Laboratory Tests in Hepatic and Renal Failure

Simon Cottam
Elizabeth Sizer

Laboratory tests of liver function are of little use unless combined with a thorough history and examination. In this situation they may be used to pursue a diagnosis, to assess degrees of acute or chronic liver failure, or as trends to map disease progression or response to treatment. With the advent of automated serum multi-channel analysis the most common indication for ‘liver function’ testing is as a screening test (often mistakenly performed to exclude a problem). Normal values for tests are defined around 95% confidence intervals, therefore multiple tests commonly produce false-positive results. True abnormal results usually represent liver dysfunction. The most common profiles include bilirubin, aminotransferases, alkaline phosphatase and γ-glutamyl transpeptidase (GGT).

True liver function tests

True liver function tests include tests of synthetic function such as estimation of serum albumin, clotting factors or dynamic tests that estimate the liver’s capacity to metabolize drugs or endogenous substances.

Albumin is the most abundant plasma protein and is largely synthesized by the liver. In stable chronic liver disease, monitoring serum albumin is a valuable indicator of hepatic synthetic function and as such is incorporated in many prognostic scoring systems (e.g. the Child–Pugh (see page 42) and Mayo End-stage Liver Disease (MELD) score). Albumin has a long half-life of 20 days; this, combined with the possibility of regulation of albumin synthesis in liver disease, can make interpretation of serum albumin levels difficult in an acute situation. Perioperative albumin levels may change as a result of supplementation, changes in vascular permeability and in volume of distribution. In these situations, measurement of albumin is an unreliable measure of liver function.

Prothrombin time (PT): in the acute situation, assessment of the coagulation factors of the extrinsic cascade (with their much shorter half-lives) are a more reliable monitor of liver failure than albumin. Failure of a prolonged PT to correct with parenteral vitamin K supplementation defines hepatocellular failure, and is one of the most reliable prognostic indicators of survival in acute liver failure. Inter-laboratory variations can occur with different thromboplastin reagents. This may also occur when the PT is expressed as the international normalized ratio (INR). Therefore, trends in prothrombin time measured in a single laboratory are more useful than isolated values.

Blood lactate concentration reflects the balance between production and elimination. Under normal conditions, the liver removes 40–60% of lactate. Hypoperfusion, hypoxia and severe ischaemic damage convert the liver from a lactate-consuming to a lactate-producing system. In acute liver failure, hyperlactataemia may be used as a marker of hepatic injury and the accompanying multiple organ failure. Assuming adequate oxygen delivery, blood lactate levels have been shown to correlate with survival in paracetamol-induced liver failure.

‘Dynamic’ tests of liver function

‘Dynamic’ tests measure the ability of the liver to clear or metabolize an infused substance.

Formation of monoethyleneglycine (MEGX): this lidocaine (lignocaine) metabolite can be measured 15–30 minutes after injection of lidocaine (lignocaine), 1 mg/kg. Theoretically, it can be used to quantify the hepatic cytochrome P450 family metabolism. However, lidocaine (lignocaine) is a flow-limited rather than capacity-limited drug. Although MEGX measurements have been shown to correlate with survival in chronic liver disease, they probably reveal more about liver blood flow than functional capacity. Inevitably there is a delay while assay results are obtained.

Indocyanine green (ICG) clearance: the elimination of injected ICG, 0.5 mg/kg, has been used to assess liver function. Interest in this method was fuelled by the introduction of a bedside non-invasive monitor of ICG clearance. ICG has a high hepatic extraction ratio and measurements reflect changes in liver blood flow. Reports suggest it is useful for assessing donor livers for transplantation and following liver resection.

Conventional tests of liver dysfunction

Bilirubin is the by-product of haem metabolism. Unconjugated bilirubin is water insoluble and transported bound to serum albumin. Hepatic conjugation produces a water-soluble compound, normally excreted in the bile. Total bilirubin levels therefore represent the balance between production metabolism and excretion. Excessive production may result from disease processes resulting in increased red cell turnover leading to unconjugated hyperbilirubinaemia. Conjugated hyperbilirubinaemia results from leakage of bilirubin into the blood directly from the hepatocytes or distal to the liver in the case of biliary obstruction. Conjugated bilirubin released into the blood stream tends to be excreted and can be measured in the urine, however, because some of the conjugated bilirubin can covalently bind to serum...
aspartate aminotransferase (AST) and - is often measured automatically when concentrations of AST and other transaminases are elevated. AST is a sensitive but nonspecific marker of hepatocellular damage. AST can be released from a number of damaged organs including liver, heart, muscle, kidney, pancreas and red blood cells. ALT is slightly more specific for liver damage with less extrahepatic production, but may be elevated in conditions such as myositis. High (> 1000 IU/litre) levels of AST usually represent hepatitis of viral, drug or ischaemic origin. Intermediate levels (200–400 IU/litre) may be seen in acute alcoholic hepatitis with more severe clinical dysfunction. Absolute levels of transaminases do not correlate with outcome.

Glutathione-S-transferase (GST): one problem with AST and ALT as measures of hepatocellular damage and necrosis is that these enzymes are not uniformly distributed throughout the liver, being predominantly concentrated in periportal hepatocytes. Centrilobular hepatocytes are most prone to hypoxia and are relatively deficient in AST and ALT. This may explain some of the difficulties when correlating absolute values of transaminases with outcome. GST is more evenly distributed throughout the liver. In addition, its relatively small molecular weight encourages rapid release following hepatocellular damage. A short half-life of 90 minutes means that acute changes can be tracked rapidly but that peak effects may be missed, depending on the sampling time after injury. GST is increasingly used as a sensitive marker for changes in hepatocellular function following surgery and anaesthesia.

Alkaline phosphatase (AP): this family of enzymes is located in liver, bone, placenta and intestine. In healthy individuals, circulating AP is derived from bone or liver. In pregnancy, AP is often twice the upper range of normal. Elevations also occur in peri-pubertal children. The wide distribution of the enzyme can cause confusion in the assessment of liver function, and extrahepatic elevation may occur as a result of hyperthyroidism, cardiac failure, hypernephroma and Paget’s bone disease. In the liver, AP is located in the microvilli of the biliary canaliculi and on the sinusoidal surface of the hepatocyte. Classically, AP levels in liver disease are elevated when there is intra- or extrahepatic obstruction to biliary drainage or due to space-occupying lesions such as tumours. The raised levels in the blood seem to be due to increased synthesis in the canicular membrane rather than failure of excretion. The diversity of AP families makes isoenzyme determination desirable, but this assay is not widely available and other markers of biliary obstruction, such as GGT, are often monitored.

GGT is a membrane-bound glycoprotein found in cells with a high secretory or absorptive activity (e.g. liver, kidney, pancreas intestine, prostate). 90% of patients with hepatobiliary disease have raised GGT, but specificity is low. Its main value is in combination with AP to convey additional liver specificity. Raised levels of GGT have been associated with obesity, alcohol use and raised cholesterol levels. In non-drinking, obese individuals the most common cause of raised GGT is a fatty liver.

Tests of renal failure
In perioperative care, laboratory tests are commonly requested to aid in the diagnosis and management of acute renal failure. This brief review concentrates on tests of function rather than those requested to confirm or refute a specific diagnosis. Classically, renal impairment (Figure 1) is classified as:

- pre-renal (poor perfusion), often correctable with volume resuscitation
- renal (intrinsic renal disease)
- post-renal (obstruction).

Post-renal failure is common and is often excluded by ultrasound. Clinical acumen is vital for the detection of hypovolaemia and low cardiac output states. Laboratory examination of the urine can sometimes be useful in the differentiation of pre-renal and ‘true’ renal failure.

Measuring urinary biochemical indices has limitations because typical values are seldom present and concomitant diuretic therapy often confuses estimates of urinary sodium in pre-renal failure. Hepatorenal failure mimics pre-renal failure with extremely low urinary sodium levels, but fails to respond to volume loading.

Urine analysis is an important, but often neglected, investigation. A normal urine analysis in the presence of impending acute failure supports the presence of pre-renal or obstructive patterns. Abnormal results may help to discriminate tubular and glomerular problems. Red blood cells suggest the presence of glomerular or vascular inflammatory disease. Urine protein excretion can occur as a result of glomerular damage (increased loss) or tubular failure of absorption.

Blood urea is often measured automatically when concentrations of sodium and potassium are requested. There is a common misconception that plasma urea usefully relates to glomerular filtration rate (GFR), however it is altered by diet, fever, gastrointestinal haemorrhage, renal blood flow, urine flow rates and in liver disease. Some laboratories no longer offer it as a routine assay. It still has a place in assessing the effect of compliance or alterations to diet in patients with stable chronic renal failure or in assessing the need for, or effects of, renal replacement therapy.

<table>
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<th>Urinary measurements in pre-renal and renal failure</th>
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<td><strong>Indices</strong></td>
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<td><strong>Pre-renal</strong></td>
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<tr>
<td>Urinary sodium (mmol/litre)</td>
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<tr>
<td>&lt; 20 (low)</td>
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<tr>
<td>Renal</td>
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<tr>
<td>&gt; 40 (high)</td>
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<tr>
<td>Urine osmolality (mosmol/litre)</td>
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<tr>
<td>&gt; 500 (high serum +100)</td>
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<tr>
<td>&lt; 350 (low)</td>
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<tr>
<td>Urine/plasma urea</td>
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<tr>
<td>&gt; 8 (high)</td>
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<tr>
<td>&lt; 3 (low)</td>
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<tr>
<td>Specific gravity</td>
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<tr>
<td>High 1.020</td>
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<td>Fixed 1.010–1.020</td>
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GFR, classically measured by inulin clearance, would be the ideal measurement to detect alterations in renal function, but in early renal disease, GFR is normal or increased. Inulin clearance is seldom measured in clinical practice and the serum creatinine and the creatinine clearance are used as estimates of GFR.

Serum creatinine is the most commonly used indirect estimate of GFR. The exponential rise in serum creatinine with falling GFR limits its use in assessing patients with low clearances. With low concentrations of creatinine, cross-reaction in the assay may overestimate the creatinine concentration and consequently underestimate creatinine clearance. Also, creatinine secretion by the tubules occurs and creatinine production is determined by muscle mass. Wasted patients have low levels of creatinine, which underestimate deterioration in renal function. Serum creatinine is also affected by age as muscle mass falls.

Attempts to correct for age and muscle mass have resulted in formulae that attempt to compensate for these changes.

\[
\text{Creatinine clearance} = \frac{1.22 \times (140 - \text{age}) \times \text{Weight}}{\text{Serum creatinine (\text{\textmu mol/litre})}}
\]

Creatinine clearance can be calculated by combining a timed urine collection with estimations of plasma and urine creatinine concentration.

\[
\text{Creatinine clearance} = \frac{\text{Urine concentration (\text{\textmu mol/litre}) \times Urine volume (ml/minute)}}{\text{Serum concentration (\text{\textmu mol/litre})}}
\]

Measuring creatinine clearance removes some of the problems associated with the use of isolated creatinine values, but it necessitates a 24-hour urine collection and assumes that serum creatinine is constant over 24 hours.

Measuring GFR using radioactive indicators: labelled chromium ethylenediamine tetraacetic acid (\(^{51}\text{Cr EDTA}\)) is the most widely used indicator. Clearance of this agent is almost identical to inulin even down to a GFR of 3–15 ml/minute. Following a single injection of 2 MBq \(^{51}\text{Cr EDTA}\), clearance can be calculated by serial blood sampling over 5 hours.

FURTHER READING
