Interpretation of liver enzyme tests

– a rapid guide

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Note 1: Single enyzme elevation

GGT

- Consider alcohol – check for elevated MCV as further evidence.
- 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 5).

Alkaline phosphatase

- Elevation of alkaline phosphatase without elevation of GGT is very suggestive of bone disease – e.g. recent fracture, Pagets disease.

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, cardiac enzyme.
- 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 – commonly elevated further with illness and fasting. Usually the levels are only up to 50umol/L (rarely up to 80umol/L). This is unconjugated bilirubin but measurement of direct/indirect fraction is rarely useful in adult practice.

Q1. Is the pattern 'hepatocellular' (mainly AST/ALT) OR 'cholestatic' (mainly Alkaline phosphatase and GGT)?

If it is a mixture of both 'patterns' then may be hepatocellular inflammation or biliary obstruction. Mild cholestasis is common with chronic hepatitis but the pattern is predominantly 'hepatocellular'. In *acute* biliary obstruction a rise in AST/ALT occurs early (first five days) but returns to near normal if obstruction persists (acute obstruction is usually associated with 'biliary-type' pain)

Q2. Is there evidence of persistent elevation of AST/ALT over more than six months?

This is an arbitary cut-off duration but does define acute vs chronic hepatitis. Many patients with newly discovered elevation of ALT/AST will prove to have chronic liver disease. However if the level of ALT/AST is greater than 10x normal then very likely to be acute liver injury.

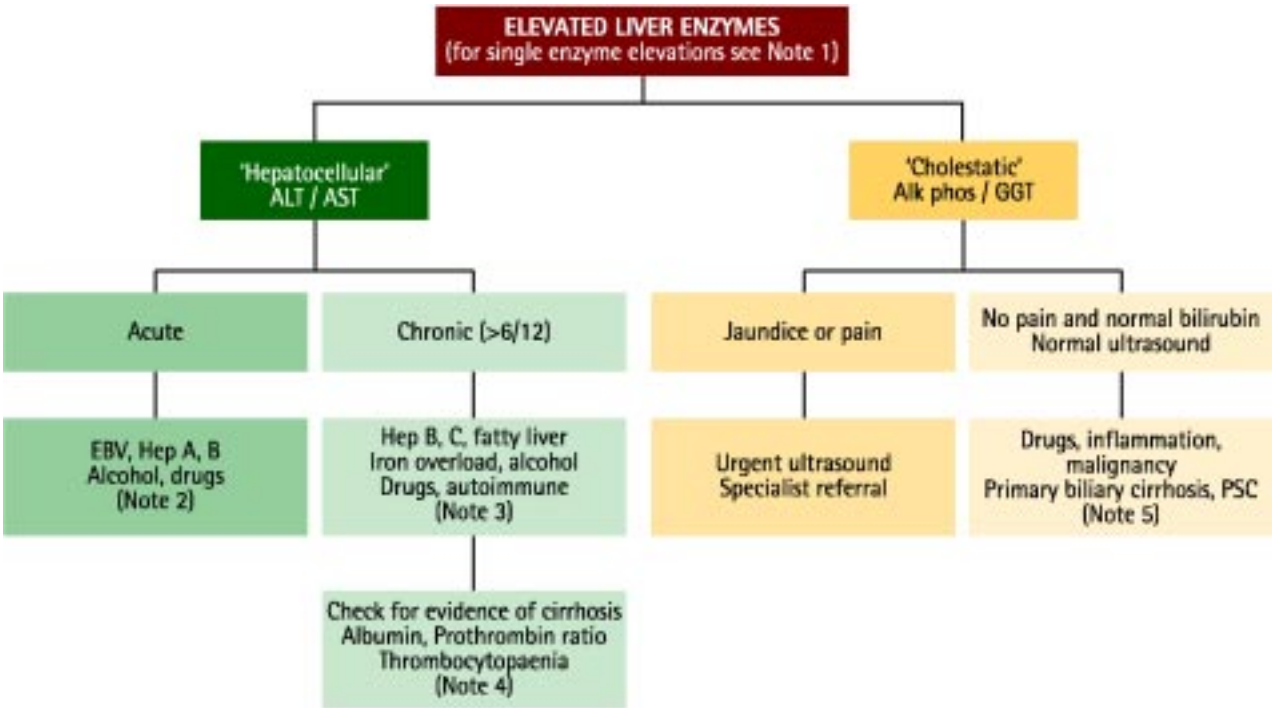
Note 2: Tests for acute hepatitis

- Usually associated with '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. (Hepatitis C does cause acute hepatitis but is almost always asymptomatic; Hepatitis D only occurs in the presence of Hepatits B infection).
- Consider drugs – may also have rash, fever and eosinophilia (Phenytoin, isoniazid, diclofenac, piriroxicam, allopurinol).
- Consider alcoholic hepatitis – 80–90% will have an AST/ALT ratio >2.0. The AST/ALT levels are relatively low for 'acute' hepatitis (100–300U/L). Also look for disproportionately elevated GGT, macrocytosis and elevated WBC. Diagnosis of hazardous alcohol intake still rests primarily on history and a high index of suspicion.
- Rarely auto-immune hepatits can present as an acute illness. Even rarer, Wilsons disease can be considered if <40 years; check serum copper and caeruloplasmin.

Note 3: Tests for chronic hepatitis

- Confirm that ALT levels have been elevated for more than six

Elevated Liver Enzymes



months (usually 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 cholestasis – i.e. mixed pattern) is *fatty liver*. If the fat deposition in the liver is associated with hepatic inflammation then this is called steato-hepatitis. This occurs with excess alcohol intake but often is present in absence of alcohol (can be called non-alcholic steatohepatits – NASH). The risk factors for this condition are diabetes, elevated trigylcerides, and obesity. Therefore should measure fasting glucose and HbA_{1c} 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 *Interpretation of an elevated serum ferritin* NZFP 2002; 29:45–48) but also occurs with liver inflammation (common with fatty liver and excess alcohol consumption).
- *Consider drugs* – can be any drug – 'statins', isoniazid, nitrofurantion, ketoconazole, NSAIDs. Consider 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 a-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)

- 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

- A normal ultrasound does not completely exclude biliary tract disease and ERCP may be required if the clinical scenario is suggestive.
- *Consider drugs (see also below)*
  - Phenothiazines; can continue if less than 2x normal. Remember stemetil.
  - Augmentin and flucloxacillin.
  - May be a progressive condition with slow resolution over several months.
  - Erythromycin; may present as acute RUQ pain and may mimic cholecystitis.
- Non-specific elevation in sepsis and in chronic inflammatory conditions (e.g. inflammatory bowel disease).

- *Congestive heart failure* – mild elevation 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 (>6 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.

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).
- Azathioprine – hepatitis may occur in first few months and require cessation of drug.
- 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 – may relate to shifts in intra-hepatic lipids and does not predict rhabdomyolsis.

Role of liver biopsy

The majority of diagnoses are made by history, physical examination, and blood tests. For the few patients undiagnosed after usual blood tests (as above) liver biopsy may be indicated. The most common diagnosis is fatty liver with or without significant inflammation (steatohepatitis).