Liver Function Tests: What is the Risk?

Clifton P. Titcomb, Jr, MD

Five laboratory assays are commonly called liver function tests (LFTs), although these tests are neither specific to the liver nor true measures of liver function. As a result, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP) and bilirubin have proven problematic for clinicians and risk selection professionals alike. Further, underwriters and insurance medical directors find these tests difficult to assess because of the lack of data directly relating LFT elevations to mortality outcome. Nonetheless, the tests are frequently encountered, so a strategy for evaluating abnormal results is critical to ensure accurate and fair pricing. This paper reviews basic information on LFTs, available mortality data and the application of this knowledge to the underwriting process.

In most cases, LFTs indicate possible hepatocellular injury (ALT and AST) or interruption of bile flow or cholestasis (ALP, GGT). Only bilirubin approaches being a marker for a deficiency of actual liver functional activity, as it is a breakdown product of the protein heme, which is found in red blood cells and processed through the liver. True indicators of hepatic function are tests that directly or indirectly measure substances synthesized in the liver and include serum albumin and cholesterol and the prothrombin time.

As a further complication, these enzymes are not found exclusively in the liver. Elevations may not even be indicative of hepatic impairment at all. Even when they are increased due to liver dysfunction, the degree of elevation may not correlate with the amount of organ damage that has occurred. It is not surprising that any attempt to assess the morbidity or mortality risk associated with LFTs requires a thorough understanding of each test and its limitations.

DEFINING LIVER FUNCTION TESTS

Hepatocellular Enzymes (ALT and AST)

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are both found within hepatocytes. When hepatocytes die or are damaged, these enzymes are released into the circulation where they can be measured, allowing them to be considered markers for hepatocellular injury. Despite their similarities, they differ somewhat in their specificity for the liver and their distribution within the hepatocytes.

ALT is found in other tissues, including the kidney, lung, pancreas, red blood cells and skeletal muscle. However, its concentration is by far highest in the liver and is, therefore, considered relatively specific for hepatic dysfunction. In addition, ALT is located only within the cytoplasm of the hepatocytes.
AST is also found in many tissues, including the heart, brain, skeletal muscle and kidney. It is more evenly distributed than ALT, so its elevation is considered less specific for liver cell injury. In addition, AST is found in both the mitochondria and the cytoplasm of the hepatocytes. It may also occasionally be detected as a larger-than-normal molecule called a macro-enzyme, which leads to elevated readings on conventional laboratory assays. This macro-enzyme may lead to an isolated increase in AST of several times normal without evidence of other disease. It is not associated with an adverse outcome.1

Another idiosyncrasy of the transaminases relates to the calculation of their normal ranges. Most laboratory test results produce a bell-shaped distribution, with 95% of individuals falling within 2 standard deviations of the mean value for the group. Values falling within 2.5% on either side of this range are considered abnormal. The transaminases are different, however, since AST and ALT do not follow a normal bell-shaped distribution. Instead, the curve skews to the right, creating a long slurred tail as values increase.

The curve varies with gender and ethnic background, so the number of individuals considered abnormal depends somewhat on the population used to establish the normal range. Males, blacks or Hispanics generally have higher values in the tail or “abnormal” portion of the curve, while the results in women are generally lower. Many obese individuals (otherwise unimpaired) have values slightly above the conventional normal range. In fact, some clinicians favor adjusting the acceptable range for overweight persons (see discussion below).2 The net result of all these exceptions is that there may be substantial overlap between the diseased and non-diseased state when transaminase values are mildly elevated. As ALT and AST levels rise, the likelihood of significant pathology increases.

However, transaminase values correlate poorly with the degree of liver pathology for several reasons:
1. The type of damage to the cell affects the degree of elevation of the enzymes. Apoptosis (programmed cell death) decreases cell activity, and thus synthesis of enzymes before the termination of cellular activity. Hence the loss of hepatocytes is accompanied by a relatively lower degree of elevation of the ALT and AST. Apoptosis is probably why transaminase values in hepatitis C are relatively low or normal despite significant liver damage.
2. Damage may occur more extensively in one portion of the cell than another. For example, alcohol will disproportionately affect the mitochondria rather than the cytoplasm, resulting in a greater rise in AST than ALT.
3. A toxic agent may affect the substrates for synthesis of the transaminases differently. Thus, the reduction of pyridoxine (vitamin B6) levels by alcohol impairs the synthesis and levels of ALT but not AST. For both of the latter reasons, individuals with alcoholic hepatitis will have only modest elevations of the transaminases and, unlike viral hepatitis, an AST higher than ALT.
4. The degree of elevation of the hepatocellular markers depends on the number of liver cells capable of releasing enzymes. In cirrhosis, which causes significant loss of hepatocytes, there may not be enough cells left to produce much elevation of ALT and AST despite the presence of end-stage disease.1±4

**Measures of Cholestasis (ALP and GGT)**

Alkaline phosphatase (ALP) is found in a number of tissues, with approximately 80% being of liver or bone origin. In normal individuals, most of the rest comes from the intestine. Non-pathologic variations are seen in pregnant women (ALP, originating from the placenta, may raise levels up to 2 times normal), infancy and adolescence (increased bony ALP during growth spurts raises levels up to 3 times normal) and individuals with blood groups B and O (increased intestinal ALP occurring after a fatty meal). In addition, ALP values normally increase between ages...
40 and 65, especially in women. Certain drugs or technical factors may also interfere with ALP assays. Acetaminophen, ibuprofen and cefotaxime may increase levels; EDTA, oxalate, citrate and prolonged storage times can lead to decreased values.\textsuperscript{1,3,4}

Differentiation of bony or hepatic origin of ALP can be accomplished by fractionation and detection of isoenzymes, but the process is cumbersome. More common in clinical practice is the use of levels of other enzymes to help determine the origin of an increased ALP. GGT and $5'$-nucleotidase are not found in bone, so their elevation in association with a high ALP value indicates hepatic origin for the latter.\textsuperscript{1,3,4}

Hepatic ALP synthesis occurs in bile duct epithelial cells. Obstruction of bile ducts leads to increased synthesis of ALP. Such obstruction may occur diffusely within the liver by hepatitis or drug reactions, extrahepatically by gallstones or tumors, locally within the liver by tumors or in a patchy intrahepatic pattern with granulomatous disease. Isolated elevations less than 1.5 times normal usually resolve spontaneously and are not generally associated with serious disease. Persistent elevations or levels greater than 1.5 times normal suggest more serious pathology. In particular, primary biliary cirrhosis may present with an isolated elevation of the ALP, especially in women. An elevated anti-mitochondrial antibody suggests this diagnosis.\textsuperscript{1-4}

Gamma-glutamyltransferase (GGT) is the most sensitive marker for biliary tract disease, but its specificity is low due to 2 factors. First, it is found in many tissues, including the heart, brain, pancreas, kidney, spleen and seminal vesicles. Second, its production can be increased or induced by substances, such as alcohol, barbiturates and phenytoin (Dilantin).\textsuperscript{5-8} Elevated levels due to increased production, unlike the transaminases, do not indicate cell damage. In addition, GGT levels are increased with age, body mass index (BMI) and male sex.\textsuperscript{9,10} This poor specificity limits GGT's usefulness in diagnosing liver disease. Its principal role in clinical practice is differentiating bone from liver origin of elevated ALP values. On liver biopsy, isolated GGT elevation has not been found to indicate significant underlying disease.\textsuperscript{11}

**Bilirubin**

Bilirubin, resulting from the enzymatic breakdown of heme, is conjugated with glucuronic acid in the liver to become water soluble and is excreted in the bile. Conjugated bilirubin levels in the serum do not increase until the liver loses half of its functional capacity. When serum conjugated levels are elevated, bilirubin can be detected with a urine dipstick. However, most mild elevations of total bilirubin in asymptomatic individuals are due to increased levels of unconjugated or unprocessed bilirubin.

The 2 most common causes for unconjugated hyper-bilirubinemia are Gilbert's syndrome and hemolysis. Gilbert's is related to a variety of partial defects in the enzyme that conjugates bilirubin; hemolysis simply overwhelms the liver with too much substrate to be processed. With Gilbert's syndrome, bilirubin levels tend to increase during infections and periods of fasting. It is rare for either hemolysis or Gilbert's to increase values above 5 mg/dL.\textsuperscript{12}

**CONDITIONS LEADING TO ELEVATED LFTS**

On biopsy, the most common diagnoses found in individuals with mild to moderately elevated LFTs are non-alcoholic steatosis (fatty infiltration of the liver), non-alcoholic steatohepatitis (fatty liver with significant inflammation), chronic viral hepatitis (primarily hepatitis C in the United States, hepatitis B in other parts of the world), and alcoholic liver disease. Other conditions that may be encountered include hemochromatosis, granulomatous hepatitis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, Wilson's disease and cryptogenic cirrhosis. However, the latter diagnoses represent a distinct minority of all cases with chronic LFT elevation.\textsuperscript{12-15}
Steatosis

The most common of the above conditions is non-alcoholic steatosis, seen in up to 65% of patients in biopsy series. Risk factors for fatty liver include obesity, hyperlipidemia, diabetes and female sex. In general, steatosis not associated with significant inflammation is a non-progressive, benign illness. However, a form of fatty infiltration called steatohepatitis is more problematic. It is found in 1.2% to 8% of liver biopsies and, in addition to fat accumulation, is characterized by liver infiltration with inflammatory cells as well as signs of cell destruction (ballooning degeneration, necrosis), with or without fibrosis. Mallory hyaline bodies, commonly seen in alcoholic liver disease, may be detected as well. Unlike steatosis, steatohepatitis can progress to cirrhosis, possibly reducing life expectancy. This progression is variable and occurs in about 10% to 20% of individuals. Risk factors for cirrhosis include the presence of fibrosis on the original biopsy, comorbidity with type 2 diabetes, higher levels of the LFTs and an AST/ALT ratio > 1 (most steatosis will have a ratio < 1).

Alcohol-related Disease

Liver biopsy findings related to alcohol use can vary considerably. They can include alcoholic steatosis or fatty infiltration, alcoholic hepatitis and/or cirrhosis. Alcoholic steatosis, like nonalcoholic steatosis, rarely leads to serious outcomes from a liver perspective. However, it is a marker for other ethanol-related risks such as trauma. Alcoholic hepatitis, on the other hand, may exhibit a broad range of clinical and pathologic features and may have a significant mortality risk related to hepatic failure in severe cases. Only about 20% to 30% of chronic alcohol abusers develop cirrhosis. However, the long-term probability of premature death is significant in those cases, both from liver failure and hepatic malignancies. Thus, the overall mortality risk in individuals with alcohol-related elevation of LFTs is highly variable.

Hepatitis

Chronic hepatitis, usually of the non-A, non-B variety, was often found in older liver biopsy series. The findings in these studies ranged from mild-chronic, persistent hepatitis to aggressive-chronic, active hepatitis with fibrosis and cirrhosis. However, most of these studies were performed before hepatitis C antibody testing. With the availability of assays for hepatitis C, most of these cases can now be correctly attributed to hepatitis C. While hepatitis B has been rare in the United States, outside the United States and Western Europe it is the more common chronic viral infection of the liver. Both hepatitis B and C present increased mortality risk, primarily due to liver failure and hepatocellular carcinoma.

ASSESSING ELEVATED LIVER FUNCTION TESTS

The mortality risk associated with liver function tests is often difficult to evaluate because the tests are not specific for a given clinical condition. Rather, the tests are markers for the constellation of possible diagnoses, any one or more of which may occur in a group of individuals with increased LFTs. As noted earlier, these conditions may range from non-progressive and benign to serious and life threatening. The overall mortality risk of any group of individuals with increased LFTs, therefore, depends on the distribution of diseases in that group. The larger the number of people with serious disease, the higher the overall risk.

The risk is not uniform for all groups largely because LFT elevations may occur in any of several patterns or combinations. Each pattern represents a different distribution of possible diagnoses. The mortality risk varies with the pattern of elevation, which can be divided into 2 broad categories—isolated increases of single enzymes or combinations of 2 or more.
Elevations of Single Enzymes

*Alanine Aminotransferase (ALT)*

A non-pathologic, isolated increase in the ALT may occur as a result of the non-bell shaped distribution of the test results noted earlier. Values for the ALT above the “normal” range may commonly be seen in obese individuals. In fact, many have suggested that normal parameters be adjusted upwards in overweight individuals. When pathology exists, an isolated elevation of ALT is seen most commonly with fatty liver and hepatitis, particularly hepatitis C. The occurrence of this pattern would be unusual with alcohol-related disease, which is supported by a review of laboratory data on insured lives. The rate of detection of a positive alcohol marker reflex test (carbohydrate deficient transferrin or CDT) was less than 1% for most isolated ALT elevations. The rate of positive hepatitis B surface antigen reflex tests was approximately 3% and hepatitis C antibody rates ranged from 4% to 7% in association with increased levels of ALT. Thus, the likelihood of disease related to alcohol or viral hepatitis is low in cases of isolated ALT elevation. By far, most of these individuals have either steatosis or other insignificant pathology. The more unusual but serious diagnoses (hemochromatosis, Wilson’s disease, etc.) are possible but not likely in this scenario.

*Gamma-glutamyltransferase (GGT)*

The major cause of an isolated increase in GGT levels of pathologic significance is alcohol abuse. However, the sensitivity of GGT for detecting ethanol-related disease is low in non-institutionalized populations, such as insurance-buying groups. Sensitivities in multiple studies have been, at maximum, in the 30% to 35% range. GGT also has a low specificity for alcohol abuse and hepatitis. Insurance lab data show that only 3% to 4% of samples with abnormal GGT values have positive CDT results, and that only 6% to 7% have abnormal values for hemoglobin acetaldehyde (HAA). The rate of positive readings for these reflex tests does not increase substantially as the level of GGT increases, pointing to a threshold effect for the detection of alcohol abuse. Additional increases in enzyme levels do not indicate higher risk. Further, the rate of hepatitis B surface antigen positive results is very low, at about 1%, and hepatitis C is positive in only 3% to 5% of reflexed assays.

Like ALT, GGT levels can be higher in individuals who are obese, further complicating the evaluation of elevated levels of this enzyme. GGT is also frequently elevated in people taking seizure medicines. Consequently, an isolated elevation of GGT is not a reliable marker of serious disease.

*Aspartate Aminotransferase (AST)*

Increased AST values in the absence of other LFT increases are most often related to non-liver-related conditions, primarily muscle disease or injury. Obesity does not appear to affect AST.

*Alkaline Phosphatase (ALP)*

As noted above, an increase of ALP alone can be a normal variant in children, adolescents and pregnant women. In most other situations, isolated elevations are due to bone isoenzymes, not liver-related pathology.

*Bilirubin*

Isolated mild-to-moderate (< 5 mg/dL) increases of total bilirubin are generally due to an elevated unconjugated fraction related to Gilbert’s syndrome or hemolysis, and rarely signify important pathology.

Elevations of Multiple Enzymes

Elevations of multiple enzymes may occur in several patterns. The transaminases (ALT and AST) alone may be increased, or GGT and one of the transaminases may be elevated, or GGT, ALT and AST may all exceed the normal range. Any of these combinations
ALT + AST

Increased values for both of the transaminases (ALT + AST) may be associated with any of the 3 major diagnoses of importance in insurance applicants: steatosis, hepatitis or alcohol abuse. However, the probability of serious disease varies with the specific pattern and the degree of elevation of the enzymes involved. Insurance laboratory data indicates a positive CDT reflex rate of 1% to 4% (2%–5% with HAA) for this pattern that does not increase as the level of ALT increases. Hepatitis B and C reflex rates are 3% and 9%, respectively, with minimal levels of ALT but climbs steadily with increasing transaminase values to levels of 13% and 25%, respectively. In steatosis and hepatitis, the absolute values of ALT will exceed those of AST (AST/ALT ratio \( \leq 1 \)). An AST/ALT ratio > 1 suggests alcohol-related disease or the presence of fibrosis and/or cirrhosis associated with one of the other potential etiologies (steatohepatitis vs. steatosis, cirrhosis vs. mild hepatitis C, etc.)\(^{23,35–38}\). For this reason, a reversal of the usual AST/ALT ratio is considered a marker for more serious disease.

ALT + GGT

The combination of ALT plus GGT has a reflex pattern similar to that of ALT alone.\(^{30}\) The diagnoses of concern are fatty liver, alcohol-related disease and hepatitis C. Steatosis is the most likely, especially with mild elevations of the values.

AST + GGT

When both the AST and GGT are above the normal range, the likelihood of more serious disease is increased. The rate of CDT positive reflex tests increases to approximately 25% and positive hepatitis C rates to about 15%.\(^{30}\) A major reason for these findings in this uncommon combination is that, by definition, the AST/ALT ratio is > 1.

ALT + AST + GGT

If ALT, AST and GGT are all elevated, the probability of alcohol-related disease or hepatitis increases significantly. In addition, the likelihood of serious pathology increases as individual enzyme values rise.\(^{30}\) Once again, an AST/ALT ratio portends a worsened outcome.

ALP or Bilirubin

A concomitant elevation of the ALP or bilirubin increases the probability of serious pathology for any combination of the other enzymes. This risk is higher if the ALP or the bilirubin is at least moderately elevated (>1.5 times normal and >2.0 mg/dL, respectively).

For any of the above combinations, the presence of an elevated HDL value significantly increased the positive reflex rate for CDT in the insured lives experience. For example, for males with isolated GGT elevations, the CDT reflex positive rate jumped from the 3% range to 15% range when the HDL was greater than 70 in males. A similar pattern is seen with most other LFT groupings.\(^{30}\)

These disease probability scenarios apply only in the absence of indicators of specific causes of serious liver disease. These indicators include historical information (personal or family history of hemochromatosis, Wilson’s disease or alpha-1-antitrypsin deficiency), imaging studies (evidence of fibrosis/cirrhosis on MRI, CAT scan or ultrasound) or additional blood tests (positive anti-smooth muscle, anti-nuclear or anti-mitochondrial antibodies, iron saturation levels \( \geq 50\% \), increased ferritin levels, reduced alpha-1-antitrypsin or ceruloplasmin levels). It’s probably safe to assume that serious liver dysfunction is present—regardless of the pattern of enzyme elevation—if one of the true markers for hepatic function, such as serum cholesterol and/or albumin (decreased) or prothrombin time (increased), is abnormal.

MORTALITY RELATED TO LFT ELEVATIONS

It’s difficult to estimate mortality risk associated with LFT elevations because there
are no clinical studies that directly measure outcome from test results alone. Most clinical articles on liver function tests simply try to assess which diagnoses are present. However, insurance risk selection is different because the underwriter or medical director is asked to assess the average mortality outcome for a group of individuals with a given pattern of enzyme elevation. The only way to make this assessment is to attempt reconstruction of the combination of diagnoses present when one of these patterns is encountered. For example, what would be the pathology profile of a hypothetical group of individuals with elevated GGT alone? How many would have steatosis? Hepatitis? Alcohol-related disease? There are 3 ways to develop answers: evaluation of clinical data, insured lives experience studies, and modeling.

Clinical Data

One can get some sense for the overall mortality associated with elevated LFTs by looking at clinical studies in which liver biopsies have been performed. In these studies, patients with persistent mild-to-moderate elevations of the liver enzymes were evaluated with a liver biopsy. Not surprisingly, a variety of conditions were detected. We estimated the overall mortality risk associated with the group by multiplying the proportion of persons in each disease category by the relative mortality associated with each of these impairments. When we applied this process to 3 of the previously noted clinical studies, the estimated mortality ratios obtained were 184%, 198% and 208%. These values are certainly elevated, but not exceedingly high.

Further manipulation of the biopsy data allows estimation of the group’s mortality risk if the more serious causes for LFT elevations (ie, hepatitis and alcohol) are eliminated. When we repeated the process with these diagnoses excluded, overall mortality of the cohorts was reduced to 121%, 166% and 129%. Since the studies were performed at referral centers, it is not surprising that some of the more uncommon causes of serious liver disease were over-represented in these cohorts and that the actual experience of the residual pool in a group of insurance applicants would likely be lower. These analyses suggest that background mortality in the population with elevated LFTs is fairly low if alcohol abuse and hepatitis can be reliably excluded.

Insurance Experience

Another approach is to evaluate the outcome in individuals who purchased life insurance policies. Data on experience of insureds with elevated liver enzymes was recently reported in the Alcohol Abuse and Liver Enzymes (AALE) Study from the Morbidity and Mortality Liaison Committee. This intercompany study reviewed the mortality of individuals underwritten for insurance from 1989–1995, followed until 1997 policy anniversaries, with Medical Information Bureau (MIB) codes reported for abnormal liver enzymes and/or GGT. Observed deaths were compared to the number of expected deaths from the sex-distinct 1990–1995 Select Basic Tables based on standard lives experience. For individuals with policies issued on a standard basis, the actual mortality ratio was 87% (all ages combined). For applicants accepted on a substandard basis, the mortality ratio was 139% (all ages combined).

Few individuals in the study who had liver test codes reported were also coded for alcohol abuse or adverse driving. However, other impairment codes could be present and could contribute to the overall mortality experience. Nevertheless, because the policies were issued and placed in force, the degree of elevation of the liver enzymes was probably mild and co-morbidities were not serious. Higher test values or the presence of major impairments would have probably led to highly substandard (offer of insurance not accepted) or declined policies. Like the clinical data, the results suggest that excess mortality is associated with abnormalities of the liver enzymes, but the risk is not excessive. Interestingly, the experience in the substandard group (139%)
resembled the mortality estimates for the clinical articles in which alcohol-related disease and hepatitis were excluded.

Modeling

While the above exercises are useful, they fail to address the fundamental problem faced by underwriters and medical directors—being able to assess mortality risk associated with different patterns and degrees of enzyme elevation (ie, what is typically encountered in underwriting individual cases). Another approach was needed, which required creating a model with data from an insurance laboratory.

The number of positive reflex tests for CDT, hepatitis B antigen and hepatitis C antibody for each of the above noted combinations of increased values for GGT, ALT and AST (GGT alone, ALT alone, ALT plus AST, etc.) were obtained. Due to the low sensitivity of the CDT assay, both the positive predictive value and the predictive value for disease of a negative test were employed in the model in the estimation of the likelihood of alcohol abuse. Using this information, the percentage of individuals in each of the enzyme combination categories with probable alcohol- or hepatitis-related disease was calculated. A relative mortality risk for each of the diagnoses was also estimated.

This diagnosis-specific relative risk estimate was varied depending on the pattern of enzyme elevation. For example, the risk of alcohol-related mortality was assumed to be higher if all 3 tests were increased, as opposed to a single elevation because of the higher risk of cirrhosis and subsequent liver failure or carcinoma. The percentages of each group that fit into each disease category were then multiplied by the relative mortality risk for each of the diagnoses. Finally, a relative mortality risk was assigned to the residual group, those not falling into the hepatitis or alcohol categories. The relative risk was also varied for this group, depending on the pattern of enzyme elevation, to account for the possible presence of other diagnoses that would pose an additional mortality risk, such as autoimmune hepatitis, steatohepatitis, etc. In general, the greater the number of tests that were elevated and the greater the increase in values, the higher the assumed risk of the residual group.

When completed, the model indicated that the overall risk for LFT elevations was indeed modest, especially if alcohol abuse was not otherwise suspected on clinical grounds. For single enzyme elevations up to 3 times normal, the estimated mortality ratios were low, less than 150%. If the HDL cholesterol level was elevated (greater than 70 for males or 85 for females), the ratios increased about 15% to 20% for the GGT and AST. There was little change for ALT, probably because isolated increases in this enzyme are not really associated with alcohol use.

When 2 enzymes were elevated (up to 3 times normal), overall mortality ratios were in the 150% to 200% range. They were relatively lower for the combination of ALT plus GGT. The presence of an elevated HDL level significantly increased the risk only in the GGT plus AST combination.

If ALT, AST and GGT all increased above the normal range (less than 3 times normal), mortality ratios were in the 175% to 225% range. Ratios increased about 30% if HDL was elevated as well. Overall risk increased substantially if the LFTs were more than 3 times normal.

In general, these estimates are consistent with the mortality ratios noted in the clinical experience and the data from the AALE study. ALP and bilirubin were not included in the model, so the impact of these tests on mortality ratios calculated for each of the patterns of the other enzymes could not be estimated.

DEVELOPING AN UNDERWRITING APPROACH

Underwriting mortality risk associated with abnormalities of liver enzymes involves assessing the composite risk of a group with similar patterns and degrees of test elevation. The group will contain a mix of diagnoses, some benign and others more serious; the
proportion of each determines the average outcome for the group. Individual risks will vary, but it is the experience of the group that matters.

The distribution of diagnoses within a given group varies with a number of factors, perhaps most important being the likelihood of a particular impairment being present based on factors other than the LFTs. Thus, a history of previous IV drug use would increase the probability of hepatitis. A smoker with an elevated HDL and a previous arrest for driving while intoxicated would be more likely to have alcohol-related liver disease. Obesity, hyperlipidemia or the presence of diabetes is associated with steatosis.

As noted above, the composition of the rating group also varies with the number of enzymes that are abnormal and the degree of elevation. In general, the more values that are elevated and the higher the levels, the more likely that the group has a greater proportion of significant diagnoses. The risk is small with single elevations of ALT, AST and GGT, higher when 2 of the 3 are increased, and highest when all 3 exceed the normal range. Significant increases in ALP or bilirubin in conjunction with these other tests also increase the probability of serious disease. Isolated, mild elevations of the ALP and bilirubin are usually benign, but higher levels warrant greater concern.

The results of reflex tests may also modify the risk by eliminating some possibilities from the diagnostic pool. Thus, a negative screen would effectively rule out hepatitis B or C, but the same cannot be said for the alcohol markers. Because of their low sensitivity, normal values for these markers do not necessarily rule out alcohol-related disease.

Other factors, such as the use of seizure medication (elevation of GGT), age and pregnancy, (increased placental ALP) also modify the impairment pool and risk assessment.

Finally, additional findings related to other specific diagnoses should be considered. These diagnoses include hemochromatosis (personal or family history, iron saturation, ferritin), Wilson’s disease (family history, ceruloplasmin, copper levels), autoimmune hepatitis (positive ANA, anti-smooth muscle antibody), primary biliary cirrhosis (anti-mitochondrial antibody), alpha-1-antitrypsin deficiency (family history, alpha-1-antitrypsin levels), cirrhosis (abnormal MRI, CAT scan, ultrasound) or liver failure (decreased serum albumin levels, elevated prothrombin time). Applicants with 1 or more of these findings should be rated according to the indicated impairment and not be evaluated in the same way as those whose cause for enzyme elevations is unknown. Individuals who have had a thorough, non-invasive workup, ie, one in which many of these conditions have been eliminated, have a greater proportion of benign causes and should be considered at lower overall risk.

REFERENCES