Management of Asymptomatic Abnormal LFTs
in Lothian Primary Care

This guidance has been developed specifically for use in primary care within NHS Lothian. General practitioners may choose to use it when mildly abnormal LFTs results have been found in asymptomatic patients. It is hoped this will increase the efficiency of investigations for liver disease whilst avoiding unnecessary tests and referrals.

There are no meta-analyses or randomised controlled trials concerning the management of abnormal liver function tests in asymptomatic people. This guidance is therefore based on a combination of prospective, retrospective or cross-sectional clinical studies and expert opinion. It has been developed partly based on Forth Valley guidelines but through extensive collaboration with hepatologists, general practitioners and laboratory staff from NHS Lothian. It is not intended to serve as a rigid protocol or to replace clinical judgement.

INTRODUCTION

Abnormal liver function tests (LFTs) are very common in primary care. They are often found co-incidentally in patients without hepatobiliary symptoms. Such patients should be investigated if the abnormalities are significant and persistent because most liver disease is silent until advanced. Investigations should determine the aetiology and therefore the treatment to arrest or reverse the disease. Investigations should also stage the disease to detect those with advanced fibrosis or cirrhosis - still often clinically silent - who require further management in secondary care.

Most persistently abnormal LFTs will be due to alcohol, non-alcoholic fatty liver disease (NAFLD) or viral hepatitis. Other causes, although rare, are equally important to diagnose because nearly all are treatable.

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Management of Asymptomatic Abnormal LFTs in Primary Care in Lothian
Guideline summary
December 2013

Asymptomatic abnormal ALT, GGT or ALP result
Suggested thresholds for investigation when elevated on at least 2 occasions > 4 weeks apart
- ALT > 70
- ALT 50-70 with an abnormal GGT/ALP (if isolated ALT 50-70 check Hep B & C serology only)
- GGT > 100
- ALP > 200 with an abnormal GGT (if ALP raised in isolation investigate for bone disease)
(NB: If ALT/ALP/GGT persistently abnormal but below thresholds for investigation consider repeat LFTs in 1 year. If still abnormal use clinical judgment and consider patient assessment/ liver screen even if remains below thresholds)

Patient assessment
- History
- Examination
- Liver screen including liver ultrasound
- Medication review
- If alcohol suspected, advise abstinence

Refer to GI if any of the referral criteria are met

If the referral criteria have not been met then:
- The abnormal LFTs are likely to be due to either NAFLD or alcohol and there is nothing to indicate advanced fibrosis/cirrhosis
- These patients can continue to be safely managed in primary care with appropriate advice e.g. diet, exercise, alcohol abstinence
- A small number will go on to develop cirrhosis if they do not make the appropriate lifestyle changes.
- At present we are unable to identify which people are most likely to progress and ongoing screening for the development of fibrosis is not currently available in primary care.
- Consider a yearly check of LFTs and AST:ALT ratio with reinforcement of lifestyle advice.

Patient assessment

History
- Alcohol intake
- Drugs (prescribed, OTC, herbal remedies)
- Hepatitis risk factors (HAV, B, C, sexual history, travel, ethnicity)
- Metabolic syndrome clues (T2DM, obesity, hypertension, hyperlipidaemia)
- Autoimmune disease clues (T1DM, thyroid disease, RA)
- Family history

Examination
- BMI
- Spider naevi, Palmar erythema
- Palpable liver or spleen

Liver Screen
- Abdominal Ultrasound
- FBC
- LFTs
- AST:ALT ratio
- Albumin,
- Caeruloplasmin (if <55 years)
- Glucose
- Cholesterol
- Ferritin (check Transferrin sat’s if ferritin raised)
- INR
- Hepatitis serology – HEsAg and anti-HCV Ab
- Immunology – Anti-smooth muscle Ab, anti-nuclear Ab, anti-mitochondrial Ab

Medication Review
- Review medications and consider discontinuing any causative drugs.
- If in doubt, discuss with GI/liver

* GI Referral Criteria
- Refer to GI if any of the following apply:
  - Diagnostic tests suggest any cause other than alcohol or NAFLD
  - Evidence of impaired liver function:
    - Total bilirubin (not due to Gilbert’s syndrome)
    - INR
    - Total albumin
  - Evidence of advanced fibrosis/cirrhosis:
    - AST : ALT ratio > 1.0
    - Platelets < 150
    - Splenomegaly
    - ALT persistently > 200
    - Diagnosis or management still uncertain

Review date: December 2016
Isolated rise in ALT in Asymptomatic Adults

- ALT is a sensitive marker of hepatocyte injury.
- However considerable liver injury may be present with normal transaminase levels.
- Serum ALT activity varies with age, sex, race, body mass index, acute illness and exercise.
- There is poor correlation between the level of rise of ALT and biopsy findings. A persistently abnormal ALT should have some investigation performed.
- If ALT remains abnormal after a period of observation and first line investigation reveals no clear cause then a referral (biopsy) threshold of >200 can be used.

Isolated rise in GGT in Asymptomatic Adults

- GGT is a sensitive marker of liver disease but it is not specific. It is mainly of use for establishing the likely origin of an elevated ALP.
- When raised in isolation it can be suggestive of alcohol excess (especially if raised MCV) or NAFLD.
- Please note that there is no current evidence base with which to guide the investigation and management of an isolated raised GGT. This guideline has therefore been produced by local experts purely to offer guidance to local GPs.

GGT & Alcohol

- GGT is neither a sensitive nor a specific marker of alcohol misuse, although changes in GGT associated with a clear history of alcohol misuse can be used to monitor abstinence, assuming that no liver disease is present.
- If alcohol is suspected to be the reason for an elevated GGT then patients should be asked to abstain from alcohol for at least 4 weeks before a repeat GGT is measured. Please note that in those with hepatic damage (particularly cirrhosis) their GGT may take longer to fall after abstinence or may never return to normal.
Isolated rise in ALP in Asymptomatic Adults

- Predominant rise in ALP is suggestive of biliary or infiltrative disease
- ALP has two main sources in the non-pregnant adult: liver and bone. Higher ALP activities are also seen as a normal variant and are associated with a range of medical conditions (congestive heart failure, hyperthyroidism, pregnancy and intrahepatic cholestasis during sepsis) and certain drugs (ibuprofen, paracetamol, cefotaxime).
- Liver and bone profiles should be checked if not already carried out, to exclude other raised indices.
- Isolated raised values up to approximately 145 IU/l are more likely to reflect a statistical rather than clinical finding.
- Although the reference range for women rises with age, the prevalence of primary biliary cirrhosis also rises. Measurement of anti-mitochondrial antibodies in cases of persistently increased ALP >200 of liver origin would therefore seem appropriate.
- Raised ALP without a concomitant rise in GGT in a non-pregnant adult is likely to be of bone origin. If doubt still exists ALP isoenzyme analysis is useful e.g. if co-incidentally on enzyme inducing drugs which elevate GGT.
Isolated rise in Bilirubin in Asymptomatic Adults

 Gilbert’s syndrome
Gilbert’s syndrome is a benign congenital defect of glucuronide conjugation present in up to 5% of the population. It results in an unconjugated hyperbilirubinaemia which is indicated by the presence of a high serum bilirubin in the absence of urinary bilirubin (as only conjugated bilirubin passes into the urine). In Gilbert’s syndrome the bilirubin level typically increases after fasting and during intercurrent illness, usually, to a level not exceeding 70 umol/l.

Please note that bilirubin should be >30umol/L for measurement of conjugated bilirubin to be valid. Therefore please do not request conjugated bilirubin testing in patients whose total bilirubin is below this level.

If diagnostic uncertainty remains then genetic analysis for Gilberts is available. However it is expensive and usually unnecessary. If it is required, send a single EDTA tube (red/FBC tube) with a haematology/biochemistry form requesting “Gilbert’s analysis”.

Haemolysis
Haemolysis is conventionally diagnosed by the laboratory appearances on a blood film, combined with reduced haptoglobin, reticulocytosis and raised lactate dehydrogenase. There is no clear evidence as to whether one or all of these tests are required. If evidence of haemolysis is found,
further investigation will be determined by the clinical context, usually in conjunction with secondary care advice.
Further Information

Statins and abnormal LFTS

Patients with normal LFTs prior to starting statins
- LFT derangement typically occurs within the first three months of therapy and is usually dose dependent.
- LFTs should be checked 6 to 8 weeks after commencing treatment or any dosage increase. A yearly check of LFTs is not required for patients who are stable on long-term treatment.
- If ALT < 150: continue statin but recheck LFTs within 4 weeks to exclude further increase in ALT. No extra monitoring required if ALT remains stable.
- If ALT > 150: stop statin and recheck LFTs within 4 weeks to ensure values settle. If they return to normal consider re-introducing a different statin at a later date with repeat LFTs at 2, 6 and 12 weeks. If the LFTs do not improve after stopping statin treatment perform initial liver screen and continue as per abnormal ALT pathway.

Patients with abnormal LFTs prior to starting statins
- Patients with abnormal LFTs should not be routinely excluded from statin treatment. There is evidence that statins are safe and have beneficial effects for patients with NAFLD.
- If ALT <100 - start statin treatment with repeat LFTs as usual in 6 weeks to check ALT remains stable. If ALT has risen at the 6 weeks a rise of up to 150 is allowable but further repeat LFTs should be arranged every 4 weeks until the ALT level is stable. The patient should also be investigated and managed as per the rise in ALT pathway (if this has not already been done) and, if felt appropriate, this could be done alongside starting statin treatment.
- If ALT 100 – 150 - ideally the abnormal LFTs should be investigated prior to starting statin treatment. Once investigated statins can be started with repeat LFTs at 2, 6 and 12 weeks.
- If ALT >150 – patients with an ALT persistently >150 should undergo GI review and statins should only be initiated following specialist advice.

Patients on long term statin treatment with abnormal LFTs
- If you are unsure whether the abnormal LFTs are related to statin treatment then the dose of the statin should be reduced and the LFTs repeated in 6 weeks. If there is no improvement following dose modification perform an initial liver screen, and continue to manage the patient as per the abnormal ALT pathway.
Further Information

Drugs associated with Abnormal LFTs

This list is not exhaustive and there may be a mixed pattern of abnormal LFTs. Please see the BNF for further information.

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<tr>
<th>Cholestatic pattern (ALP/GGT)</th>
<th>Cytotoxic pattern (ALT)</th>
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<td>Co-amoxiclav</td>
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<td>Anabolic steroids</td>
<td>Amiodarone</td>
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<td>Chlorambucil</td>
<td>Aspirin</td>
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<td>Chlorpromazine</td>
<td>Azathioprine/6-Mercaptopurine</td>
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<td>Chlorpropamide</td>
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<td>Estrogen (oral contraceptives)</td>
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<td>Terbinafine</td>
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<tr>
<td>6-Mercaptopurine</td>
<td>Methyl dopa</td>
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<td></td>
<td>Nicotinic acid (especially sustained-release)</td>
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<td>Nitrofurantoin</td>
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<td>Propylthiouracil</td>
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<td>Rifampin</td>
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<td>Risperidone</td>
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<td>“Statins”</td>
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<td>Trazodone</td>
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<td>Valproate</td>
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(Taken from: http://www.medicinenet.com/liver_blood_tests/page4.htm#6whatmedications)
## Common clinical clues and diagnoses for Abnormal LFT’s

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<th>Clinical Clue</th>
<th>Possible Diagnosis</th>
<th>Initial test</th>
<th>Additional tests</th>
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<tr>
<td>AST&gt;ALT, MCV</td>
<td>Alcoholic liver disease</td>
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<td>Drug / herbal remedy history</td>
<td>Drug induced liver disease</td>
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<td>Chronic hepatitis B</td>
<td>HBsAg</td>
<td>HBeAg/eAb</td>
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<td>transfusion. Tattoos</td>
<td>Chronic hepatitis C</td>
<td>HCV antibody</td>
<td>HBV DNA</td>
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<td>HCV RNA</td>
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<tr>
<td>Raised ALP + inflammatory bowel disease</td>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Raised ALP</td>
<td>Primary biliary cirrhosis</td>
<td>AMA and IgM</td>
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<tr>
<td>Other autoimmune disease</td>
<td>Autoimmune hepatitis</td>
<td>ASMA, ANA</td>
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<tr>
<td></td>
<td>Primary biliary cirrhosis</td>
<td>AMA and IgM</td>
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<tr>
<td>Diabetes/joint pain</td>
<td>Haemochromatosis</td>
<td>↑ ferritin</td>
<td>Haemochromatosis genotype test</td>
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<td>Pigmentation</td>
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<td>↑ transferrin sat %</td>
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<tr>
<td>Neurological signs</td>
<td>Wilsons disease</td>
<td>↓ Caeruloplasmin</td>
<td>↑ 24hr urinary Copper</td>
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<tr>
<td>Lung disease</td>
<td>Alpha 1 antitrypsin</td>
<td>↓ α₁ antitrypsin level</td>
<td>α₁ antitrypsin phenotype</td>
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<tr>
<td>Metabolic syndrome (BMI, diabetes, hypertension)</td>
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