Assessing liver function and hyperbilirubinemia in the newborn

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In clinical practice, “liver function” is assessed by either measuring the concentration of substances produced by the hepatocyte, measuring the serum content of substances that are changed by hepatocyte damage, evaluating the serum concentrations of substances released from the cells as a result of injury, assessing the ability of the liver to perform a metabolic task such as conjugation or detoxification, or by measuring enzyme activity and substrate content of the cell and its organelles. After birth, with cessation of placental function, the neonatal liver must assume many different tasks. Distinct developmental sequences rapidly progress for numerous hepatic functions as the newborn adapts to its environment. This manuscript is an attempt to provide guidelines for the evaluation and management of the newborn infant when assessing liver function and hyperbilirubinemia. These guidelines, like all sets of guidelines, are only recommendations and do not substitute for good clinical judgment based upon the individual circumstances of each patient.

INDEXING TERMS: hepatic synthesis • coagulation • cholestasis

Tests of Hepatic Synthetic Function

ALBUMIN

Serum albumin is frequently utilized as an index of the hepatocyte’s ability to carry out synthetic function. Serum albumin does not change in mild liver injury but readily declines in the face of submassive liver necrosis. Albumin synthetic capacity is typically preserved even in severe cirrhosis. Albumin is the most abundant protein in serum. Low concentrations may be the result of loss via gastrointestinal or renal causes, poor protein intake, or failed hepatic synthesis. Because the half-life of albumin is 19–21 days, serum albumin may not reflect acute changes in liver synthetic ability. Hypoalbuminemia is associated with the development of congestive heart failure, edema, or ascites.

Little data is available regarding reference ranges for serum albumin concentrations in preterm and term infants [1–5] (See Table 1). In general, postnatal albumin concentrations follow the gestational trend and increase with gestational age. Acute-phase proteins may react as albumin, causing false increases in some assays. Method interferences include hemolysis, icterus, lipemia, and turbidity, and such affected specimens may need to be corrected for with a blank.

Serum albumin concentrations <20 g/L may be associated with the development of clinically apparent edema or ascites. Because serum albumin concentrations do not change acutely in chronic liver disease, they may be monitored weekly unless an acute change in gastrointestinal or renal losses or edema or ascites occurs. Serum albumin measurements should be available throughout the day with a turnaround time of 8 h.

COAGULATION FACTORS

A rapid test of liver synthetic ability involves the one-stage prothrombin time (PT) test [6, 7]. Vitamin K-dependent clotting factors have relatively short half-lives and are synthesized by hepatocytes. Determination of the PT before and after parental administration of vitamin K has been widely utilized to distinguish abnormal absorption of vitamin K resulting from poor fat-soluble vitamin absorption from true liver-cell dysfunction. The PT is a measure of the time it takes for prothrombin (factor II) to be converted into thrombin in the presence of tissue extract (thromboplastin), calcium, and activated clotting factors I, II, V, VII, and X. This reaction is a measure of the extrinsic pathway of coagulation and is prolonged (>2 s above control) when factors I, II, V, VII, or X are deficient alone or in combination.

1 Nonstandard abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; DIC, disseminated intravascular coagulation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; and γGT, gamma glutamyltransferase.
The partial thromboplatin time (PTT) measures the generation of thrombin by the intrinsic pathway involving all coagulation factors, including IX and VIII and excluding factor VII. All the factors except factor VIII are synthesized in the liver, so an increased PTT with normal factor VIII concentrations suggests hepatic dysfunction.

Caution must be exercised in attributing prolonged PT or PTT in liver patients to only hepatic disease because vitamin K deficiency or disseminated intravascular coagulation (DIC) as seen in sepsis can also prolong these values. A prolonged PTT with low factor VIII concentrations may suggest consumption of clotting factors (DIC) because factor VIII is not synthesized in the liver.

PT and PTT are generally prolonged in the healthy premature infant as compared with the older child or adult, and reference values have been published [8–10] (see Table 1). PT and PTT should be available 24 h daily with a turnaround time of <4 h. Specimens should preferably be drawn by a clean venipuncture to avoid tissue thromboplastin contamination. Because the PT and PTT measurements are sensitive to the plasma-to-citrate anticoagulant ratio, adjustment should be made in the ratio of blood to the citrate anticoagulant in the specimen tube for hematocrits >50% or <20%. A 5-mL blue-top tube often used for PT and PTT specimens contains 0.5 mL of 32 g/L sodium citrate. Special care should be taken for specimens drawn from a line flushed with heparin, as heparin can alter the PTT.

AMMONIA

The majority of ammonia clearance occurs in the liver via the urea cycle. Details of ammonia metabolism are beyond the scope of this article, and may be obtained in standard texts [11]. In a single pass, 80% of ammonia is removed from the portal vein by the liver. In chronic liver disease, shunting and altered hepatic function allow ammonia to bypass the liver and reach the central nervous system. A rising plasma ammonia concentration may precede the onset of hepatic encephalopathy. Unfortunately, the stage of hepatic encephalopathy and the concentration of plasma ammonia have a poor correlation [12]. I have found that the trend of rising plasma ammonia concentrations may represent a better indicator of impending hepatic encephalopathy than a single measurement alone. Ammonia may also be increased in patients with inherited defects of the urea cycle, Reye syndrome, defects in mitochondrial fatty acid β-oxidation, porto-systemic shunts of either congenital or surgical origin, or in patients with chronic liver disease who have increased protein loads to the intestine from diet or gastrointestinal bleeding.

The most critical aspect of plasma ammonia testing is the collection and transport of the specimen. Arterial or venous blood can be used. The heparinized blood sample should be placed in an ice–water mixture immediately to stabilize samples and minimize erythrocyte conversion of glutamine to ammonia. Blood ammonia will increase at ~17 µg/L per min at 25 °C [13]. Samples should be transported to the laboratory as rapidly as a blood-gas sample, and the plasma separated immediately. The separated plasma may be stored at 4–8 °C until analysis. The plasma should be frozen if there will be any significant (>1 h) delay in measurement. Reference ranges have been published for infants and children [13, 14] (see Table 1). Ammonia determinations should be available on a stat basis daily, with a rapid turnaround time because the test should ideally be performed within 20 min of sample collection.

Tests of Hepatic Integrity

AMINOTRANSFERASES

Enzymes and substrates involved in intermediary metabolism and stored in hepatocytes are released when hepatocytes are acutely damaged. Increases in serum concentrations of these enzymes provide important clues to involvement of hepatocytes. Serum aminotransferases [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] are sensitive tests of hepatocyte injury [15–17]. Although often referred to as “liver function” tests, they do not measure hepatocyte function but instead hepatocyte damage. Before abnormalities are attributed to hepatocyte injury, exclusion of other nonhepatic conditions that can increase serum aminotransferases should be excluded, such as myocardial injury, circulatory congestion, muscle injury, central nervous system disease, hemolysis, and postoperative states. AST is present in high concentrations in many tissues including liver, heart, kidney, skeletal muscle, pancreas, and erythrocytes. Damage to any of these tissues from trauma, ischemia, or drugs can cause increases in serum AST. Determination of isoenzymes to differentiate sources of AST are not routinely clinically utilized. Hemolysis, resulting from poor specimen handling or difficult blood drawing, among other causes, can artificially increase AST concentrations. Rhabdomyolysis can also increase serum AST. Reports of myopathies in children with a normal liver have been reported [18, 19]. AST and ALT rise in a variety of hepatic disorders such that abnormal values do not aid in the differential diagnosis. A rising AST/ALT ratio in infants with liver disease may signify a poor clinical outcome, whereas a decreasing AST/ALT ratio in infants may predict a good clinical outcome [20]. A falling AST or ALT value may not necessarily predict improved hepatic disease. A falling ALT or ALT in conjunction with a rising bilirubin and prolonged PT may suggest hepatic necrosis.

Reference ranges have been reported for infants and children [21, 22] (see Table 1). Many automated methods are available for the measurement of these enzymes, and reference ranges for the population and instrument utilized should be acquired ideally by each institution. Pyridoxal phosphate is the coenzyme for both AST and ALT. In situations in which vitamin B₆ (pyridoxine) is deficient, such as a population with a significant proportion of neonates, low concentrations, especially for ALT,
may occur because enzyme activity is used in the assay as the basis for measurement [23]. These assay reagents contain pyridoxal phosphate. One may wish to check the assay used at each laboratory. Low serum concentrations of AST may also occur with uremia [24, 25]. Transaminases should be available once each day with a turnaround time of 8 h.

**LACTATE DEHYDROGENASE**

The dehydrogenases that catalyze oxidation-reduction reactions may also be utilized to assess hepatic injury. Lactic dehydrogenase (LDH) is most commonly measured. LDH exists in five isoenzymes distinct for different tissues. Liver-specific LDH (LD₅) may be useful in helping to discriminate hepatic disease. Increases in LDH may be observed with myocardial infarction, liver disease, neoplasm, infectious mononucleosis, hypothyroidism, lung disease, central nervous system disease, infections, inflammation, hemolytic anemia, muscle damage and dystrophy, and collagen disease. Hemolysis falsely increases LDH results, and lipemia may interfere. Reference ranges have been reported in premature infants and children.

<table>
<thead>
<tr>
<th>Test</th>
<th>Units</th>
<th>Age</th>
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<th>Female</th>
<th>Male/Female</th>
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<td>0–5 days (&gt;2.5 kg)</td>
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<td>1–30 days</td>
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<td>183–365 days</td>
<td>28–48</td>
<td>33–48</td>
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<td>10.0–13.6</td>
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<td>s</td>
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<td>11.5–13.1</td>
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<td></td>
<td>s</td>
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<td>31.8–39.2</td>
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<td>Ammonia</td>
<td>μmol/L</td>
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<td>42–144</td>
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<td></td>
<td>3–11 months</td>
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<td>0–5 days</td>
<td>35–140</td>
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<td>U/L</td>
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<td>82–383</td>
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<td>U/L</td>
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<td>1–182 days</td>
<td>12–122</td>
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<td>Total bilirubin</td>
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<td>3–5 days</td>
<td>&lt;200</td>
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<td></td>
<td></td>
<td>1 month–adult</td>
<td>&lt;17</td>
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</table>

* Adapted from refs. 1, 3, 9, 10, 13, 14, 21, 31, 39, 44, 61 for full-term infants unless specifically noted.
Blood should be collected by venipuncture because tissue concentrations of LDH are 500-fold higher than whole-blood values. This test has limited usefulness because of its nonspecificity, and its routine use is not recommended.

Tests of Cholestasis

Alkaline Phosphatase

Alkaline phosphatase concentrations in serum are routinely utilized in adults to assess obstructive jaundice. Although increased alkaline phosphatase activity is observed in cholestasis, the values are incapable of distinguishing the etiology or whether the obstruction is intra- or extrahepatic. Alkaline phosphatase is present in several tissues including the liver canalicular membrane, osteoblasts in bone, brush border enterocytes in the small intestine, and in the proximal convoluted tubules of the kidney. In neonates, growth and bone activity make interpretation of increased serum alkaline phosphatase concentrations problematic. The serum gamma glutamyltransferase (γGT) value may be useful in such a case.

Alkaline phosphatase reference ranges have been reported for infants and children [28–31] (see Table 1). At 1 month, alkaline phosphatase values may be 5–6 times higher than adult normal values. Alkaline phosphatase concentrations decrease slowly until puberty where they may be 3–4 times higher than adult values. Alkaline phosphatase values reach adult values between ages 16–20 years. Determination of fractionated alkaline phosphatase and heat-stable or heat-labile alkaline phosphatase may be helpful in determining if increased alkaline phosphatase concentrations are of hepatic or osseous origin. These assays have not found a place in neonatology. Routine alkaline phosphatase testing should be available daily with an 8-h turnaround time.

Specimens should be collected in red-top tubes; EDTA tubes should be avoided, as EDTA can complex the magnesium and zinc required to catalyze the enzyme reaction, greatly decreasing test results.

γGT

γGT is a sensitive but not a specific indicator of hepatic disease. This enzyme is present in intra- and extrahepatic bile ductular cells and in hepatocytes. It may also be found in renal tubules, the pancreas, spleen, brain, breast, and small intestine. γGT does not rise with bone disease or active growth as occurs with alkaline phosphatase, making γGT a useful test when alkaline phosphatase is increased and its origin is unclear [32]. γGT is frequently increased in acute hepatitis and also in cholestasis [33]. Because it is a highly sensitive test, it may remain increased even during convalescence from liver injury. Serum γGT may also rise after initiation of certain drugs (i.e., phenobarbital) that induce microsomal enzyme synthesis [34, 35]. Newborns may have very high serum γGT, up to 5–8 times the upper limit of normal for adults, that rapidly declines to adult concentrations by age 6 months [3, 36–39] (see Table 1). Premature infants may have even higher γGT values than full-term infants during the first several days after birth. Immaturity has been proposed as the cause of the high γGT concentrations observed in newborns.

γGT should be available, as a nonprofile test, once each day, with an 8-h turnaround time. Gross hemolysis may invalidate the value obtained and such specimens should be discarded.

Hyperbilirubinemia

In the newborn, increased serum unconjugated bilirubin concentrations predispose the infant to kernicterus or brain injury and neurologic impairment. Lipid-soluble unconjugated bilirubin can cross the poorly established blood–brain barrier in a newborn if bilirubin binding sites on albumin are saturated or if acidosis or sepsis contribute to further opening of the blood–brain barrier. However, most studies have failed to demonstrate a substantial association between IQ or neurologic impairment and a specific total serum bilirubin concentration in a term newborn [40–43]. In healthy full-term infants, a serum bilirubin concentration >400 μmol/L is in a range many physicians consider at-risk [44]. However, in a hyperbiliruminemic, acidic newborn, such as a premature infant, this may occur at a much lower serum bilirubin concentration. Laboratorians should consult with their neonatologists to determine medical decision concentrations for serum bilirubin, which must be called to clinicians as critical values.

Evaluation of the clinically jaundiced infant should proceed in a rapid cost-effective and efficient manner [45, 46]. Maternal prenatal testing of ABO and Rh(D) typing and a serum screen for unusual isoimmune antibodies should be reviewed if available. If this has not been performed, is not available, or if the mother is Rh-negative, then a direct Coombs test, blood type, and Rh(D) type on the infant are indicated, ideally from cord blood. Cord blood should be saved if at all possible on all infants and certainly if the mother is blood group O. This will allow for testing if required so that blood drawing can be kept to a minimum in the infant. If family history, ethnicity, or geography suggest the possibility of glucose-6-phosphate dehydrogenase deficiency or other hemolytic condition, appropriate laboratory confirmation is indicated. All infants visibly jaundiced within the first 24 h of birth should have a total serum bilirubin concentration obtained. Jaundice may be detected by blanching or pushing down on the skin. Icterus progresses from head to toe in a caudal distribution so that the progression of cephalocaudal jaundice may be helpful in quantifying the degree of jaundice. The use of an icterometer or jaundice meter may be helpful but is not mandatory [47]. All infants with feeding difficulty, behavioral fluctuations, apnea, or temperature instability with or without jaundice must be evaluated for the possibility of underlying illness. Mandatory follow-up within 2–3 days by a trained health-
care professional should be provided to all newborns discharged home <48 h after birth. Approximately one-third of healthy breast-fed babies will have persistent jaundice after age 2 weeks [48]. However, dark urine or light-colored (acholic, chalky, white) stools mandates quantification of conjugated (or direct-reacting bilirubin by diazo methods) bilirubins. Caution must be exercised when utilizing diazo methods because many diazo methods measure direct bilirubin even when it is not present [49]. If jaundice persists beyond age 3 weeks, measurement of total and direct-reacting bilirubin is mandatory to distinguish pathologic conditions that cause conjugated hyperbilirubinemias, usually resulting from obstruction or cholestasis (i.e., biliary atresia), from unconjugated hyperbilirubinemias.

Bilirubin measurements are susceptible to interference from hemolysis and lipemia. This is particularly problematic in the newborn, in whom blood acquisition may require a heelstick, resulting in hemolyzed specimens. Sunlight and ultraviolet light can lower bilirubin values in specimens left standing unprotected from light, especially in the nursery setting where phototherapy is routinely being utilized, so care must be taken to wrap specimens in aluminum foil or utilize amber-colored tubes for collection. Lipemia may cause significant increases in the bilirubin result, especially with direct spectrophotometric methods. Specimen blanking or use of the Jendrassik–Graf method may be utilized to diminish the effect of lipemia on bilirubin measurements. Calibrators for bilirubin glucuronide conjugates do not exist and surrogate calibrators (such as ditaurobilirubin) for direct-reacting bilirubin methods must be used. Bilirubin must be capable of being measured over a large range: <17.1–513 μmol/L (<1–30 mg/dL). Further, precise measurement of bilirubin becomes critical not only to discriminate normal from abnormal values, but to decide whether there is need for therapeutic intervention [50]. Because critical therapeutic decisions may depend on the result, accurate results with a rapid turnaround time (usually <1 h but dependent on each clinical site and situation) must be available for total bilirubin concentration measurement.

Analytical sample volumes of ≤10 μL are strongly recommended. This recommendation may obviate the use of “bilirubinometers,” which tend to use larger sample volumes for measurement of total bilirubin. Measurement of bilirubin–protein conjugates (delta bilirubin) has been investigated in children [51–54]. Because most newborns have unconjugated hyperbilirubinemia, the clinical need for delta bilirubin measurements in the nursery is nonexistent. Thus, measurement of delta bilirubin is not recommended for neonates or adults because of no known diagnostic value.

Treatment of unconjugated hyperbilirubinemia in the newborn is based on history, clinical course, and physical examination [45, 46, 55–61]. Of course, the benefits of any intervention must outweigh the risks. Because severe unconjugated hyperbilirubinemia is associated with bilirubin encephalopathy and kernicterus, timely decisions must be made. Treatment recommendations are based upon the age of the newborn and the total serum bilirubin concentration [44, 61] (see Table 1).

In an infant <24 h old, any jaundice is considered pathologic and requires evaluation. This evaluation should minimally include a serum bilirubin (preferably fractionated) and a workup for hemolytic disease. Phototherapy or exchange transfusion should be considered for any infant with a rapidly rising bilirubin concentration within the first 24 h of life.

Guidelines for therapy [44, 61] depend on the serum concentrations of bilirubin and the patient’s age. For full-term infants 25–48 h of age, phototherapy usually is considered if the total serum bilirubin concentration is ≥170 μmol/L (12 mg/dL) and is likely to be instituted if the total serum bilirubin is ≥260 μmol/L (15 mg/dL). If phototherapy fails to lower a total serum bilirubin concentration of ≥340 μmol/L (20 mg/dL), exchange transfusion is considered. If the total serum bilirubin concentration rises to ≥430 μmol/L (25 mg/dL) when the full-term infant is first seen, intensive phototherapy is usually begun while exchange transfusion preparations are made. If phototherapy does not lower the bilirubin, exchange transfusion proceeds. A high bilirubin in a full-term infant age 25–48 h suggests pathology and warrants investigation of the cause.

For full-term infants 49–72 h of age, phototherapy is usually considered [44, 61] if the total serum bilirubin concentration is ≥260 μmol/L (15 mg/dL). Phototherapy is seriously entertained if the total serum bilirubin concentration is ≥310 μmol/L (18 mg/dL). If phototherapy does not keep the serum total bilirubin <430 μmol/L (25 mg/dL), exchange transfusion is usually considered. If the total serum bilirubin concentration is ≥510 μmol/L (30 mg/dL) when the full-term infant first presents, intensive phototherapy is usually begun while exchange transfusion preparations are made. If the total serum bilirubin concentration does not diminish with phototherapy, exchange transfusion is usually performed.

For full-term infants >72 h old, phototherapy is usually considered if the total serum bilirubin is 290 μmol/L (17 mg/dL). Phototherapy is often utilized if the total serum bilirubin concentration is ≥340 μmol/L (20 mg/dL). If intensive phototherapy does not lower a total serum bilirubin concentration ≥430 μmol/L (25 mg/dL), an exchange transfusion is usually warranted. If the total serum bilirubin concentration is ≥510 μmol/L (30 mg/dL), intensive phototherapy is usually begun during preparations for an exchange transfusion. If phototherapy fails to lower the serum bilirubin concentration, an exchange transfusion is usually performed.

Although breast-feeding should be encouraged in full-term healthy newborns, persistent jaundice may demand consideration of supplementation of breast-feeding with formula or temporary discontinuation of breast-feeding. Phototherapy can usually be safely discontinued in the
full-term healthy newborn when the total serum bilirubin concentration falls below 239–257 μmol/L (14–15 mg/dL). Rebound after phototherapy discontinuation is usually <17.1 μmol/L (1 mg/dL).

Critical clinical decisions are based on accurate total bilirubin measurements. The laboratory must be capable of accurate total bilirubin measurements at critical bilirubin concentrations of 205 μmol/L (12 mg/dL), 257 μmol/L (15 mg/dL), 308 μmol/L (18 mg/dL), 342 μmol/L (20 mg/dL), 428 μmol/L (25 mg/dL), and 513 μmol/L (30 mg/dL). Precision of ±5% to detect changes in response to therapy is imperative at the above total bilirubin concentrations. Routine calibrators and proficiency testing samples in the laboratory usually contain bilirubin in concentrations of 21–81 μmol/L (1.2–4.7 mg/dL), well below the range required for neonatal specimens. Laboratories must strive to become proficient in measuring bilirubins in the neonatal range so that clinicians caring for newborns may make clinical decisions on the basis of accurate bilirubin determinations.

References
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