Liver Function Testing in primary care
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in primary care

Points to consider

While reading this document, you may like to consider the following points and how you manage these situations within your day to day practice.

When are LFTs indicated?

How are isolated borderline LFT results managed?

Is LFT monitoring necessary for people on statins?

What are the best tests of liver failure?

Who is at risk of chronic hepatitis?

How is acute hepatitis managed in primary care?

Is non-alcoholic liver disease a benign condition?

What is the role of GGT in screening for excessive alcohol intake?
INTRODUCTION

The majority of liver problems are managed in primary care, with referral to secondary care usually reserved for a specific range of conditions. Consequently, most liver function testing is initiated and interpreted in primary care.

Knowing when to test is a challenge in primary care. Testing asymptomatic people or those with vague symptoms may return results just outside the reference range making it unclear how to proceed with follow up testing.

Interpretation of liver function tests (LFTs) is not always easy. Patterns of test results across several parameters are usually more useful than single parameters. Also, levels of LFT results are not always a good indication of disease severity. For example, some LFTs may be normal in advanced liver failure but results may be markedly increased in acute hepatitis, from which most patients will recover well.

This difficulty in interpreting LFTs means that, as for all laboratory tests, they must be considered carefully in the context of clinical findings, previous liver function tests and other test results.

The purpose of this document is to provide guidance to primary care clinicians in the use of liver function testing. For an overview of individual liver function tests see Appendix 1.

This is a consensus document, as there is no unanimous international agreement on liver function testing protocols.

We thank the members of the advisory panel for their expertise and guidance in the development of this resource:

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REQUESTING LIVER FUNCTION TESTS

Liver function testing is not indicated for asymptomatic people without risk factors

There is no evidence to support routine or opportunistic screening of asymptomatic people without known risk factors. It is rare to discover significant abnormal LFTs in these people.

People at risk of abnormal liver function tests

Asymptomatic people at risk of abnormal LFTs

The majority of abnormal LFTs in asymptomatic people occur in those with:

- Diabetes or metabolic syndrome (increased risk of NAFLD)
- Excessive alcohol intake
- Chronic hepatitis B
- Chronic hepatitis C

Identification and early management depends largely, on the recognition and management of these conditions.

Table 1: Risk factors for non-alcoholic fatty liver disease

<table>
<thead>
<tr>
<th>The risk factors for these conditions have not yet been quantified in the same way as risk factors for cardiovascular disease, but include the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Maori, Pacific or Indian ethnicity</td>
</tr>
<tr>
<td>- Increasing age</td>
</tr>
<tr>
<td>- Glucose intolerance</td>
</tr>
<tr>
<td>- Polycystic ovary syndrome</td>
</tr>
<tr>
<td>- History of gestational diabetes or having a baby over 4kg</td>
</tr>
<tr>
<td>- Family history of diabetes</td>
</tr>
</tbody>
</table>
Diabetes or metabolic syndrome

Diabetes, metabolic syndrome, insulin resistance and dyslipidaemia, in particular high triglycerides, all increase the risk of non-alcoholic fatty liver disease (NAFLD) (Table 1). This is not a benign condition, leading to long term scarring of the liver in 10–15% of people, and eventual cirrhosis in some.

People identified with diabetes, metabolic syndrome or insulin resistance will benefit from occasional measurement of LFTs. Appropriate times are:

- At diagnosis
- At the start of antidiabetic drug therapy
- At any other time indicated by clinical judgment

Excessive alcohol intake

Gamma glutamyl transferase (GGT) and a number of other laboratory results, such as macrocytosis and elevated triglycerides or uric acid, may give indications of excessive alcohol intake. These tests are neither sensitive nor specific enough to screen for this problem in the general population. Better results are obtained by using screening questionnaires (Appendix 2) despite the fact that people tend to underestimate or deny their alcohol intake. Screening is best followed up by direct but sensitively asked detailed questions, if indicated.

The predictive value of elevated GGT is however, better when there is strong suspicion of alcohol excess. Some clinicians may use it when they suspect people are hiding excessive alcohol intake. There may be some discussion about whether this use is appropriate, if the reason for the test is not discussed with the patient.

Incidental finding of elevated GGT, or the other tests mentioned, may raise suspicion of excessive alcohol intake and can be followed up by non-judgmental direct questions. However, specificity is low and other causes for the changes need to be considered.
Chronic hepatitis B

Less than 5% of adults infected with hepatitis B will develop chronic infection. The remainder clear the infection spontaneously, usually following an acute icteric hepatitis illness.

In contrast, acute icteric hepatitis is a rare event in children. More than 90% of neonates infected through vertical transmission (mother to child during the perinatal period) and more than 50% of children infected through early horizontal (so-called “playground”) infection will develop chronic hepatitis B infection. These are the group at life-long risk of cirrhosis and hepatocellular carcinoma.

People with chronic hepatitis B have a significant risk (approximately 25%) of developing liver damage, with significant risk of cirrhosis, liver failure and liver cancer. LFTs should be tested at least 6 monthly.

Chronic hepatitis B is particularly common in those of Māori, Pacific or Asian ethnicity. Screening for hepatitis B infection, using HBsAg, is recommended for all people of Māori, Pacific or Asian ethnicity over the age of 15 years, who have not previously been immunised (Appendix 3). Testing is only required once, as it is childhood infection that leads to chronicity. People who are infected in adult life usually clear the infection and do not become chronically infected.

Chronic hepatitis C

Hepatitis C is transmitted by blood transfer. Most people will not be symptomatic during the acute infection but approximately 70% will remain infected. Chronic infections carry a substantial risk of liver damage, cirrhosis and liver cancer.

At particular risk are people who had blood transfusions prior to the introduction of screening of blood products for hepatitis C in 1992 or inject street drugs or share needles. It is recommended that people in these categories be tested for hepatitis C with anti-HCV antibodies (Appendix 4).
People at risk of abnormal LFTs because of other illnesses

Liver disease is associated with a wide range of other illnesses, including
- Haemochromatosis
- Autoimmune diseases, including coeliac disease
- Chronic inflammatory bowel disease
- Metastatic cancer
- Clinically significant thyroid disease
- Right heart failure

People at risk of abnormal LFTs because of drugs

Many drugs and herbal remedies increase the risk of abnormal LFTs. However, the benefit and cost effectiveness of LFT monitoring has not been established.

However, LFT monitoring is recommended for some medications. Table 2 lists the drugs for which monitoring is recommended, that are probably of most importance to primary care clinicians. Monitoring may also be required for other drugs initiated in secondary care. A number of other drugs (for example, warfarin) require LFT before initiation of therapy.

Table 2: Drugs for which LFT monitoring is recommended in primary care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Dantrolene</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Synthetic retinoids</td>
</tr>
<tr>
<td>Anti-tuberculosis drugs</td>
<td>Chemotherapy drugs</td>
</tr>
</tbody>
</table>

Adapted from: Sleisenger et al²

It is important to consider drugs as a cause of LFT abnormalities, should they occur.
The risk to the liver from statin therapy is negligible. Statins should NOT be withheld in patients with baseline abnormal LFTs and monitoring is of no benefit.

Routine monitoring of LFTs no longer considered necessary for statin use

There is increasing evidence that the risk of liver damage from statin use has been overstated, although asymptomatic aminotransferase elevations are common³.

Liver failure appears to occur at a rate approximately equal to the background rate for liver failure in the general population. The National Lipid Association (USA) Expert Liver Panel concludes:

- Irreversible liver damage resulting from statin therapy is exceedingly rare
- Routine monitoring is not likely to identify the very rare individual who may develop significant liver injury
- Routine monitoring will detect isolated increases in aminotransferases levels, which may lead to unnecessary alteration or discontinuation of statin therapy

In the Himmer Zimmerman State of the Art lecture⁴ on Statin Hepatotoxicity at last year's American Association Study of Liver, Professor Wallace Maddrey stated that a review of 475,000 patients receiving statins found no increased risk of liver-related events. He said monitoring for hepatotoxicity was not justified unless the patient became jaundiced i.e. asymptomatic liver dysfunction is not an indication to stop therapy.

In conclusion, the risk to the liver from statin therapy is negligible. Statins should not be withheld in patients with baseline abnormal LFTs and monitoring is of no benefit.

The risk to the liver from statin therapy is negligible. Statins should NOT be withheld in patients with baseline abnormal LFTs and monitoring is of no benefit.

People at risk of abnormal LFTs because of other abnormal blood tests

In some situations, LFTs may be indicated following abnormalities in apparently unrelated tests. Examples are:

- Abnormal iron studies/elevated ferritin
- Abnormalities on blood film
  - Macrocytosis
  - Neutropenia
  - Thrombocytopenia
Liver function testing when there are clinical features of liver disease

Although clinical features of liver disease are indications for LFT testing, signs and symptoms may be poorly defined in both early and advanced disease (Table 3).

Jaundice is a common and usually obvious presenting sign, but less recognisable are fatigue, pruritis and vague right upper-quadrant pain. Other features may suggest more advanced liver disease.

Table 3: Physical features of liver disease

<table>
<thead>
<tr>
<th>Physical features of liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, pruritis, vague RUQ pain</td>
</tr>
<tr>
<td>Jaundice</td>
</tr>
<tr>
<td>Wasting</td>
</tr>
<tr>
<td>Abdominal pain, fever</td>
</tr>
<tr>
<td>Spider naevi</td>
</tr>
<tr>
<td>Gynaecomastia</td>
</tr>
<tr>
<td>Testicular atrophy</td>
</tr>
<tr>
<td>Palmar erythema</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Acute GI bleeding</td>
</tr>
<tr>
<td>Coagulopathy</td>
</tr>
</tbody>
</table>

(Adapted from: BC Health services 2004)
INTERPRETATION OF LIVER FUNCTION TESTS

Abnormal liver function tests must be interpreted with regard to clinical context and results of previous tests

LFT results can only be interpreted with careful consideration of the clinical context because, as stated previously, levels of derangements in LFTs are not always indicative of the severity of the disease and clinical context is necessary to determine the underlying aetiology.

Clues from the history could include:

History of symptoms: Symptomatic liver disease may be suggested by symptoms such as fatigue, pruritus, and vague right upper-quadrant pain. Other symptoms, such as sleep-wake reversal, memory or concentration difficulties, easy bruising, or peripheral edema, suggest more advanced liver disease.

Medication history: A careful medication history including prescription drugs, OTC medicines and herbal remedies may indicate the cause of abnormal LFTs.

Occupational exposure to some industrial solvents may be associated with hepatocyte injury, while some epoxy resin hardeners can cause cholestasis. Granulomatous hepatitis and hepatoportal sclerosis (non-cirrhotic portal hypertension) may also occur from occupational exposure to chemicals.

Family history may identify increased risk of genetic diseases such as haemochromatosis, Wilson's disease, and alpha-1-antitrypsin deficiency. In addition, a genetic predisposition to such traits as obesity, type 2 diabetes, and high triglycerides are recognised risk factors for liver disease.

Social history, including high-risk sexual habits, overseas travel and other risk factors for viral hepatitis, is an important part of the patient encounter. Patients often under report these risks, especially alcohol consumption.

Physical examination of a patient may help elucidate the cause and severity of liver disorders. For example:

- Hepatomegaly is more commonly associated with alcoholic liver disease, haemochromatosis, and primary biliary cirrhosis than other diseases
- Skin hyperpigmentation and arthralgias may suggest haemochromatosis
- Kayser-Fleischer rings and neurologic motor abnormalities are features of Wilson's disease
- Muscle wasting, jaundice, spider angiomas, palmar erythema, gynaecomastia, testicular atrophy, ascites, asterixis, and splenomegaly may indicate cirrhosis
Liver function tests reflect several different aspects of liver disorder

Individual LFT results are not usually specific to a particular disease; but the pattern of alteration can be more useful. Common liver disorders have typical patterns of LFT alteration (Table 4). These patterns are not always distinct as several aspects of liver disorder may occur together.

Generally, hepatocyte injury produces changes in aminotransferases, cholestasis causes changes to the alkaline phosphatase, bilirubin and GGT and liver synthetic function is measured by serum albumin and INR. Although certain liver diseases may display a mixed biochemical picture, the ability to distinguish between these three subgroups is fundamental to narrowing down the differential diagnosis.

Table 4: Key biochemical markers in hepatic systems and function
Reference CAMJ, 2005

<table>
<thead>
<tr>
<th>System or function</th>
<th>Marker</th>
<th>Site or significance</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte integrity</td>
<td>Aspartate aminotransferase</td>
<td>Liver, heart, skeletal muscle, kidney, brain, red blood cell</td>
<td>Catabolises amino acids, permitting them to enter the citric acid cycle</td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase</td>
<td>Liver</td>
<td>Canicular enzyme that plays a role in bile production</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Alkaline phosphatase</td>
<td>Bone, intestine, liver, placenta</td>
<td>Correlated levels with alkaline phosphatase indicate hepatobiliary origin</td>
</tr>
<tr>
<td></td>
<td>γ-Glutamyl-transferase</td>
<td>Correlated levels with alkaline phosphatase indicate hepatobiliary origin</td>
<td>Catalyzes transfer of γ-glutamyl group from peptides to other amino acids</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>Elevations may indicate hepatic or extrahepatic disorder</td>
<td>Breakdown product of haemolysis taken up by liver cells and conjugated to water-soluble product excreted in bile</td>
</tr>
<tr>
<td>Liver function mass</td>
<td>Serum albumin</td>
<td>Diet or liver</td>
<td>Liver synthesises albumin</td>
</tr>
<tr>
<td></td>
<td>Prothrombin time</td>
<td>Liver synthesises vitamin K-dependent clotting factors</td>
<td>Bile salts are synthesised in the liver and necessary for vitamin K absorption</td>
</tr>
</tbody>
</table>

Reference CAMJ, 2005
Hepatocyte injury: usually results in ALT and/or AST elevation

The most commonly used markers of hepatocyte injury are aspartate aminotransferase (AST)* and alanine aminotransferase (ALT)**. Injury to hepatocytes causes these enzymes to leak into the circulation, raising serum levels.

- ALT elevation is most specific for hepatocyte injury as its concentration in the liver far exceeds that in any other organ.
- AST is less specific as elevation is also caused by damage to skeletal muscle, kidney, brain and red blood cells (see Appendix 5).

Most likely causes of hepatocyte injury are:

- Non-alcoholic fatty liver disease
- Viral hepatitis
- Alcohol, drugs, and herbal remedies
- Haemochromatosis
- Autoimmune disease

Guidelines for follow-up for abnormal aminotransferase results:

The following points are guides only:

- If only AST is elevated, consider non-liver causes
- Review risk factors and clinical features
- If risk factors and clinical features are not suggestive of a cause, investigation as outlined in the following section is appropriate

How should I investigate abnormal transaminases in asymptomatic patients without risk factors or clinical features of liver disease?

When further testing is indicated for a predominant increase in transaminases, the following table may be useful. Testing is, as previously stated, guided by presence of risk factors and clinical features. The tests are usually requested in a step wise fashion – selecting relevant first tier tests, then if necessary relevant second tier tests.

*formerly serum glutamate oxaloacetate transaminase (SGOT)
**formerly serum glutamate pyruvate transaminase (SGPT)
### First Tier

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormality</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Macrocytosis</td>
<td>Possible alcohol excess if GGT also raised</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Portal hypertension (possible hypersplenism)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>&gt;5.5 mmol/L</td>
<td>Glucose intolerance (GTT may be indicated)</td>
</tr>
<tr>
<td>Fasting lipid profile (including triglycerides)</td>
<td>Abnormal</td>
<td>Contributor to fatty liver</td>
</tr>
<tr>
<td>Ferritin/Iron studies</td>
<td>High</td>
<td>Possible haemochromatosis. Check HFE genotype if repeat test in fasting, well patient remains high</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Chronic HBV infection</td>
</tr>
<tr>
<td>Anti-HCV antibodies</td>
<td>Positive</td>
<td>Suggests chronic HCV infection. Needs confirmation by PCR for HCV RNA</td>
</tr>
</tbody>
</table>

### Second Tier

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormality</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver ultrasound*</td>
<td>Echogenic liver, mass or dilated ducts</td>
<td>Suggests fatty liver, tumour or stones</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>AMA positive, IgM raised</td>
<td>Probable primary biliary cirrhosis</td>
</tr>
<tr>
<td></td>
<td>ASM/ANA positive</td>
<td>Suggestive of autoimmune hepatitis</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin</td>
<td>Low</td>
<td>Suggests deficiency</td>
</tr>
<tr>
<td>Others: for example, caeruloplasmin, urine copper, as dictated by clinical context.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Liver ultrasound is a first tier test when cholestasis is suspected
Transaminases in general

- <3 times ULN: recheck in 1–3 months
- If two results 3 months apart remain raised, investigate as in table 5
- >3 times ULN investigate as in table 5

AST/ALT ratio

- The AST/ALT ratio is ≤1 in the majority of cases of acute hepatocellular injury
- An AST/ALT ratio >1 may be seen in alcoholic liver disease, drug-induced liver injury, malignancy, cirrhosis or non-liver disease (e.g. muscle inflammation, haemolysis). In acute alcoholic liver disease, the ratio is often >2

Isolated GGT elevation

This has limited use as primary liver test and there is no clear consensus on follow up. Suggestions are:

- Although an imperfect marker, consider alcohol intake as possible cause. Also review risk factors for non-alcoholic fatty liver disease
- Mild rises <3 times ULN: test three monthly and consider further investigation if elevation persists or rises
- >5 times ULN or both GGT and alkaline phosphatase raised without explanation: consider ultrasound to exclude a space-occupying lesion or biliary obstruction

*ULN = Upper Limit of Normal or upper limit of reference range
Cholestasis: alkaline phosphatase, bilirubin and GGT are main indicators

Cholestasis occurs when bile flow into the duodenum is reduced. It is usually due to obstruction, but adverse effects of medications, genetic defects or autoimmune processes may also interfere with bile flow.

Extrahepatic biliary obstruction occurs either within the biliary system from stones or stricture or from extrinsic compression such as from malignant lymphadenopathy. Intrahepatic cholestasis occurs either from direct canulicular injury or from compression due to hepatocyte swelling, as in severe hepatitis.

Most likely causes of cholestasis include:
- Gall stones
- Abdominal masses
- Medications (erythromycin, phenytoin, flucloxacillin, amoxicillin-clavulanic acid, combined oral contraceptive pill, some antipsychotics)
- Pregnancy
- Primary biliary cirrhosis
- Paraneoplasia (especially lymphoma)
- Systemic sepsis

A cholestatic pattern of LFT disturbance: ALP and bilirubin usually both elevated

A cholestatic pattern is when alkaline phosphatase (ALP) and bilirubin are elevated. However, sometimes in cholestasis, alkaline phosphatase is raised in isolation with a normal bilirubin. There are also some common non-liver causes of elevation of bilirubin or alkaline phosphatase levels.

Non-liver causes of alkaline phosphatase elevation

Elevated alkaline phosphatase levels are not specific for liver disorders. Other major sources of alkaline phosphatase are bone, intestine, and placenta.

Bony causes of alkaline phosphatase elevation include: bony metastases, hyperparathyroidism, renal impairment, healing fractures and Paget's disease.

Congestive heart failure, hyperthyroidism, pregnancy and vitamin D deficiency can also elevate alkaline phosphatase levels. These levels are also normally elevated in children while bone growth continues and rise modestly during the perimenopausal years.
**Raised alkaline phosphatase plus raised GGT makes liver problems more likely**

A raised alkaline phosphatase level accompanied by a rise in GGT, indicates a liver cause is most likely. However if GGT is normal, a bony cause is more probable.

**Follow up of elevated alkaline phosphatase levels**

Follow up depends on the clinical context, other laboratory abnormalities, and clinical review for possible causes.

Liver ultrasound is useful if cholestasis is suspected. When there are no clinical indications of the cause and the likelihood of systemic or liver disease is low, table 6 may be a useful guide:

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**Table 6: Response to elevated alkaline phosphatase levels when likelihood of systemic or liver disease is low**

<table>
<thead>
<tr>
<th>Level</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1.5 times ULN</td>
<td>Small raises may be statistical rather than clinical and some people have small rises after food due to increased release of intestinal ALP. Comparison with any previous result is often helpful – a clear rise from previous level suggests a disease process even if the rise above the population range is small. Recheck fasting level in 3 months.</td>
</tr>
<tr>
<td>Greater than 1.5 times ULN</td>
<td>Two measurements taken 3 months apart warrant further investigation but care must be taken to exclude clinical signs of malignancy before waiting 3 months</td>
</tr>
<tr>
<td>Greater than 3.0 times ULN</td>
<td>Immediate investigation warranted</td>
</tr>
</tbody>
</table>

**Causes of bilirubin elevation**

In liver disease, bilirubin elevation is almost always accompanied by disturbance in other LFTs. Isolated bilirubin levels can occur in familial hyperbilirubinaemias, the most common is Gilbert’s syndrome, which is discussed later. Bilirubin is also elevated in haemolysis as increased red cell breakdown leads to elevated levels of unconjugated serum bilirubin.
Haemolysis can occur as a result of inherited haemolytic anaemias, such as spherocytosis or thalassaemia, or secondary to a wide range of other conditions. Examples include:

- Immune reactions, such as haemolytic transfusion reaction or haemolytic disease of the newborn
- Auto-immune disorders, such as systemic lupus erythematosus or rheumatoid arthritis
- Systemic disease, such as renal or liver failure
- Drugs and chemicals, such as arsenic or sulphasalazine
- Infections, such as malaria and Clostridium perfringes
- Mechanical, such as valve prosthesis or march haemoglobinuria
- Hypersplenism
- Burns

**Follow up of elevated bilirubin levels when no clinical indications of cause**

Follow up is, as always, determined by clinical and other laboratory findings. When there are no other indications, table 7 may guide follow up:

*Table 7: Managing elevated bilirubin levels in primary care*

<table>
<thead>
<tr>
<th>Bilirubin levels</th>
<th>Response when no other clinical or laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 1.5 times ULN</td>
<td>Retest when well in 3 months</td>
</tr>
<tr>
<td>Greater than 1.5 times ULN</td>
<td>Test unconjugated portion. Unconjugated &gt;70% in a well patient with otherwise normal LFTs, if CBC and TSH are normal it is likely to be Gilbert's syndrome.</td>
</tr>
<tr>
<td>Greater than 3 times ULN</td>
<td>Unconjugated &gt;70% consider haemolysis. Conjugated &gt;50% consider ultrasound</td>
</tr>
</tbody>
</table>
Liver failure: reflected in serum albumin and INR

Failure of the liver to perform its synthetic functions is most often related to loss of functioning liver mass. It is usually assessed by levels of serum albumin and coagulation factors, represented indirectly by the INR. In severe liver disease, production of other proteins and glucose may also fall.

Failure of the liver to synthesise albumin results in reduction of serum albumin. Albumin has a long half-life and therefore, may not yet be low in an acute liver insult. Albumin levels may also be reduced in cachexia, catabolic states such as sepsis and cancer, nephrotic syndrome and protein-losing enteropathy.

INR results reflect the synthesis of all liver-derived clotting factors including those which are vitamin K dependent. Decreased synthesis of these clotting factors raises the INR. Vitamin K malabsorption, usually due to cholestasis, can also increase INR. If INR elevation is related to vitamin K malabsorption, rather than decreased liver synthetic function, it will resolve within 24 hours of parenteral injection of vitamin K (NOT oral).

As failure of liver synthetic function means loss of functioning liver mass, this is an indication of severe liver disease and further investigation is indicated.
PEOPLE WHO REQUIRE SPECIALIST REFERRAL FOR DISTURBED LIVER FUNCTION

- Anyone who is HBsAg positive and has an ALT above the ULN for at least 6 months requires referral. In the meantime, alpha-foeto protein (AFP) should be tested six monthly. If AFP is above 100 on any occasion, the patient should be seen urgently by the specialist. If AFP is between 20 and 100, the test should be repeated in one month and if still in this range, the patient should again be seen urgently.

- Anyone who has hepatitis C should be referred to a specialist, however anti-HCV antibody testing indicates past or current infection. Anyone who is anti-HCV antibody positive but has persistently normal LFTs, and two negative HCV RNA tests three months apart, does not need specialist referral, as active hepatitis C is extremely unlikely.

- Anyone with evidence of acute or chronic failure of liver synthetic function.

- Anyone with abnormal LFTs, hepatomegaly or ferritin >1000 µg/L at the initial diagnosis of haemochromatosis.

- Anyone else with persisting unexplained LFT abnormalities.
MANAGEMENT OF SPECIFIC CONDITIONS

Acute hepatitis

Serum ALT or AST greater than 500 is usually suggestive of acute hepatitis. Common causes are acute infections with the hepatitis B virus (usually acute adult infection acquired through either sexual contact or injecting street drugs), hepatitis A virus (through faecal-oral transmission) and Epstein-Barr virus (through transfer of oral secretions).

**Hepatitis A:** contaminated food, men who have sex with men
- <1% develop chronic autoimmune hepatitis

**Hepatitis B:** adult infection – sexual, intravenous drug use
- Acute hepatitis B is unlikely in adults of Māori, Pacific or Asian ethnicity (likely to be immune or chronically infected due to infection at an early age)
- <5% of adults develop chronic infection

**Hepatitis C:** adult infection, intravenous drug use
- >80% develop chronic hepatitis

**Epstein-Barr viral hepatitis:** usually adolescent (infectious mononucleosis)
- None develop chronic hepatitis

For an algorithm of acute hepatitis testing see Appendix 6.

The only indications for hospital admission are either evidence of acute liver failure (confusion, hypoglycaemia or increased INR), rising creatinine, or the need for rehydration due to vomiting and/or diarrhoea. 90% of acute hepatitis can be managed outside hospital.

Monitoring in acute hepatitis

Monitoring for acute hepatitis managed at home includes twice weekly testing of:

- ALT - Bilirubin
- AST - Serum creatinine
- INR - Glucose

Testing frequency is decreased as the results return to normal.
Liver function testing not indicated in infectious mononucleosis

Liver function testing is rarely indicated in infectious mononucleosis. It does not lead to chronic liver disease and discovering disordered LFTs does not influence management. It may be indicated if the patient becomes jaundiced.

Fatty liver (steatohepatitis)

Fatty liver is associated with alcoholic liver disease but non-alcoholic causes are becoming increasingly common. Non-alcoholic fatty liver disease suspected when a person with risk factors develops a hepatocyte injury pattern on liver function testing, and there are no other causes. An ultrasound showing increased echogenicity supports the diagnosis.

The risks of cirrhosis with alcoholic liver disease are well known, and treatment is aimed at stopping alcohol intake. However, less well known is that non-alcoholic fatty liver can also lead to permanent liver damage. Long term scarring occurs in 10–15% of people with non-alcoholic fatty liver, leading to eventual cirrhosis in some.

Non-alcoholic fatty liver disease is associated with metabolic syndrome, insulin resistance, diabetes, and hyperlipidaemia. Management includes:

- Identifying and addressing lifestyle issues
- Managing diabetes or metabolic syndrome
- Managing cardiovascular risk factors
- Excluding hepatitis B & C infections
- Checking for elevated ferritin levels

Abnormal LFTs are not usually contraindications to the use of metformin or statins.
Occasional monitoring of LFTs is useful, but especially indicated for people at risk of fibrosis or progression. People at particular risk include those with:

- BMI greater than 30 (especially with central obesity)
- Diabetes
- Significant dyslipidaemia, especially elevated triglycerides
- ALT greater than twice normal
- Ferritin over 1000 µg/L
- Steatohepatitis/fibrosis identified on liver biopsy

Liver metastases

Monitoring of LFTs is not routinely indicated for people with cancer as it is rare to get liver failure from liver metastases. Biliary obstruction may occur but leads rapidly to jaundice. However, monitoring of LFTs is worthwhile for people on chemotherapy.

Gilbert’s syndrome

Gilbert’s syndrome is the most common familial hyperbilirubinaemia occurring in 2–10% of the population. It is usually detected when an incidental blood test demonstrates slightly raised bilirubin with otherwise normal LFTs and no other signs of liver disease or haemolysis. The bilirubin is mostly unconjugated and levels fluctuate, often higher at times of illness and fasting. Although tiredness is frequently attributed to Gilbert’s syndrome, this is not thought to be a true association and therefore repeated testing is not appropriate.

Patients can be assured that Gilbert’s syndrome is not a serious disease and is asymptomatic. In pregnant women, the syndrome contains no risk of kernicterus to the foetus.
APPENDICES

Appendix 1 - Pathophysiology of liver function tests

- **ALT** – (alanine aminotransferase) an enzyme involved in the recycling of the amino acid alanine into glucose (gluconeogenesis). This is the most specific test for hepatocellular liver injury, although it is present in low concentrations in other tissues.

- **AST** – (aspartate aminotransferase) is involved in metabolism of the amino acid aspartic acid. It is also sensitive for hepatocellular disease, but is less specific as it is also raised with muscle inflammation and haemolysis. High levels of liver origin suggest possible alcohol use (pyridoxine deficiency) and infiltrative liver damage (e.g. malignancy).

- **GGT** – (gamma glutamyl transferase) is a sensitive marker of liver injury. Although induced by alcohol and some drugs (e.g. rifampicin), mild elevation is non-specific and may reflect other liver pathologies (e.g. non-alcoholic fatty liver disease).

- **ALP** – (alkaline phosphatase) also mainly reflects hepatobiliary processes and is raised in cholestasis. ALP is not specific for liver disorders as it is produced by other tissues including bone, intestine and placenta. These sources should be considered, especially in patients with isolated elevation with concurrent elevation of GGT.

- **Bilirubin** – is a product of red cell (haem) breakdown. Bilirubin is initially carried loosely attached to albumin as the unconjugated form. It is then taken up into hepatocytes, solubilised to form the smaller conjugated form, and excreted by the biliary system. The unconjugated form is increased by red cell breakdown (e.g. haemolysis) or reduced uptake and conjugation (e.g. Gilbert’s syndrome). The conjugated form is increased by impaired liver processing and bile flow (e.g. hepatitis, bile duct obstruction).

- **Total protein** – the total of albumin and other plasma proteins (mostly immunoglobulins). Changes in the total protein are non-specific as there may be increases and decreases in different components. For example chronic severe inflammatory liver disease may be associated with a low albumin and other liver globulins, but raised levels of immunoglobulins.

- **Albumin** – the most abundant plasma protein, produced in adults entirely by the liver. A falling level may reflect reduced liver production, usually indicating significant liver damage, but may also reflect increased protein loss, e.g. nephrotic proteinuria, GI loss. Levels may still be normal in patients with severe acute liver damage because the half-life of albumin in plasma is about three weeks.

- **INR** – a reflection of liver synthesis of vitamin K dependent clotting factors II, VII, IX, X. Raised INR may indicate decreased liver synthetic ability or cholestasis with reduced vitamin K absorption. Levels rise quickly with acute liver disturbance because of the short half-life of the clotting factors.
Appendix 2 – Alcohol Screening tests

The RAPS4 Alcohol Screening test for dependent drinking

Please answer these 4 questions:

- During the last year, have you had a feeling of guilt or remorse after drinking?
- During the last year, has a friend or a family member ever told you about things you said or did while you were drinking that you could not remember?
- During the last year, have you failed to do what was normally expected from you because of drinking?
- Do you sometimes take a drink when you first get up in the morning?

Alcohol Advisory Council of New Zealand ‘Drink Check’

The ALAC drink check questionnaire, *(Is your drinking OK?)* based on the AUDIT tool, is available online from ALAC: [http://www.alac.org.nz/TestYourDrinking.aspx](http://www.alac.org.nz/TestYourDrinking.aspx) or alternatively it is available as a brochure from [www.bpac.org.nz](http://www.bpac.org.nz)
Is your drinking ok?

What your score means

**High risk**

- **WOMEN**: 13 points or more
- **MEN**: 15 points or more

Your drinking will cause you or may already have caused you problems.

**Medium risk**

- **WOMEN**: 6 – 12 points
- **MEN**: 7 – 14 points

Your drinking is putting you at risk of developing problems.

**Low risk**

- **WOMEN**: 0 – 5 points
- **MEN**: 0 – 6 points

Your drinking is not likely to cause you problems if it remains at this level.

Adapted from Alcohol Advisory Council of New Zealand (ALAC) Drink Check
**Answer each question by circling your choice. Pick the answer that is closest to your situation.......**

**How often do you have a drink containing alcohol?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td>Two to four times a month</td>
<td>2</td>
</tr>
<tr>
<td>Two to three times a week</td>
<td>3</td>
</tr>
<tr>
<td>Four or more times a week</td>
<td>4</td>
</tr>
</tbody>
</table>

**How many standard drinks do you have on a typical day when you are drinking?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>One to two</td>
<td>0</td>
</tr>
<tr>
<td>Three to four</td>
<td>1</td>
</tr>
<tr>
<td>Five to six</td>
<td>2</td>
</tr>
<tr>
<td>Seven to nine</td>
<td>3</td>
</tr>
<tr>
<td>Ten or more</td>
<td>4</td>
</tr>
</tbody>
</table>

**How often do you have six or more drinks in one session?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td>Monthly</td>
<td>2</td>
</tr>
<tr>
<td>Weekly</td>
<td>3</td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td>4</td>
</tr>
</tbody>
</table>

**How often during the last year have you found you were not able to stop drinking once you had started?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td>Monthly</td>
<td>2</td>
</tr>
<tr>
<td>Weekly</td>
<td>3</td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td>4</td>
</tr>
</tbody>
</table>

**How often during the last year have you failed to do what was normally expected from you because of drinking?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td>Monthly</td>
<td>2</td>
</tr>
<tr>
<td>Weekly</td>
<td>3</td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td>4</td>
</tr>
</tbody>
</table>

**How often during the last year have you needed a drink in the morning to get yourself going after a heavy drinking session?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td>Monthly</td>
<td>2</td>
</tr>
<tr>
<td>Weekly</td>
<td>3</td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td>4</td>
</tr>
</tbody>
</table>

**How often during the last year have you had a feeling of guilt or remorse after drinking?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td>Monthly</td>
<td>2</td>
</tr>
<tr>
<td>Weekly</td>
<td>3</td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td>4</td>
</tr>
</tbody>
</table>

**How often in the last year have you been unable to remember what happened the night before because you have been drinking?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1</td>
</tr>
<tr>
<td>Monthly</td>
<td>2</td>
</tr>
<tr>
<td>Weekly</td>
<td>3</td>
</tr>
<tr>
<td>Daily or almost daily</td>
<td>4</td>
</tr>
</tbody>
</table>

**Have you or someone else been injured as a result of your drinking?**

<table>
<thead>
<tr>
<th>Injury</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes, but not in the last year</td>
<td>2</td>
</tr>
<tr>
<td>Yes, during the last year</td>
<td>4</td>
</tr>
</tbody>
</table>

**Has a relative, friend, doctor or other health worker been worried about your drinking or suggested you should cut down?**

<table>
<thead>
<tr>
<th>Worry</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes, but not in the last year</td>
<td>2</td>
</tr>
<tr>
<td>Yes, during the last year</td>
<td>4</td>
</tr>
</tbody>
</table>

**Add up all your scores to find out what sort of drinker you are......**

Your total score
Appendix 3 – Screening for hepatitis B in people not previously immune

**HBsAg**

- **Negative**
  - No evidence of chronic hepatitis B infection

- **Positive**
  - If positive for >6 months, consistent with chronic hepatitis B infection

**Investigation for Evidence of Previous Infection or Immunisation with hepatitis B**

See footnote a

**Anti-HBs**

- **Negative**
  - No evidence of previous infection or immunisation
  - See footnote (b)

- **Positive**
  - Compatible with previous infection or immunisation

---

a. Following a previous vaccination with documented immune response, the patient can then be presumed to be protected long term, unless they are immunosuppressed. If in doubt, revaccinate and recheck anti-HBs in 3 weeks.

b. A small number of patients may be positive for anti-HBc from a previous HBV infection, in the absence of anti-HBs. If there is a strong suspicion of previous infection or high risk, then order an anti-HBc.
Appendix 4 – Investigation for Evidence of Chronic HCV Infection

A negative test does not exclude infection within the previous eight weeks.

b. Positive anti-HCV is followed up by a HCV RNA test. Persistently normal LFTs and two negative HCV RNA tests 3 months apart indicate that active HCV is extremely unlikely.
Appendix 5 - Isoenzymes

In some situations, the interpretation of hepatic enzyme results may be difficult due to the occurrence of isoenzymes. These are different molecular forms of the same enzyme, which originate from different sites in the body but react in a similar manner when tested with a particular laboratory test. It is worthwhile considering other explanations for a single unexpected result.

ALP isoenzymes may originate from liver, bone, placenta, intestinal or tumour cells. Therefore elevations of ALP are often seen in children in times of bone growth (bone isoenzyme) or in pregnant women (placental isoenzyme).

ALT is the most specific liver enzyme, but occasionally originates from sources other than the liver.

AST from cardiac muscle is commonly elevated following myocardial infarction (cardiac isoenzyme). Haemolysis may also elevate AST (red blood cell isoenzyme).

GGT isoenzymes have been identified in kidney, heart and pancreas but these are not commonly encountered.
Appendix 6: Investigation for Evidence of Acute Viral Hepatitis

ALT elevated >5 x ULN

Hepatitis A

Anti-HAV IgM

Negative

Hepatitis B

No evidence of acute hepatitis A infection

Positive

Compatible with acute hepatitis A infection

Hepatitis C

See footnote a

Hepatitis B

Anti-HBc IgM

Negative

Positive

Compatible with acute hepatitis B infection

Compatible with acute or chronic hepatitis B infection

See footnote b

HBsAg

Negative

Positive

No evidence of acute hepatitis B infection

Compatible with acute or chronic hepatitis B infection

a. Hepatitis C cannot reliably be diagnosed in the acute phase because of the prolonged period of sero-conversion. Testing may be done for people with known risk factors. However, if HCV is negative and other causes of viral hepatitis have been ruled out, a second sample should be specifically tested for HCV one to three months later.

b. If HBsAg is positive for a period of greater than six months, it is consistent with chronic hepatitis B infection. Positive HBsAg represents acute HBV only if anti-HBcore IgM is also positive.
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