Liver Function Tests

Introduction
The term "liver function tests" is actually a misnomer. Standard Liver Function Tests (LFT's) consist of the enzymes Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP) and Gamma Glutamyl Transferase (GGT), together with bilirubin, albumin, total protein and globulin; when considered together, these analytes open a diagnostic window into multiple organ systems. Doctors obviously appreciate this broad utility; LFTs comprise 32% of all Biochemistry testing done by Clinipath Pathology.

Cellular origins of LFTs
To better understand the genesis of various patterns, the possible sources of each LFT component needs to be appreciated.

• The hepatocytes are rich in ALT and AST, with ALT predominant in the cytoplasm and AST mainly intramitochondrial; some GGT is also present in hepatocytes. The typical hepatitic picture thus comprises ALT elevation, accompanied by (usually) lesser AST and GGT rise.

• GGT and ALP are mainly located in the bile ducts; biliary obstruction induces increased levels of both GGT and ALP and in addition GGT is induced (and thus elevated) by medications, drugs and alcohol. Predominant elevation of GGT and ALP are thus termed the cholestatic pattern which may be due to intrahepatic obstruction (bilirubin may be normal or raised) or less commonly extrahepatic obstruction (bilirubin elevated).

• Bilirubin, derived from the breakdown of red cell haemoglobin, is conjugated by the hepatocyte and excreted via the bile ducts into the bile.

• Albumin, with a biological half-life of about 3 weeks, is synthesised exclusively by the liver and levels are thus a measure of long term hepatic health. Albumin may, however, be normal early in severe acute hepatitis (due to its long half-life), and only falls late in chronic liver damage (due to the large hepatic functional reserve). The liver also synthesises most other serum proteins or globulins (but not the gamma globulins) and thus has a major effect on the serum total protein level.

Pitfalls and approach to interpretation
Interpreting LFTs would be complex enough were it not for the following pitfalls:

1. The liver is not the only source of the enzymes, in particular AST (also in muscle, red cells etc) and ALP (also bone, placenta, tumours) are found elsewhere;

2. Albumin, globulins and total protein levels may also be affected by non-hepatic pathology (eg nephrosis) as may bilirubin (eg haemolysis).

3. A single cause may result in multiple different patterns. A prime example of this last problem is medication effects; drugs can cause virtually every known LFT abnormality and should always be considered in the differential.

4. Overlap often exists between patterns.

I find it helpful, on inspecting a set of LFTs to first pose the simple questions:

• Is this pattern likely to be due to liver pathology or not?
• Could there be more than one organ involved?
• Is this pattern chronic or acute and is the patient relatively well or acutely or chronically ill?

Clearly, as for all laboratory tests, knowledge of the clinical setting is critical for interpreting LFT abnormalities correctly. Follow-up of abnormal LFTs is also very useful as any trend gives important diagnostic information.

I have arbitrarily categorised the patterns seen as simple (up to two abnormalities) and complex and have tried to incorporate some basic diagnostic hints when discussing each pattern. Space and time (mainly yours!) precludes a comprehensive review of LFTs; rather I have tried to cast some light in a few dark corners and concentrated on the commoner scenarios seen in daily clinical practise.
Liver Function Tests continued

Simple Patterns

Elevated albumin with or without increased total protein, other LFTs normal
This is a common, mostly benign finding and usually reflects stasis due to a tight tourniquet or prolonged erect posture, or occasionally is secondary to dehydration. A urea which is elevated disproportionately compared to the creatinine would support dehydration as cause.

Elevated globulin with or without elevated total protein, other LFTs normal
Usual causes are polyclonal increases of gamma globulin due to chronic infection or inflammation, or monoclonal gammapathy as seen in B cell neoplasia eg myeloma. Serum protein electrophoresis should be requested to differentiate.

Elevated bilirubin, other LFTs normal
When bilirubin is significantly elevated, the conjugated and unconjugated fractions should be measured. Jaundice is usually clinically visible when bilirubin reaches approximately 40 umol/L.

Isolated unconjugated hyperbilirubinaemia
(conjugated bilirubin <10 umol/L)
- Gilberts syndrome, a benign condition present in about 5% of the population, is the commonest cause. Elevation of bilirubin is usually mild (generally less than 50umol/L but rising up to 100umol/L with concomitant illness or fasting). Gilberts syndrome can be confirmed by genotyping (No Medicare rebate available, a fee may be charged by the referral laboratory) but this is only indicated if reassurance is needed for the patient.
- Haemolysis; a full blood count, reticulocytes and haptoglobins should be done to exclude this possibility. Patients with haemolysis may also have elevated AST levels.
- Drugs such as sulphonamides, rifampicin and probenecid
- Rarely, congenital defects of conjugation are implicated.

Isolated conjugated hyperbilirubinaemia
is uncommon in a well patient, but may be seen in Dubin Johnson syndrome and some medications eg anabolic steroids, phenothiazines, sulphonamides and carbimazole.

Elevated GGT, other LFTs essentially normal
This usually indicates induction by ethanol or medications particularly anticonvulsants, benzodiazepines, tricyclics, and warfarin. It is not, however, a reliable measure of ethanol intake; and may remain elevated for years in abstinent patients who have previously had viral or other hepatitis, or in fatty liver. Some apparently normal individuals may also have GGT up to 150 IU/L in the absence of ethanol, medications or illness. Elevation to very high levels (>500 IU/L) is, however, usually due to ethanol. Concomitant macrocytosis, hyperuricaemia, and hypertriglyceridaemia are also suggestive of ethanol. Carbohydrate deficient transferrin (cost $60, no Medicare rebate available) is considered a more reliable indicator of ethanol use than GGT.

Elevated ALP, other LFTs essentially normal
This pattern has very different causes in different demographic groups. The cause may be fairly obvious:
- In well children and adolescents it may be associated with a growth spurt and is not a cause for undue concern; it is, however, advisable to check vitamin D levels (there is an association with deficiency) and recheck the LFTs in a few months.
- In young women, pregnancy (usually the third trimester, and occasionally unsuspected by the doctor!) is a common cause;
- In elderly men, bone secondaries from prostatic cancer should be top of the list and a PSA requested
- Healing fractures may be the cause at any age.

If the above scenarios are excluded, ALP isoenzymes should be performed as an isolated ALP elevation, although usually derived from bone, may also be due to hepatic cholestasis (eg in primary biliary cirrhosis) or due to malignancy (the Regan isoenzyme, seen in Ca lung, ovary and pancreas).

If bone is confirmed as the source, Pagets disease, hyperparathyroidism (check calcium and PTH) hyperthyroidism (TFTs) vitamin D deficiency, chronic renal failure with renal osteodystrophy and bone malignancy (primary or secondary) should be excluded.

Predominant elevation of GGT and ALP, other LFTs essentially normal (cholestatic pattern)
This pattern is seen in intrahepatic cholestasis which may have a normal bilirubin if only part of the liver is involved (localised intrahepatic cholestasis) as unaffected areas can still secrete bilirubin. Causes include medications eg antibiotics and phenytoin, hepatic space occupying mass, (patients with a concomitant AST elevation are more likely to have hepatic tumours) the post-acute phase of viral hepatitis, ethanolic cirrhosis or primary biliary cirrhosis (antimitochondrial antibodies, increased IgM). Medication and alcohol review, hepatitis serology, anti mitochondrial antibodies and hepatic ultrasound and other imaging studies may be useful. ALP isoenzymes may be required to confirm hepatic origin as GGT elevation is such a common (often incidental) finding and the patient may well have concomitant liver and other (usually bone) pathology.

Elevated AST and ALT with increased AST/ALT ratio, other LFTs normal
In liver disease, ALT is generally elevated more than AST. When only AST and ALT are abnormal (ie GGT is not elevated) with AST at least 2-3 times greater than ALT, muscle damage is the usual cause. In young patients strenuous exercise regimes are often the culprits; in older patients toxins, medications eg statins or myocardial infarction may be implicated. The other common source of AST is from erythrocytes; haemolysis, both in vivo or in vitro must be considered.
Liver Function Tests continued

Complex Patterns

**Mild to moderate hepatic pattern**
Mild, persistent elevations of ALT (up to about 200 IU/L) with or without lesser elevations of AST and GGT constitute a very common pattern particularly in overweight patients with Metabolic Syndrome and resultant non-alcoholic fatty liver disease (NAFLD). NAFLD now affects up to 30% of Australian adults with the NAFLD spectrum spanning hepatic steatosis, non-alcoholic steato-hepatitis (NASH), and progressing on to cirrhosis. Fasting glucose, lipids and U&Es should be checked and hepatic ultrasound may be confirmatory. Be aware that NAFLD may be present with variations of this pattern and also that the majority of patients with NAFLD have completely normal LFTs; however, patients with NAFLD commonly have elevated ferritins secondary to liver damage.

Other causes of the mild hepatic pattern are acute and chronic viral hepatitis including Hep A, B and C; EBV, CMV, coxsackie and adenovirus; medications, toxins including ethanol; less commonly haemochromatosis (especially in males; check iron studies) auto-immune hepatitis (check ANA, anti smooth muscle antibodies, anti LKM antibodies) Wilsons disease (low serum copper and caeruloplasmin, increased random urine copper), alpha 1 antitrypsin deficiency (low alpha1 antitrypsin level) and in up to one third of patients with coellic disease, with the LFTs usually normalising on a gluten-free diet.

Early acute biliary obstruction (eg biliary stones) will elevate the ALT and AST (mild to moderate rise) before ALP and bilirubin start to rise; but occasionally ALT and AST elevations of up to 1000 IU/L are seen. A hepatic picture may also occur in anoxia due to cardiac failure.

**Acute severe hepatic pattern**
Acute viral hepatitis (Hep A and B; EBV, CMV, coxsackie and adenovirus; EBV can cause severe hepatitis in adolescents and younger adults) and acute toxic or drug-induced hepatitis (eg Paracetamol, valproate, carbon tetrachloride) can elevate the ALT and AST from ten times the upper limit of normal up to the hundreds with lesser elevations of GGT and ALP.

AST elevation which is greater than ALT is a danger sign in this context as it signals severe hepatic damage and possible hepatic necrosis. Albumin is often normal in the early phases due to its long half-life of 3 weeks; globulin is also usually normal early on. Rising bilirubin with a cholestatic pattern may develop later. Acute ischaemia and shock may also cause a severe acute hepatic picture.

**Predominantly cholestatic picture with increased conjugated bilirubin**
These patients will have dark urine (due to conjugated bilirubin) and pale stools (due to absent bilirubin and stercobilin). In the blood ALP, GGT and bilirubin predominate; in elderly patients with progressive painless jaundice, pancreatic and biliary cancer must be excluded; consider bile stones if colicky pain is present. All ages may be affected by medications, and a cholestatic picture may evolve in the later stages of viral or toxic hepatitis. Cirrhosis including primary biliary cirrhosis must be considered, antimitochondrial antibodies should be checked. Marked hypercholesterolaemia may be present in patients with cholestatic jaundice.

**Mixed hepatic/cholestatic picture**
This consists of similar elevations of ALT, AST, GGT, ALP, usually >200 IU/L, and sometimes of bilirubin. Viral, medication induced or toxic hepatitis, autoimmune hepatitis, chronic active hepatitis (increased IgG levels), hepatic space occupying mass, biliary disease, cirrhosis and ethanol are possibilities. Investigation is covered above.

**Ethanolic Hepatitis**
Isolated GGT elevation in regular drinkers can progress to ethanolic hepatitis when exposure to toxic levels of ethanol occurs. Typical ethanolic hepatitis has AST elevated more than the ALT, and gamma GGT is high and may be very high. As the disease progresses to cirrhosis and liver failure, the ALP also rises, the albumin falls and the (gamma) globulins (mainly IgA) rise due to non-removal of antigenic compounds by the damaged liver. Bilirubin usually rises when hepatic failure is at hand.

**Chronic end stage liver disease**
The signature features are a low albumin, elevated globulin (usually due to increased IgA) and sometimes elevated (and rising) bilirubin. AST is mildly elevated, ALT is often normal. GGT and ALP are mildly elevated or unremarkable. Once ascites and elevated bilirubin are present, prognosis is poor and hepatic failure is imminent.

Variations on this pattern exist; occasionally quite severe chronic hepatic disease may have totally normal LFTs due to the liver’s large reserve capacity! Prothrombin time, elevated ammonia and lactate and the presence of hypoglycaemia may help in assessing severity if required.

**Pregnancy**
LFT abnormalities in pregnancy may be due to any of the above conditions, however pregnancy specific conditions should be considered (especially in later pregnancy) as failure to diagnose them may have severe consequences.

- **Intrahepatic cholestasis of pregnancy** presents with severe pruritis in the second or third trimester. LFTs may show a cholestatic pattern or may be essentially normal (apart from the expected ALP elevation of pregnancy) in which case serum bile acids should be measured to make the diagnosis. Maternal prognosis is good, however foetal distress and prematurity may occur.

- **Acute fatty liver of pregnancy** usually presents with nausea, vomiting, lethargy, abdominal pain, jaundice, and sometimes bleeding, and mental status changes. Diagnosis is mainly based on the clinical picture; LFTs show a hepatic picture, outcome is improved by prompt delivery of the foetus.

- **HELLP syndrome**. The combination of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) is a severe form of pre-eclampsia that can occur from the middle of the second trimester to the immediate postpartum period (usually within 2 days of delivery). Provided prompt delivery is expedited, prognosis is good.
### Simple Patterns

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Comment</th>
<th>Likely causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Albumin</td>
<td>Usually benign</td>
<td>Tight tourniquet, prolonged erect posture, Dehydration</td>
</tr>
<tr>
<td>Elevated globulin</td>
<td>+/- total protein</td>
<td>Chronic infection/inflammation or monoclonal gammapathy</td>
</tr>
<tr>
<td>Elevated Bilirubin (other LFT's normal)</td>
<td>Unconjugated</td>
<td>Gilberts Syndrome, haemolysis</td>
</tr>
<tr>
<td></td>
<td>Conjugated</td>
<td>Some medications, anabolic steroids, sulphamides</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Dublin Johnson syndrome</td>
</tr>
<tr>
<td>Elevated GGT (other LFT's normal)</td>
<td>High</td>
<td>Ethanol induced</td>
</tr>
<tr>
<td></td>
<td>Very high (&gt;500 IU/L)</td>
<td>Usually ethanol induced</td>
</tr>
<tr>
<td>Elevated ALP (other LFT's normal)</td>
<td>In Children and adolescence</td>
<td>May be associated with growth spurt (check Vit D)</td>
</tr>
<tr>
<td></td>
<td>Young women</td>
<td>Pregnancy third trimester</td>
</tr>
<tr>
<td></td>
<td>Elderly men</td>
<td>Bone secondaries from Prostate Ca</td>
</tr>
<tr>
<td></td>
<td>Any age</td>
<td>Healing fractures, vitamin D deficiency</td>
</tr>
<tr>
<td>Elevated GGT + ALP</td>
<td>Cholestatic pattern</td>
<td>Medications: antibiotics, phenytoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatic space occupying mass (more probable if accompanied by ↑ AST)</td>
</tr>
<tr>
<td>Elevated AST+ALT with AST&gt;&gt;ALT</td>
<td>GGT typically not elevated</td>
<td>Muscle damage, cirrhosis</td>
</tr>
</tbody>
</table>

### Complex Patterns

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Comment</th>
<th>Likely causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Hepatitic</td>
<td>↑ ALT slight ↑ AST slight ↑ GGT</td>
<td>Common in overweight patients with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease, Medications</td>
</tr>
<tr>
<td>Acute Severe Hepatitic</td>
<td>↑↑↑↑ ALT + AST ↑ GGT+ALP</td>
<td>Acute viral infection (eg Hep A/B), Toxins and Drugs (eg paracetamol, valproate)</td>
</tr>
<tr>
<td>Conjugated Bilirubin</td>
<td>↑↑ GGT ↑↑ ALP ↑↑ Bilirubin (conjugated) Dark urine and pale stools</td>
<td>Exclude pancreatic and biliary Ca Consider bile stones Viral hepatitis, medications</td>
</tr>
<tr>
<td>Mixed Hepatic / cholestatic</td>
<td>Similar elevations of ALT, AST, GGT, ALP</td>
<td>Viral, medication induced, auto immune hepatitis, biliary pathology, hepatic space occupying mass</td>
</tr>
<tr>
<td>Ethanolic Hepatitis</td>
<td>↑ AST &gt; ↑ ALT ↑↑ GGT +/-↑ALP</td>
<td>Acute binge drinking</td>
</tr>
<tr>
<td>Chronic end stage liver disease/ hepatic failure</td>
<td>↓ Albumin ↑ Globulin ↑ Bilirubin ↑ AST ALT often normal</td>
<td>May be due to ethanol, chronic viral or auto-immune hepatitis</td>
</tr>
<tr>
<td>Abnormal LFT's in pregnancy (usually 3rd trimester)</td>
<td>Normal rise in ALP (placental) occurs in 3rd trimester</td>
<td>For other abnormal liver enzymes, consider possibility of intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy or HELLP syndrome as well as other non-pregnancy related causes.</td>
</tr>
</tbody>
</table>

---

Dr Sydney Sacks  Chemical Pathologist  T: 9476 5211  E: ssacks@clinipath.net