Abnormal Liver Function Tests:

April 01, 2003
By \[\text{[1]}\] and \textbf{Consultantlive Staff} \[\text{[2]}\]

\textbf{ABSTRACT:} Serum levels of aspartate aminotransferase and alanine aminotransferase that exceed 1000 IU/L indicate acute viral hepatitis (A, B and, rarely, C), acute drug toxicity (eg, acetaminophen overdose or isoniazid hepatotoxicity), or ischemic liver injury. In chronic hepatitis (ie, hepatitis B or C or autoimmune), values range from mildly elevated to usually less than 400 IU/L. Elevated levels of alkaline phosphatase and gamma;-glutamyltransferase (GGT) are consistent with cholestatic disease: primary biliary cirrhosis, primary sclerosing cholangitis, idiosyncratic drug reactions, or mechanical biliary obstruction (eg, biliary stones or tumor). Elevation in the GGT level can also be induced by alcohol consumption or medications (eg, phenytoin). Isolated unconjugated hyperbilirubinemia suggests Gilbert syndrome or a hematologic disorder; conjugated hyperbilirubinemia reflects impaired hepatic excretion. Serum bilirubin and albumin and INR have prognostic significance in chronic liver disease; bilirubin and INR are more useful in acute liver failure because albumin has a long half-life.

Serum or plasma biochemical tests are widely available, convenient, and sensitive tools for the detection, diagnosis, and monitoring of liver disease. Proper interpretation of these tests involves consideration of the clinical context (patient history, physical examination results, concurrent medical conditions, and medication use), the pattern of liver enzymes and their evolution over time, and the use of additional diagnostic tests. Liver biochemical tests can be divided into 4 categories:

\begin{itemize}
  \item Hepatocellular enzymes (serum aminotransferases).
  \item Markers of cholestasis (alkaline phosphatase [ALP], gamma;-glutamyltransferase [GGT], 5′ nucleotidase).
  \item Tests of liver excretion (bilirubin).
  \item Tests of liver synthetic function (albumin, INR).
\end{itemize}

A pattern may emerge in which the elevation of levels of one group of enzymes predominates, suggesting hepatocellular or cholestatic liver injury (\textbf{Table 1}). Often, however, levels of hepatocellular and cholestatic enzymes increase simultaneously and a mixed pattern appears in which case, the differential diagnosis remains broad and both hepatocellular and hepatobiliary diseases must be considered.

Here I provide an overview to help you determine which tests to order, how to interpret the results, and how (and when) to proceed with additional diagnostic testing.

\textbf{HEPATOCELLULAR ENZYMES}

The aminotransferases are normally present within liver parenchymal cells (hepatocytes) and enter the systemic circulation after injury to the hepatocyte. The serum aminotransferases, or transaminases, of clinical value are aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Although levels of these 2 enzymes are often elevated together, they are not interchangeable, and measuring both is more informative than measuring only one.

ALT is regarded as more specific to the liver, since AST is also present in skeletal and cardiac muscle and is elevated in cases of muscle injury or inflammation. The finding of an elevated level of muscle enzyme, such as creatine kinase, distinguishes between diseases of skeletal or cardiac muscle and those of the liver.

In many acute and chronic inflammatory liver diseases, ALT values tend to be higher than AST values. An often-cited exception is alcoholic hepatitis, in which the AST:ALT ratio is typically greater than 2. This is attributed to the effects of long-term alcohol use on intracellular aminotransferase levels; it also reflects alcohol-mediated mitochondrial injury (AST is present in mitochondria and cytosol, whereas ALT is only cytosolic).

The magnitude and evolution of AST and ALT can provide useful clues to the nature of the underlying liver disease (\textbf{Case I}). Aminotransferase values greater than 1000 IU/L reflect significant hepatocyte
Injury, which can be found in the following settings:

**Acute viral hepatitis** (hepatitis A, B and, rarely, C).

**Acute drug toxicity** (most commonly acetaminophen overdose, which can occur accidentally when maximal therapeutic doses are taken during heavy alcohol consumption; however, any idiosyncratic drug reaction can produce these values).

**Ischemic liver injury** (typically associated with prolonged hypotension).

**Alcoholic hepatitis** never causes a flare in aminotransferase levels to this degree-AST levels typically approach 250 IU/L and do not significantly exceed this, even in patients with severe alcoholic hepatitis associated with jaundice and synthetic dysfunction.

Spectacular aminotransferase flares in which levels exceed 5000 IU/L are uncommon in viral hepatitis and are usually a consequence of a massive confluent hepatocyte injury, as can be seen with severe drug hepatotoxicity and ischemia. Since the injury in such cases is generally brief, functional impairment may be transient and the recovery rapid.

In any patient who has acute liver disease, however, it is important to monitor clinical status (to detect hepatic encephalopathy) and laboratory parameters of liver function (ie, bilirubin levels and INR), since AST and ALT values may "improve" in a patient whose disease is progressing to fulminant hepatic failure because most of the liver parenchyma has died.

**Chronic hepatitis**, whether viral or autoimmune in origin, is characterized by persistent elevations in levels of serum aminotransferases that are typically 2 to 10 times the upper limit of normal. ALT levels may fluctuate in chronic hepatitis, especially with chronic hepatitis C virus infection; serial measurements over 6 or more months may be required to adequately assess disease activity. Furthermore, even though the degree of aminotransferase elevation generally correlates with disease activity, liver biopsies in patients who have hepatitis C may reveal significant active hepatitis even with a near-normal ALT level.

Also keep in mind that serum aminotransferase levels provide no information about the degree of liver fibrosis and are often completely normal in patients with advanced but inactive cirrhosis. A liver biopsy is the most accurate method of evaluating fibrosis and is also the most accurate way to assess iron overload in patients with suspected hemochromatosis.

### Cholestatic Enzymes

The 2 enzymes most widely used as markers of cholestasis are ALP and GGT (Case II). 5’ Nucleotidase may also be used as a liver-specific biliary marker, but it is less sensitive than ALP and may not be helpful if ALP levels are only mildly elevated.

ALP and GGT are localized to the apical region (bile canaliculi) of the hepatocytes. Their synthesis by the liver is induced by impaired bile flow (cholestasis)-whether it is the result of mechanical bile duct obstruction (postsurgical strictures; biliary stones; tumors, including cholangiocarcinoma; and, commonly, cancers at the head of the pancreas) or dysfunction at the level of the canaliculus (estrogen; drugs [potentially any drug but, classically, chlorpromazine and erythromycin]; and autoimmune cholangiopathy, such as primary biliary cirrhosis and primary sclerosing cholangitis). The biliary enzyme values are also increased in infiltrative liver disorders, such as granulomatous hepatitis, steatosis (fatty change), hepatic amyloidosis, and malignancies.

Because active synthesis of both ALP and GGT is required for serum levels to increase, there may be a delay of 1 day or more after acute bile duct obstruction before serum levels start to increase. This can be misleading because acute bile duct obstruction can be heralded by an abrupt but transient rise in serum aminotransferase levels up to 500 IU/L within the first 24 to 48 hours; only later does a typical cholestatic or "obstructive" pattern with elevated ALP and GGT values become apparent.

ALP is not specific to the liver; it is also present in extrahepatic organs, including bone, placenta, and fallopian tubes. Levels of ALP in bone may be elevated in any condition associated with osteoblastic activity, such as Paget disease, bone metastases, and osteomalacia; it may also be elevated in children (before epiphyseal fusion). The osseous isoenzyme of ALP is less heat-stable than the liver isoenzyme; this allows fractionation of serum ALP into bone- and liver-derived components. In practice, it is simpler and more accurate to measure another biliary enzyme, such as GGT, which is not present in bone.

GGT is a sensitive marker, and levels are almost always elevated if the patient's increased level of serum ALP is from the liver. A rare exception occurs in familial benign recurrent intrahepatic cholestasis, in which GGT values classically remain normal despite significantly increased ALP levels and hyperbilirubinemia. GGT, however, is not specific for cholestasis; serum elevations occur in patients who consume excessive amounts of alcohol or are receiving long-term therapy with microsomal enzyme-inducing drugs, such as phenytoin.

Under most circumstances, it is not possible to make a specific diagnosis based on elevation of
enzyme levels alone. Additional studies may include abdominal ultrasonography, cholangiography, liver biopsy, and/or more specific laboratory tests (Box).

TESTS OF LIVER EXCRETION
Bilirubin is the end product of heme metabolism and is present in serum in both unconjugated and conjugated forms (reported by the laboratory as indirect and direct serum bilirubin, respectively). Unconjugated hyperbilirubinemia may reflect an extrahepatic disorder of the hematologic system, reflecting ineffective hematopoiesis or hemolysis.

A common and benign hepatic cause of unconjugated hyperbilirubinemia is Gilbert syndrome. It is important to emphasize that Gilbert syndrome is not a true disease. Rather, it is a genetically determined normal variant characterized by relatively less efficient uptake of unconjugated bilirubin. In Gilbert syndrome, the level of unconjugated hyperbilirubinemia increases with concurrent illness and physiologic stress; however, all liver enzyme values remain within normal limits. Liver biopsy is not indicated in Gilbert syndrome; the results are typically normal.

Levels of both conjugated and unconjugated serum bilirubin are elevated in patients with liver disease. Conjugated hyperbilirubinemia reflects impaired hepatic excretion. Clinical jaundice is usually not apparent until the total bilirubin level exceeds twice the normal limit. Jaundice results from both cholestatic and hepatocellular liver disease and may be exacerbated by concurrent renal dysfunction (impaired urinary excretion of hyperbilirubinemia) and hemolysis (increased production of bilirubin in addition to impaired hepatobiliary excretion). Acute Wilson disease, with both hepatocellular failure and significant hemolysis, is an example of the latter and may present with marked hyperbilirubinemia and a normal, sometimes even below normal, serum ALP level.

In the chronic autoimmune cholangiopathies (primary biliary cirrhosis and primary sclerosing cholangitis), the degree of hyperbilirubinemia predicts survival. Although many prognostic mathematical models that include serum bilirubin have been developed-of which the Mayo model is the best known-a general rule of thumb is to refer patients with chronic autoimmune cholangiopathies to a transplant center if their total serum bilirubin level exceeds 50 µmol/L (3 mg/dL). In the absence of contraindications to transplantation, patients should be waitlisted when the level approaches 100 µmol/L (6 mg/dL).

TESTS OF SYNTHETIC FUNCTION
The liver synthesizes albumin and the clotting factors, specifically fibrinogen and factors II (prothrombin), V, VII, IX, and X. Serum albumin levels and INR are widely used as indicators of the synthetic properties of the liver. These tests, however, are not very sensitive markers of liver function; hypoalbuminemia and coagulopathy are present only when hepatic functional impairment exceeds 90%.

Furthermore, serum albumin levels may be low for a number of nonhepatic reasons, including urinary (nephrotic syndrome) or gastrointestinal loss (protein-losing enteropathies), microvascular redistribution (sepsis), and malnutrition. INR may be elevated secondary to consumptive coagulopathy, vitamin K deficiency, or warfarin therapy. The serum half-life of albumin is about 20 days, whereas the half-life of factor VII (the factor with the shortest half-life) is only a few hours. In chronic liver disease, both serum albumin and INR are useful prognostic indicators and are incorporated into the Child-Pugh scoring classification (Table 2). In acute liver failure, however, serum albumin may not reflect the degree of failure, and INR is the more useful measure. A significant coagulopathy (as well as jaundice and encephalopathy) in the setting of acute liver failure warrants consultation with the regional transplant center.

References: FOR MORE INFORMATION:

**Source URL:** [http://www.diagnosticimaging.com/articles/abnormal-liver-function-tests](http://www.diagnosticimaging.com/articles/abnormal-liver-function-tests)

**Links:**
[2] [http://www.diagnosticimaging.com/authors/consultantlive-staff](http://www.diagnosticimaging.com/authors/consultantlive-staff)