Interpretation of liver enzyme tests

– A rapid guide

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This guide (updated from an earlier version published in the NZFP in 2002[1]) is intended to provide easily accessible information on appropriate investigation and likely diagnoses. First view Figure 1, then look at notes as indicated.

- For single enzyme elevations see Note 1.
- If multiple enzyme abnormalities refer to Question 1.

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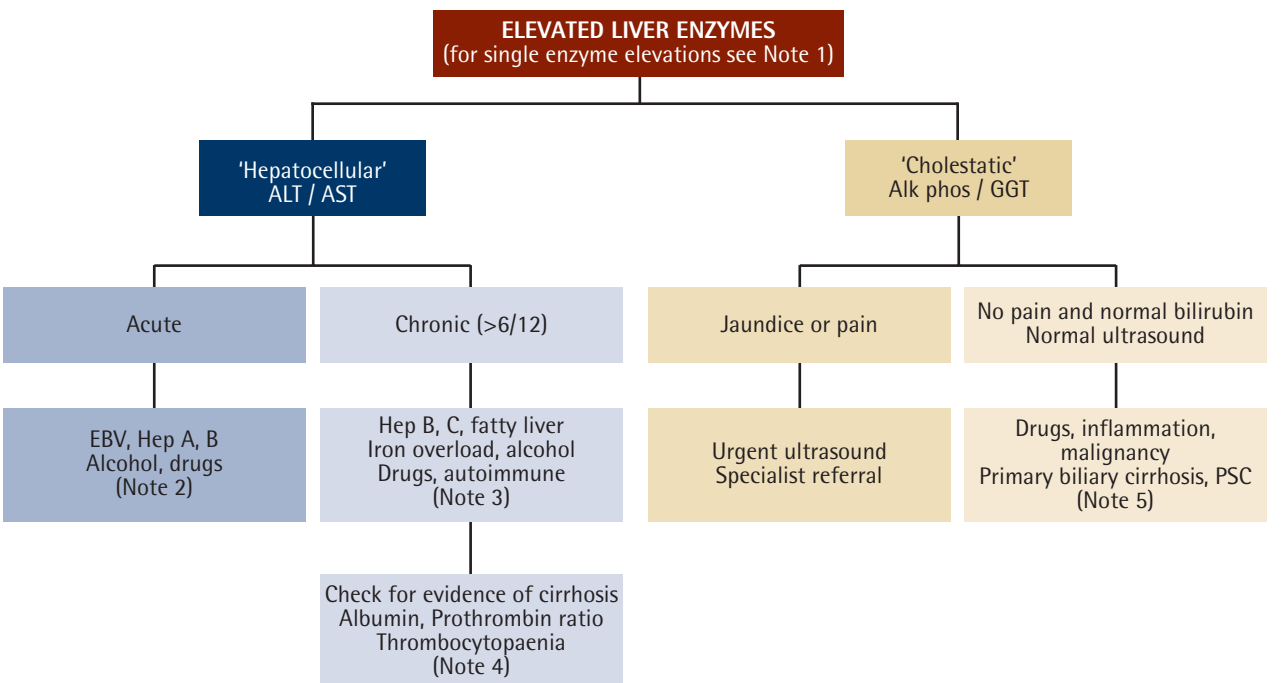
Figure 1. Elevated liver enzymes



Note 1: Single enzyme elevation

GGT

- Consider alcohol – check for elevated MCV as further evidence. Heavy weekend drinking leads to elevation of 1–3x; peak at two to three days. Higher levels may take several weeks to resolve after abstinence from alcohol.
- Check drugs – in particular phenytoin, carbamazepine, OC, rifampicin.
- Consider fatty liver – risk factors are obesity, diabetes and elevated lipids. Ultrasound may confirm fatty liver by showing increased echogenicity (see also Note 3).

Alkaline phosphatase

- Elevation of alkaline phosphatase without elevation of GGT is very suggestive of bone disease – e.g. recent fracture, Pagets disease.
- Normal elevation – adolescents, 3rd trimester of pregnancy.

ALT

- Can be mildly elevated with obesity and does not represent liver disease. Seems to relate directly to BMI (same is true for AST).
- In mild chronic hepatitis ALT may be elevated and the AST normal because of the higher sensitivity of ALT to hepatic inflammation.

AST

- Consider recent muscle injury or bruising. May have acute rise of 2–3x after strenuous exercise. Check for haemolysis – blood screen, haptoglobins, Coombs test.
- If persistent and no suggestion of liver disease, consider chronic muscle diseases, e.g. polymyositis – measure creatinine kinase.

Bilirubin

- Gilberts syndrome – persistent but mild elevation of bilirubin but normal liver enzymes – commonly elevated further with illness and fasting. Usually the levels are only up to 50umol/L (rarely up to 80umol/L).
- The measurement of direct/indirect fraction (conjugated/unconjugated) is rarely useful in adult practice.

Question 1. Is the pattern 'hepatocellular' (mainly AST / ALT) OR 'cholestatic' (mainly alkaline phosphatase and GGT)

- If mainly hepatocellular then refer to Question 2.
- If it is a mixture of both 'patterns', the predominant problem is usually obvious.
- Mild cholestasis is common with chronic hepatitis but the pattern is predominantly 'hepatocellular'.
- In acute biliary obstruction a rise in AST/ALT may occur during the first two to three days (in addition to cholestatic picture) but returns to near normal if obstruction persists. Note that acute obstruction is usually associated with 'biliary-type' pain.

Question 2. Is there evidence of persistent elevation of AST/ALT over more than one to two months?

- More than six months of abnormal ALT/AST defines chronic hepatitis.
- In practical terms chronic hepatitis should be considered from the onset and becomes more likely if persistent abnormalities after one to two months.
- Many patients with newly discovered elevation of ALT/AST will prove to have chronic liver disease.
- If the initial level of ALT/AST is greater than 500IU then most likely to be acute hepatitis/liver injury.

Note 2: Tests for acute hepatitis

- Acute hepatitis is usually associated with symptoms of an 'acute illness'. Commonest cause of acute elevation of ALT/AST in the community is infectious mononucleosis.
- Main tests for acute viral hepatitis are Hepatitis A IgM and Hepatitis BsAg and tests for EBV (50%) and CMV (<2%). (Hepatitis C does cause acute hepatitis but is almost always asymptomatic. Hepatitis D only occurs in the presence of Hepatitis B infection).
- Consider drugs – may also have rash, fever and eosinophilia (phenytoin, isoniazid, diclofenac, pirioxicam, allopurinol, azathioprine).
- Consider alcohol-induced liver disease. May cause 'hepatitis' – AST/ALT levels are relatively low for 'acute' hepatitis (100–300U/L). Also look for elevated GGT (100–300) but normal alkaline phosphatase, macrocytosis, AST greater than ALT (ratio >2.0 very suggestive), elevated WBC and fever if more severe hepatitis. Diagnosis of alcohol-related liver disease rests primarily on history and a high index of suspicion rather than pattern of liver test.
- Rarely auto-immune hepatitis can present as an acute illness. Even rarer – Wilson's disease can be considered if <40 years – check serum copper and ceruloplasmin.

Note 3: Tests for chronic hepatitis

- Order relevant tests if ALT levels have been elevated for more than one to two months.
- In chronic hepatitis ALT usually only 1.5–3x upper limit of normal range.
- Request Hepatitis BsAg, Hepatitis C Ab (following by Hep C PCR if antibody positive), auto-antibodies (antinuclear antibody and smooth muscle antibody), serum ferritin and iron studies (serum Fe and TIBC).
- Commonest cause of raised ALT/AST (usually associated with mild elevation of GGT) is fatty liver.
- If the fat deposition in the liver is associated with hepatic inflammation then this is called steatohepatitis. This occurs with excess alcohol intake but often is present in absence of alcohol (can be called non-alcoholic steatohepatits – NASH).
- The risk factors for this condition are diabetes, elevated triglycerides (more important than cho-

lesterol), and obesity (waist circumference most predictive). Therefore should measure fasting glucose (sometimes GTT), HbA1c and fasting lipids.
- The fatty infiltration in the liver is detected by ultrasound of the liver in 60–70% of cases.
- Raised ferritin may be due to hemochromatosis (see article on raised ferritin[2]) but also occurs with liver inflammation (common with fatty liver and excess alcohol consumption). Raised ferritin and normal iron saturation more likely to be fatty liver – request liver ultrasound. If high iron saturation (>55%) order gene test for haemochromatosis (Cys282).
- Consider drugs – can be any drug – isoniazid, nitrofurantion, ketoconazole, NSAIDs. Consider also illicit drugs, anabolic steroids and herbal treatments.
- Auto-immune hepatitis is associated with raised serum globulins (often >2x normal). Check auto-antibodies (ANA and smooth muscle Ab).
- Check α-fetoprotein (elevated in primary hepatocellular cancer) – particularly if suspicion of cirrhosis.

Note 4: Check for evidence of impairment of hepatic function or portal hypertension (i.e. cirrhosis)

- Important for all patients with chronic hepatitis.
- Check serum albumin and prothrombin ratio (even borderline abnormal levels are likely to be significant in the setting of 'chronic hepatitis').
- Thrombocytopenaenia suggests portal hypertension. Spleen may be enlarged but only detected by ultrasound.

Note 5: 'Cholestasis' pattern of elevated liver enzymes with no pain or jaundice and normal ultrasound

- Ultrasound is the key test.
- If dilated bile ducts and no biliary type pain then likely to be malignant bile duct obstruction.
- Biliary-type pain and cholestatic liver tests requires urgent specialist review even if ultrasound normal. Most likely stones in common bile duct.
- ERCP or MRC may be required if diagnostic uncertainty.
- Consider drugs (see also below)
  - Phenothiazines – can continue if less than 2x normal. Remember stemetil may cause cholestasis.
  - Augmentin and flucloxacillin may cause a progressive cholestasis with slow resolution over several months (after drug has been discontinued).
  - Erythromycin – may present as acute RUQ pain and may mimic cholecystitis.
- Non-specific cholestasis in sepsis and in chronic inflammatory conditions (e.g. inflammatory bowel disease).
- Congestive heart failure – mild elevation (mixed picture) common with predominant right-sided heart failure related to hepatic congestion.
- Malignancy – may be non-specific feature of disseminated cancer. Metastatic disease of the liver usually has a mixed pattern, mild elevations only; usually detected by ultrasound. Further examination by CT scan may be required particularly for solitary lesions.
- If chronic (> than six months) and progressive cholestasis consider chronic liver disorders such as primary biliary cirrhosis and sclerosing cholangitis. Specialist referral required for liver biopsy +/- ERCP. Order anti-mitochondrial antibody.
- Asymptomatic benign liver lesions (usually haemangiomas) are common and are not associated with liver test abnormalities.

Drugs and monitoring of liver enzymes

There are only a few examples of definite benefit from regular monitoring of liver enzymes:
- Isoniazid – usually only transient elevation but must stop medication if progressive rise in liver enzymes (fulminant hepatitis may occur – higher risk if >50 years).
- Methotrexate – early elevation of AST/ALT in first few months may not be important; progressive changes may suggest hepatic fibrosis and need for liver biopsy.
- Azathioprine – hepatitis may occur in first few months and require cessation of drug. 6-mercaptopurine may be a useful alternative.
- Cyproheptadine (used primarily for carcinoma of the prostate). Monthly liver enzymes in first few months – stop if progressive elevation.
- 'Statins' – mild elevations of ALT common, particularly in first few months – usually related to underlying fatty liver (there may be shifts in intra-hepatic lipids during initial treatment). Mild changes in LFTs do not predict serious liver disease and are not related to the risk of rhabdomyolysis.

Role of liver biopsy in investigation of abnormal liver tests

The majority of diagnoses are made by history (careful review of drug history), physical examination, and blood tests. For the few patients undiagnosed after usual blood tests (as above) liver biopsy may be indicated. In this situation the most common finding on liver biopsy is steatohepatitis (this may occur in absence of usual risk factors).

Competing interests

None declared.

References

1. Fraser A. Interpretation of liver enzyme tests – a rapid guide. NZFP 2002; 29(2):117-120.
2. Berkhan L. Interpretation of an elevated serum ferritin. NZFP 2002; 29(1):45–48.