Tests of the liver's biosynthetic capacity (eg, albumin, coagulation factors, prothrombin time)

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INTRODUCTION

A number of blood tests are available that reflect the condition of the liver. The most common tests used in clinical practice include the serum aminotransferases, bilirubin, alkaline phosphatase, albumin, and prothrombin time. These tests are often referred to as "liver function tests," although this term is somewhat misleading since most do not accurately reflect how well the liver is functioning, and abnormal values can be caused by diseases unrelated to the liver. In addition, these tests may be normal in patients who have advanced liver disease.

Several specialized tests have also been developed (such as indocyanine green clearance), which, although uncommonly used in clinical practice, can measure specific aspects of hepatic function.

Despite their limitations, liver biochemical and function tests have many applications in clinical medicine:

- They provide a noninvasive method to screen for the presence of liver disease. The serum aminotransferases, for example, were used in the past to screen all blood donors in the United States for the presence of transmissible viruses before specific viral tests were available.

- They can be used to measure the efficacy of treatments for liver disease (such as immunosuppressant agents for autoimmune hepatitis). (See "Management of autoimmune hepatitis".)

- They can be used to monitor the progression of a disease such as viral or alcohol-associated hepatitis.

- They can reflect the severity of liver disease, particularly in patients who have cirrhosis. As an example, the Child-Turcotte-Pugh score, which incorporates the prothrombin time and serum bilirubin and albumin concentrations, can predict survival (table 1).

The pattern of abnormalities on these tests is more accurate than any of the individual tests. Elevation of serum aminotransferases indicates hepatocellular injury, while elevation of the alkaline phosphatase indicates cholestasis. Recognition of patterns that are consistent with specific diseases can prompt appropriate additional testing.

The liver biochemical and function tests that are used commonly in clinical practice and that are used occasionally for specific circumstances can be categorized as follows:

- Tests that detect injury to hepatocytes – Most of these tests measure the activity of hepatic enzymes, such as the aminotransferases, in the circulation. These enzymes are normally intracellular, but are released when hepatocytes are injured. (See "Liver biochemical tests that detect injury to hepatocytes".)

- Tests of the liver's capacity to transport organic anions and metabolize drugs – These tests measure the liver's ability to clear endogenous or exogenous substances from the circulation. The best studied include serum measurements of bilirubin, bile acids, caffeine, and lidocaine metabolites, a variety of breath tests, and clearance tests such as bromsulphalein (BSP) and indocyanine green (ICG).

- Tests of the liver's biosynthetic capacity – The most commonly performed tests to assess the biosynthetic capacity of the liver are the serum albumin and the prothrombin time (which requires the presence of clotting factors produced in the liver). Other tests which have been use are the serum concentrations of lipoproteins, ceruloplasmin, ferritin, and alpha 1-antitrypsin.

- Tests that detect altered immunoregulation or viral hepatitis – These tests include the immunoglobulins, hepatitis serologies, and specific autoantibodies. Most of these substances are proteins made by B lymphocytes, not by hepatocytes. However, some are quite specific for certain liver diseases, such as antimitochondrial antibodies in primary

biliary cholangitis. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis".)

This topic will review the role of the serum albumin and prothrombin time in the evaluation of the liver's biosynthetic capacity. The other categories of liver function tests are discussed separately. (See "Approach to the patient with abnormal liver biochemical and function tests" and "Liver biochemical tests that detect injury to hepatocytes" and "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)" and "Clinical aspects of serum bilirubin determination" and "Tests of the liver's capacity to transport organic anions and metabolize drugs".)

SERUM PROTEINS

The liver is the major site where serum proteins are synthesized. These include albumin and the coagulation factors.

Albumin — Albumin is quantitatively the most important plasma protein. Approximately 300 to 500 g of albumin is distributed in the body fluids, and the average adult liver synthesizes approximately 15 g per day (200 mg/kg per day). The synthesis rate can double in situations in which there is rapid albumin loss or a fall in the serum albumin concentration.

The serum albumin concentration reflects the rate of synthesis, rate of degradation, and volume of distribution. Albumin synthesis and function are regulated by a variety of factors, including nutritional status, serum oncotic pressure, cytokines, and hormones [1-3]. How these factors operate on a cellular level is not precisely known but may involve the formation of albumin messenger ribonucleic acid (mRNA) polysomes within the liver [1,2,4]. Substances that stimulate albumin synthesis increase the efficiency of this process. By contrast, inhibitory substances associated with inflammatory states, such as tumor necrosis factor and interleukin-1, impede albumin synthesis [5-7] and may affect non-oncotic (eg, antioxidant, scavenging, immune-modulating, endothelial protective) functions of albumin [3].

Little is known about the clearance of albumin, which is primarily by catabolism [8]. The half-life of albumin in serum is approximately 20 days, with 4 percent of the total albumin pool being degraded daily.

Clinical significance — Hypoalbuminemia does not always reflect the presence of hepatic synthetic dysfunction since a variety of other conditions may be responsible including systemic inflammation, the nephrotic syndrome, and malnutrition. Some general observations can be made in patients with liver disease who do not appear to have these other disorders:

- Serum albumin concentrations tend to be normal in acute viral hepatitis, drug-related hepatotoxicity, and obstructive jaundice. The possibility of chronic liver disease should be considered when the serum albumin concentration is below 3 g/dL (30 g/L) in these patients.

- Hypoalbuminemia is more common in chronic liver disorders such as cirrhosis. The fall in albumin concentration usually reflects severe liver damage with reduced albumin synthesis [9]. An exception may occur in patients with ascites who may become hypoalbuminemic despite good hepatic synthetic function because of the often marked increase in plasma volume [10].

- Serum albumin levels have prognostic value in cirrhosis and hepatocellular carcinoma and after partial hepatectomy [11,12]. Effective albumin concentration, which refers to the albumin portion presenting structural and functional integrity, may be more closely associated with disease severity and albumin dysfunction [13,14].

The serum albumin concentration should **not** be measured for screening in patients in whom there is no suspicion of liver disease. This was illustrated in a study that included 449 patients seen in a general medical practice in whom serum albumin was measured routinely; 13 percent had an abnormal value, which was found to be clinically significant in only two patients [15].

Serum albumin levels persistently above the laboratory's reference range are usually observed in normal people who are at the extreme right of the bell-shaped curve. Acute hyperalbuminemia is seen most commonly in patients with volume depletion [8], in whom it is often associated with hemoconcentration as well. A case report described hyperalbuminemia in a patient consuming a high-protein diet [16]. Hyperalbuminemia is also theoretically possible in patients with genetic variants that prolong the half-life of albumin in serum.

Coagulation factors — The liver is the major site of synthesis of 11 blood coagulation proteins. These include:

- Factor I (fibrinogen)
- Factor II (prothrombin)
- Factor V
- Factor VII
- Factor IX
- Factor X
- Factor XII
- Factor XIII

Clotting factor deficiency frequently occurs during the course of liver disease. These proteins can be measured individually or indirectly by more general measures of clotting ability such as the prothrombin time.

Clinical significance — A prolonged prothrombin time is not specific for liver disease, since it can result from various congenital or acquired conditions including consumption of clotting factors (such as disseminated intravascular coagulation or severe gastrointestinal bleeding) and certain drugs. When these conditions have been excluded, a prolonged prothrombin time usually reflects one of two disorders:

- A deficiency of vitamin K, which may be induced by inadequate dietary intake, prolonged obstructive jaundice, intestinal malabsorption, or the administration of antibiotics that alter the gut flora. In such cases, the prothrombin time typically returns to normal within 24 hours after a single parenteral injection of vitamin K. This response is particularly helpful diagnostically when evaluating patients who are jaundiced.

- Poor utilization of vitamin K due to advanced parenchymal liver disease. Vitamin K supplementation is generally ineffective in this setting.

The prothrombin time does not accurately reflect the coagulation status of patients with cirrhosis [17] or correlate with the risk of bleeding because of concomitant reductions in the hepatic synthesis of anti-hemostatic factors [18-20]. In fact, patients with cirrhosis and a prolonged prothrombin time may actually be relatively hypercoagulable with an increased risk of clot formation [21]. (See "Hemostatic abnormalities in patients with liver disease".)

However, the magnitude of elevation of the prothrombin time above control does correlate with prognosis in some conditions. As an example, an elevation more than five seconds above control should raise concern about a fulminant course in patients who have acute viral, toxic, or alcohol-associated hepatitis [22,23]. A prothrombin time above 100 seconds has been considered an indication for liver transplantation [22]. However, some patients, particularly those who have acetaminophen overdose, recover despite marked elevations in the prothrombin time. A progressive decline in the prothrombin time in such patients usually heralds recovery. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis" and "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation" and "Acetaminophen (paracetamol) poisoning in adults: Treatment".)

International normalized ratio — The international normalized ratio (INR) is often used to express the degree of anticoagulation in patients receiving warfarin. The INR standardizes prothrombin time measurement based upon characteristics of the thromboplastin reagent

used in the laboratory. This helps to eliminate variability between measurements in which different thromboplastin reagents are used and thereby assures a stable level of anticoagulation.

In contrast to its use in patients on warfarin, the INR may not be the best expression of coagulation derangement in patients with liver failure, especially if the same thromboplastin reagents are not consistently used for measurement [24-27]. This was illustrated in a study in which various expressions of the prothrombin time (seconds above control, ratio to control, activity percentage, and INR) were evaluated in 27 patients with chronic or acute liver failure compared with controls [24]. Only the activity percentage expression eliminated variability in the prothrombin time results in individual patients when different thromboplastin reagents were used. This observation implies that, in an individual patient with liver failure, interpretation of changes in the INR may only be accurate when the same thromboplastin is used. Furthermore, comparison of the degree of synthetic dysfunction using the INR in patients who underwent testing at centers using different thromboplastin reagents may not be valid [28,29]. This may be particularly relevant when prioritizing patients for liver transplantation [29]. (See "Model for End-stage Liver Disease (MELD)".)

A new standardization method for the INR would make the INR more applicable in patients with liver disease [19]. Modifications in which calibration of the INR is based on plasma from patients with cirrhosis, rather than from those on a vitamin K antagonist, have been proposed to reduce variability in calculating the MELD score [30,31]; however, they are not used in practice. (See "Hemostatic abnormalities in patients with liver disease".)

Des-gamma-carboxy prothrombin — The synthesis of factors II, VII, IX, and X requires vitamin K for the addition of carboxylic acid moieties to the gamma position of glutamic acid residues in these proteins [32] (see "Vitamin K and the synthesis and function of gamma-carboxyglutamic acid"). Gamma carboxylation permits these proteins to bind calcium, which is necessary for them to function normally. An abnormal prothrombin form (des-gamma-carboxy prothrombin) is released in the absence of vitamin K, in the presence of vitamin K antagonists such as warfarin, and by certain tumors, such as hepatocellular carcinoma (HCC) [33]. Des-gamma-carboxy prothrombin is produced by the malignant hepatocyte, which appears to acquire a posttranslational defect in the vitamin K-dependent carboxylase system [34]. The serum concentration of des-gamma-carboxy prothrombin has been evaluated for screening patients at risk for hepatocellular carcinoma but may have lower sensitivity than alpha fetoprotein (AFP) for tumors <3 cm and in East and South Asian populations [35]. (See "Clinical features and diagnosis of hepatocellular carcinoma".)

SUMMARY AND RECOMMENDATIONS

- The most commonly performed tests to assess the biosynthetic capacity of the liver are the serum albumin and the prothrombin time (which is based upon the presence of clotting factors produced in the liver). Other tests which have been used are the serum concentrations of lipoproteins, ceruloplasmin, ferritin, and alpha 1-antitrypsin.
- The liver is the major site where serum proteins are synthesized. These include albumin and the coagulation factors. The clinical significance of low and high values is described above. (See 'Serum proteins' above.)
- In contrast to its use in patients on warfarin, the international normalized ratio (INR) may not be the best expression of coagulation derangement in patients with liver failure. (See "Hemostatic abnormalities in patients with liver disease" and 'International normalized ratio' above.)

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GRAPHICS

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

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