. Galactose is given as a single IV bolus (0.5 g/kg), and blood samples are collected. Patients with cirrhosis and chronic hepatitis have reduced galactose clearance from serum as compared with healthy controls. In a study of 781 patients with newly diagnosed cirrhosis and a decreased GEC, the GEC was a strong predictor of short- and long-term all-cause and cirrhosis-related mortality.[58]

Caffeine Clearance

Caffeine clearance tests quantify functional hepatic capacity by assessing the activity of cytochrome P450 1A2, *N*-acetyltransferase, and xanthine oxidase. Caffeine is given orally (200 to 366 mg), and levels are measured in blood, urine, saliva, breath, or scalp hair. The alternative methods correlate well with the plasma clearance method. Tobacco use increases caffeine clearance, and drug interactions can affect results. Increasing age correlates with decreased caffeine clearance. Overnight salivary caffeine clearance has been shown to correlate with ICG measurements and galactose clearance as well as with results of the aminopyrine breath test (see later).[59]

Lidocaine Metabolite Formation

Lidocaine is metabolized to its major metabolite monoethylglycinexylidide (MEGX) by the hepatic cytochrome P450 system.[60] Serum samples are taken 15, 30, and 60 minutes after IV administration of lidocaine (1 mg/kg). Neither MEGX formation nor galactose elimination was found to be superior to the Child-Turcotte-Pugh (CTP) (see Chapter 92) or MELD (see Chapter 97) score in predicting prognosis in patients with cirrhosis secondary to viral hepatitis (see later).[61] Other studies have suggested that a decline in MEGX concentration correlates well with histologic worsening in patients with chronic liver disease.[62]

Aminopyrine Breath Test

The ^{15}C and ^{14}C aminopyrine breath tests (ABTs) measure hepatic mixed-function oxidase mass. The radioactive methyl groups of aminopyrine undergo demethylation and eventual conversion to labeled CO_2, which is then exhaled and can be measured. After an overnight fast, a known dose of ^{15}C aminopyrine (1 to 2 µCi) is administered orally, and breath

samples are taken every 30 minutes for 4 hours; some investigators check a single sample at either 1 or 2 hours. Healthy subjects excrete 6.6% ± 1.3% of the administered dose in the breath in 2 hours; patients with hepatocellular injury excrete considerably less. The degree of decrease in excretion of aminopyrine overlaps considerably in patients with all types of severe liver disease, including cirrhosis, chronic hepatitis, alcoholic liver disease, and hepatocellular carcinoma.[63] Although data have been conflicting regarding the ability of this test to predict survival in patients with chronic liver disease, a study in 2012 of 50 patients showed that the ABT accurately predicted the risk of disease progression in patients with HCV-related chronic hepatitis.[64]

BILE ACIDS

Bile acids are synthesized from cholesterol in hepatocytes, conjugated to glycine or taurine, and secreted into bile (see Chapter 64). After passage into the small intestine, most bile acids are actively reabsorbed. The liver efficiently extracts bile acids from the portal blood. In healthy persons, all bile acids in serum emanate from the reabsorption of bile acids in the small intestine. Maintenance of normal serum bile acid concentrations depends on hepatic blood flow, hepatic uptake, secretion of bile acids, and intestinal transit. Serum bile acids are sensitive but nonspecific indicators of hepatic dysfunction and allow some quantification of functional hepatic reserve. Serum bile acid levels correlate moderately well with the results of ABTs in patients with chronic hepatitis.[65] Unfortunately, the correlation between serum bile acid levels and the histologic severity of chronic hepatitis and alcoholic liver disease is poor.[66] Serum bile acid levels are elevated in patients with cholestatic liver diseases but normal in patients with Gilbert's syndrome and Dubin-Johnson syndrome and can be used to make the distinction. Although decreased serum bile acid levels are highly specific indicators of liver dysfunction, they are not as sensitive as initially hoped.

SPECIFIC APPLICATIONS OF LIVER BIOCHEMICAL TESTING

Liver biochemical tests have been used to monitor for and assess the severity of drug-induced liver injury, assess operative risk, identify candidates for liver transplantation, and direct donor organ allocation.

Drug-Induced Liver Injury

Most drugs that are hepatotoxic cause idiosyncratic liver injury, defined as injury that is unpredictable, occurs at therapeutic drug levels, and is infrequent (see Chapter 88). The estimated frequency of idiosyncratic drug-induced liver injury for any particular medication ranges from 1 in 1000 to 1 in 100,000. These reactions are marked by a variable latency period ranging from 5 to 90 days, or even longer.[67] Other drugs produce dose-dependent toxicity. These injuries are predictable, have a high incidence, and generally have a well-understood mechanism. Acetaminophen is the classic example of a drug that causes dose-dependent liver injury. The dose of acetaminophen exceeds 15 g, almost 4 times the recommended daily dose, in 80% of cases. Acetaminophen doses within the therapeutic range (<4 g/day) can be sufficient to cause liver injury in susceptible persons, such as those who use ethanol chronically. The King's College criteria identify patients with a poor prognosis from acetaminophen-induced liver injury: those with an arterial pH below 7.3 or those with an INR above 6.5, serum creatinine level above 3.4 g/dL, and stage 3 to 4 hepatic encephalopathy (see Chapters 88 and 95).[68]

Most occurrences of drug-induced liver injury are mild and respond promptly to drug withdrawal with complete resolution. Isolated elevation of the serum aminotransferase levels, even to values greater than 3 times the upper limit of normal, is associated with a positive outcome. When aminotransferase elevations are associated with clinical jaundice (so-called Hy's Law, after the late Dr. Hyman Zimmerman), the risk of mortality is increased to as high as 10% (see Chapter 88).[69]

Surgical Candidacy and Organ Allocation

Patients with acute and chronic liver disease are potentially at increased risk of morbidity and mortality if they undergo surgery. The risk depends on the etiology of the liver disease, severity of the liver disease, and planned operation. Although routine preoperative liver biochemical testing is not recommended in otherwise healthy people, the identification of unexpected elevated liver enzyme levels should prompt a postponement of surgery until the cause of the abnormalities has been identified. A retrospective analysis found that patients with acute viral hepatitis who undergo laparotomy had an operative mortality rate of approximately 9.5%.[70] Elective surgery should be postponed in patients with acute hepatitis. The surgical risk in patients with chronic hepatitis correlates with the severity of histologic inflammation in the liver. Those with only portal inflammation and interface hepatitis have low operative risk, whereas those with panlobular hepatitis have an increased risk. The etiology of chronic hepatitis does not influence outcome.

Examination of histology is also critical in assessing the surgical risk in patients with alcoholic liver disease. Hepatic steatosis alone is associated with a low operative risk, whereas alcoholic hepatitis is associated with a mortality rate as high as 55% in patients undergoing portosystemic shunt surgery, for example. A period of abstinence of 3 to 6 months before elective surgery is recommended in these patients. Few data exist for surgical risk in patients with NAFLD, but the mortality rate appears to correlate with the severity of steatosis in patients undergoing liver resection. Steatohepatitis may carry a higher risk than that for steatosis.

An estimated 10% of patients with advanced liver disease undergo surgery in the last two years of their lives. Cirrhosis is associated with increased operative risk, particularly with certain types of surgery, including cardiothoracic surgery, hepatic resection, and other abdominal operations. The data evaluating the surgical risk in these patients were derived retrospectively but point consistently toward the usefulness of the CTP scoring system for predicting perioperative mortality. Two studies performed more than 10 years apart examined mortality after abdominal surgery in cirrhotic patients and reported nearly identical rates of mortality for patients with Child-Pugh class A, B, and C cirrhosis: 10%, 30% to 31%, and 76% to 82%, respectively,[71,72] although lower mortality rates have been reported with greater use of laparoscopic surgery at an expert center.[73] In general, surgery may be undertaken in patients with Child-Pugh class A cirrhosis, whereas the medical condition of patients with Child-Pugh class B cirrhosis should be optimized prior to planned surgery. The mortality rate in patients with Child-Pugh class C cirrhosis is prohibitive, and surgery should be avoided.

The MELD score was created originally to predict survival in patients with cirrhosis and portal hypertension undergoing placement of a transjugular intrahepatic portosystemic shunt

(TIPS).[74] The score has subsequently been validated as an accurate predictor of survival in patients with advanced liver disease. The MELD score incorporates 3 objective variables into a mathematical formula: $9.57 \times \log_e(\text{creatinine}) + 3.78 \times \log_e(\text{total bilirubin}) + 11.2 \times \log_e(\text{INR}) + 6.43$. The working range is 6 to 40, and the score has been shown to correlate with mortality in patients undergoing surgery other than liver transplantation, including hepatic resection, other abdominal procedures, and cardiac surgery.[75-77] MELD is used most often for prioritizing the allocation of donor organs for liver transplantation.[78] Since implementation of the MELD score for prioritizing organ allocation, the number of deaths among patients on the wait list has decreased, suggesting that use of the MELD score is achieving its primary goal—allocation of organs to the sickest patients first (see Chapter 97).

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