HEPATIC FUNCTION TESTING

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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BACKGROUND

The liver carries out important metabolic, synthetic, and excretory functions. A failure of one of these functions can ultimately lead to cirrhosis, an irreversible condition that causes liver failure and cancer. Laboratory tests can detect abnormalities before there are overt symptoms and direct the workup in patients presenting with signs of liver disease, such as jaundice.

Because there is no one test that is specific for any one liver disease, a panel of tests can help characterize the type of liver pathology present when patients present with nonspecific symptoms such as abdominal pain or fatigue. A hepatic function panel includes serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), direct bilirubin, total bilirubin, serum albumin, and total serum protein. The
panel provides a snapshot of the synthetic function of the liver and can classify hepatic damage as secondary to cholestasis or hepatocyte injury. Hepatocellular damage typically causes an elevation of the transaminases with only a slight increase in ALP. Cholestasis causes a more marked elevation of ALP than the transaminases. Intrahepatic cholestasis can also elevate transaminases in addition to ALP. Disease diagnosis can be pursued with further laboratory testing, radiographic imaging or tissue biopsy, if necessary. Thus, a hepatic function panel can lead to the judicious selection of tests for further patient workup.

It is not uncommon for patients with an abnormal hepatic function panel to have elevations of unexplained etiology. Often, the elevation can be self-resolving upon recheck. Clinical patient history, including the use or exposure of medications and chemicals, duration of hepatic function panel abnormalities, or the presence of accompanying sickness, is key in evaluating patients with an abnormal hepatic function panel.

AST and ALT, collectively known as the transaminases, are markers of hepatocyte injury. Not all laboratories have different reference ranges for males and females, but the levels tend to be slightly higher for males. The ratio of AST to ALT, the De Ritis ratio, is useful to further characterize the etiology of the hepatocellular damage. For example, patients with alcoholic liver disease may have mild transaminase increases and an AST/ALT ratio of > 2.0.1

The degree of the transaminase elevation is also helpful. When the increase in transaminases is mild, nonalcoholic fatty liver disease (NALFD) and chronic viral hepatitis are diagnostic considerations. NALFD is the most common cause of a mild increase in transaminases in adults in the United States, and it can progress to nonalcoholic steatohepatitis.1 Risk factors for NALFD include obesity, diabetes, hyperlipidemia, and hypertension. The prevalence of NALFD in the US is 25%.2 Although the prevalence of hepatitis C is 1.8% and hepatitis B is lower than 1%, viral hepatitis is an important cause of mild transaminase elevation because of the risk of chronic liver disease. Patients with chronic viral hepatitis may be asymptomatic. Studies have shown transaminase levels do not correlate well with histologic findings from liver biopsy. Normal transaminase levels have been reported in 16% of patients with viral hepatitis and 13% of patients with NAFLD.3 In one study, hepatic fibrosis was found in a third of chronic hepatitis B patients with normal transaminases.4 Furthermore, patients with advanced cirrhosis may have normal AST and ALT levels. For these reasons, if there is clinical suspicion of viral hepatitis, normal transaminase levels should not preclude viral serologic testing.

Markedly elevated transaminases (15-fold increases) are generally seen in acute viral hepatitis, toxic ingestions and ischemic liver. A cardiovascular etiology is present in almost 70% of cases of liver ischemia.5

Total serum protein measures albumin and globulin. Albumin accounts for sixty percent and is produced in the liver; globulins (some of which derive from nonhepatic sources) account for forty percent. Malnutrition and liver disease both impair protein synthesis. Chronic liver disease decreases protein synthesis and can cause hypoproteinemia that can be offset by an increase in gamma globulins so total protein levels may in fact rise. In these cases, the albumin to globulin ratio may be abnormal in situations where total serum protein is normal. Critical protein losses also occur in nephrotic syndrome, an example of how an abnormality in the hepatic function panel may indicate malfunction of an organ other than the liver. Dehydration causes an increase in total serum protein, and volume expansion (as occurs in pregnancy, for example) decreases total serum protein. Patients with low total serum protein levels have a more subdued acute phase response.
Albumin is an acute phase protein and a marker of the nutritional status of a patient. Albumin is a negative acute phase protein, that is, levels fall during the acute phase response. These changes occur more slowly than those of other acute phase reactants due to albumin’s relatively long half-life of 19 days. Stress-induced hypoalbuminemia follows infection, injury and trauma and resolves when these conditions are ameliorated. Decreases in serum albumin can follow decreased production due to states of malnutrition such as kwashiorkor. A 10% drop in serum albumin levels can be seen following two weeks of a protein-deficient diet.\(^6\) Increased losses of albumin also occur due to nephrotic syndrome. Because albumin is the major protein responsible for maintaining colloid oncotic pressure, edema can result from a decrease in serum albumin. Albumin is a transport protein that plays an important role in binding to drugs; when serum albumin levels fall, more unbound drug circulates. Decreased serum albumin is a predictor of hospital mortality.\(^7\)

Increases in alkaline phosphatase and bilirubin generally indicate a cholestatic pattern of liver malfunction. Cholestasis can be due to extrahepatic etiologies (biliary stricture, choledocholithiasis, primary sclerosing cholangitis, and cholangiocarcinoma) and intrahepatic etiologies (toxins, granulomatous disease, primary biliary cirrhosis, and cancer).

Cholestasis causes hepatocytes to synthesize ALP. Elevations of ALP are seen in cholelithiasis, malignancy, amyloidosis, sarcoidosis, inflammatory diseases such as ulcerative colitis, and autoimmune diseases such as primary biliary cirrhosis and primary sclerosing cholangitis. Serum ALP derives from bone and liver; therefore, not all increased concentrations are due to a cholestatic derangement. Elevations can also be seen with sepsis. Although zonal electrophoresis can be used to determine which ALP isoenzyme is elevated when total ALP is increased, obtaining a serum γ-glutamyltransferase (GGT) is a relatively inexpensive way to gain additional information.\(^1\) Because the majority of GGT derives from the liver and because it is a sensitive marker of hepatobiliary disease, an increase in GGT would support a liver origin for the increase in ALP. If the GGT were not elevated, a bone source, such as bone metastases, would be a more likely source for the increase in ALP.

One of the more important processes of the liver is its role in the degradation of heme. Bilirubin, a product of heme degradation, is conjugated in the liver and secreted into the biliary system before passing into the gastrointestinal tract where it is resorbed by the ileum before being re-excreted by the liver. In situations where excess bilirubin is produced, such as hemolytic anemia, there can be a rise in unconjugated bilirubin. Unconjugated hyperbilirubinemia is marked by an elevation of total bilirubin with less than 20% direct bilirubin. Hepatocyte damage can result in an increase in conjugated bilirubin first, followed by an increase in both conjugated and unconjugated bilirubin when the hepatocyte loses the ability to conjugate. Obstruction of the biliary tree results in an increase in conjugated bilirubin.

Bilirubin is usually reported as total and direct (conjugated) bilirubin. Indirect bilirubin can be estimated from total and direct levels by subtraction. Elevations in unconjugated bilirubin most commonly result from hemolysis and Gilbert’s syndrome. Gilbert’s syndrome is caused by a mutation that reduces the activity of the enzyme, glucuronyltransferase, which conjugates bilirubin. Although the syndrome can cause jaundice, treatment is not usually necessary.

Infants with jaundice most commonly have elevated unconjugated bilirubin levels, often due to an increased turnover and decreased lifespan of red blood cells. Additionally, neonates have nonmature liver enzymes, which are responsible for converting unconjugated (indirect) bilirubin to conjugated bilirubin.\(^8\) There is also increased enterohepatic circulation of bilirubin. These infants are generally followed with individual analyte
levels (total and direct bilirubin)\textsuperscript{9} instead of a hepatic function panel. Kernicterus can ensue when unconjugated bilirubin levels are markedly elevated.

Some of the clinically useful derivatives of the hepatic function panel include the De Ritis ratio, the Child-Pugh score, and the Model for End-stage Liver Disease (MELD) score. The Child-Pugh score places cirrhosis patients into prognostic categories on the basis of the serum albumin and total bilirubin concentrations, along with prothrombin time and clinical information about ascites and hepatic encephalopathy. MELD score is also useful for prognosticating outcomes in patients with cirrhosis; it is calculated from total serum bilirubin, INR (international normalized ratio), and serum creatinine.

One to nine percent of asymptomatic patients will have an abnormal value when screened with a liver panel.\textsuperscript{2} It is estimated that in a third of patients, test results will return to normal on repeat testing.\textsuperscript{10} It is recommended that asymptomatic patients with an abnormal hepatic function panel should undergo a complete history and physical examination. Signs of portal hypertension, such as splenomegaly, and its attendant laboratory findings (thrombocytopenia, for example) would be particularly relevant. Information about travel, diet, sexual practices, family history, and alcohol and drug use are critical.

A patient’s medications and alternative medicine practices can also affect test results. In hospitalized patients with drug hepatotoxicity, antimicrobials are most commonly implicated,\textsuperscript{5} but acetaminophen is another important pharmacologic cause of hepatotoxicity. Oral contraceptives can cause cholestasis. Erythromycin can cause hepatocyte necrosis in addition to cholestasis. Some drugs, such as methotrexate and isoniazid, cause non-dose-related injury after repeated exposure, and then cause significant and acute damage, with resultant hepatocyte necrosis and even death. In patients with mild transaminase elevations (< 3 times the upper limit of normal), one recommended approach is to advise weight loss if appropriate, discontinue hepatotoxic medications, and advise curtailing alcohol consumption with repeat testing in 3 months unless there is a clinical feature suggestive of liver disease\textsuperscript{11}; another approach endorsed by the American Gastroenterology Association and the Centers for Disease Control and Prevention is to screen patients for hepatitis B and C earlier.\textsuperscript{3} The latter approach could putatively allow for the diagnosis of viral hepatitis while the viral load is still low. Liver biopsy is a consideration if transaminase values greater than 1.5 times the upper limit of normal persist for 6-12 months.\textsuperscript{1} If alkaline phosphatase and GGT are elevated, further studies might include ultrasound, antimitochondrial antibody and other autoimmune markers. Abdominal ultrasound is typically the first imaging study done to detect hepatobiliary disease.\textsuperscript{5} If there is a clinical suspicion of biliary structural disease, magnetic resonance cholangiopancreatography, endoscopic ultrasound, or endoscopic retrograde cholangiopancreatography are considerations.

Hepatic function testing is not routinely recommended as a preoperative screen.\textsuperscript{12} Preoperative testing accounts for the expenditure of 20 to 30 billion dollars annually in the United States.\textsuperscript{13} For this reason, clinicians are attempting to reduce nonessential testing. Nonetheless, serious postoperative complications, most commonly, pneumonia, infection, ventilator dependency and ascites, can occur in cirrhotic patients.\textsuperscript{14}

Healthcare providers make decisions about preoperative laboratory testing on a case by case basis, based on findings from the patient’s history and physical examination. As a general rule, patients with acute hepatitis are not good candidates for elective surgery.\textsuperscript{15} The same is true of patients with a Child-Pugh score of grade C.\textsuperscript{15} One approach would entail ordering a hepatic function panel preoperatively for patients with clinical evidence or history of malnutrition, liver disease, hepatitis, jaundice, pancreatic disease, cancer, alcoholism and/or
hepatosplenomegaly. There have not been many clinical studies that have evaluated transaminase and alkaline phosphatase levels preoperatively. The Child-Hugh classification and the MELD score correlate with preoperative risk.

A retrospective study found that albumin determination and correction of nutritional deficiencies decreased complications in hip fracture patients. Serum albumin is also a predictor of postoperative mortality. A study of 54,215 multicenter Veterans Affairs patients undergoing noncardiac operations had an increase in mortality from 1% to 29% when preoperative serum albumin was less than 21 g/L. The authors of this study also looked at a healthier (American Society of Anesthesiologists Patient Classification of I or II, with I for healthy and II for mild disease), younger (age < 70) subgroup of 15,555 subjects in the study population and still observed increased mortality with a low albumin level.

Patients at known risk for liver disease are often followed with liver enzyme testing at frequent intervals. Because methotrexate is toxic to the liver, liver function panels are often part of the pretreatment evaluation and on-drug monitoring of patients who must take the drug for long periods of time, such as rheumatoid arthritis patients and cancer patients. Patients taking valproate are likewise at risk for liver disease. Patients with NAFLD are followed with frequent serum liver tests. Albumin, transaminase, bilirubin and ALP levels are recommended as part of the initial laboratory testing for a patient diagnosed with HIV.

POLICY

For the following CPT code(s) in Table 1, the patient should have a diagnosis (ICD-10-CM) code(s) listed in the attached files below.

Table 1. HCPCS Codes (Alphanumeric, CPT© AMA)

<table>
<thead>
<tr>
<th>HCPCS Code</th>
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<tr>
<td>80076</td>
<td>Hepatic Function Panel (ALT, AST, albumin, alkaline phosphatase, direct and total bilirubin, total protein)</td>
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ICD-10 Diagnosis Codes (Proven)

CMP-034 Hepatic Function ICD20_v1.1
REFERENCES


### POLICY HISTORY/REVISION HISTORY

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<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
</tr>
<tr>
<td>10/01/2015</td>
<td>Removed ICD9 table. Embedded ICD9/ ICD10 PDF files.</td>
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