Southern Derbyshire

Shared Care Pathology Guidelines

Abnormal Liver Function Tests (LFTs) in Adults

Purpose of Guideline

The management of patients with abnormal liver function test results

Scope

This guideline will provide best practice information for abnormalities in each of the liver function tests

Definition

Liver function tests can be requested as part of the Derby Initial Profile (IP) or on their own. The actual LFT’s with adult reference ranges are as follows:

- Bilirubin \( (< 21 \text{ µmol/L}) \)
- ALT \( (< 40 \text{ IU/L}) \)
- ALP \( (♀ \text{ below } 60y \text{ } 35 – 104 \text{ IU/L}; \ ♂ \text{ & } ♀ \text{ above } 60y \text{ } 40 – 129 \text{ IU/L}) \)
- Total Protein \( (60 – 80 \text{ g/L}) \)
- Albumin \( (35 – 50 \text{ g/L}) \)

Please note that Gamma GT does not form part of the basic LFT, but will be added to results if ALP is raised to distinguish liver or bone source.

- GGT \( (♀ \text{ } 7 – 33 \text{ IU/L}; \ ♂ \text{ } 11 – 51 \text{ IU/L}) \)

Sample type: all the tests listed above can be carried out on a serum sample (yellow top)

When to suspect liver damage

- Jaundice
- In many instances patients with acute and chronic liver disease may be asymptomatic.
- The first sign of liver damage may be a raised liver enzyme in an asymptomatic patient.
- The symptoms may be vague, such as weakness and lethargy
- Thrombocytopenia is frequently seen as a consequence of liver cirrhosis and its unexplained presence in a patient with abnormal LFTs should trigger referral to Hepatology

Resources

More information on liver diseases can be found at the British Liver Trust website:
**Importance of abnormal liver function tests**

There may not be any symptoms of liver damage present until the disease has reached an advanced stage, although in many instances the investigation of liver disease is prompted by the finding of an elevated liver enzyme result in an asymptomatic patient. It is therefore important that these patients are investigated appropriately.

Dependent upon clinical details (when given) and previous LFT results the laboratory usually telephones the following abnormal results Monday to Friday when the GP practices are open:

- Albumin < 15g/L
- Bilirubin > 200 µmol/L
- ALT > 200 IU/L

In patients where the LFTs are persistently grossly abnormal results are not generally telephoned through to the practice.

Dependent upon clinical details (when given) and previous LFT results the laboratory may telephone **ALT results > 600 IU/L** to Derbyshire Health United when the GP practice is closed.

- Appropriate action to take will depend on the clinical context, for example if the patient is on potentially hepatotoxic medications.
- An urgent referral may be indicated if the patient is unwell for example: Severe jaundice, severe ascites, encephalopathy or septic.
Individual LFTs

Bilirubin
Hyperbilirubinaemia can be broadly defined due to the whether the increase is conjugated or unconjugated. Many patients have a mixed picture. Enzyme analysis will point to the correct diagnosis and appropriate referral. Slight increases in bilirubin (22-30 µmol/L) are not unusual and usually not clinically significant.

The actual determination of conjugated (Direct) and unconjugated (Indirect) bilirubin is seldom required in adults, except when the rise in bilirubin is isolated, i.e. the liver enzymes are within the reference range.

Causes of isolated unconjugated hyperbilirubinaemia:
- Gilbert’s syndrome (bilirubin level usually < 70 µmol/L)
- Stress/fasting
- Drugs e.g. rifampicin, sulfonamides
- Haemolytic disease

Causes of isolated conjugated hyperbilirubinaemia:
- Drugs e.g. phenothiazines, sulfonamides and carbimazole
- Dubin-Johnson syndrome
- Rotor’s syndrome

Role of the Laboratory
As the most common cause of an isolated unconjugated hyperbilirubinaemia is Gilbert’s syndrome, we will add on a Direct and Indirect (D&I) bilirubin and haptoglobin to ascertain if the patient may have Gilbert’s syndrome. In most cases these results, along with the clinical picture will provide sufficient information for a confident diagnosis, and the directive report will include a Gilbert’s Syndrome link.

Gilbert’s Link:
www.britishlivertrust.org.uk/home/the-liver/liver-diseases/gilberts-syndrome.aspx

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Expiry Date: 31st October 2016
Authors: Dr L Rashid, Dr N Lawson, Dr A Austin, Dr A Lawson, Dr C Salmon
Authorised by Julia Forsyth
Alanine Transferase (ALT)

ALT is a cytosolic enzyme, which is expressed predominantly in liver cells and is used as a marker to assess liver cell damage.

ALT < 120 IU/L are generally considered mild
ALT > 120 IU/L are generally considered severe

Please remember that some patients can have severe liver disease with only slightly abnormal liver enzymes

Common causes:
- Alcohol
- Viral hepatitis
- Steatosis
- Medications/toxins e.g. NSAIDs, antibiotics, statins, antiepileptics, antituberculosis drugs

Less Common causes:
- Autoimmune hepatitis
- Haemochromatosis
- Alpha1-antitrypsin deficiency
- Wilson’s disease

Non-hepatic causes of raised ALT (usually small rises, <120 U/L):
- Coeliac disease
- Strenuous exercise
- Muscle disease
- Endocrine disease e.g. Hypo- and hyper-thyroidism

Aspartate Aminotransferase (AST)

AST is expressed in the liver, as well as in the heart, skeletal muscle, kidneys, brain and red blood cells and therefore is not as liver specific as ALT. AST and ALT differ in their cellular location within the liver, as ALT is predominantly cytoplasmic and AST is present in both cytoplasm and mitochondria.

AST is not part of the initial LFT, but the ratio of AST to ALT may provide useful information about the possible cause of liver disease and the likelihood that the patient has advanced fibrosis.

AST:ALT ratio ≥ 2.1 may be suggestive, but not diagnostic of alcohol related liver disease, while AST:ALT ratio < 2.1 may suggest hepatic steatosis or chronic viral hepatitis.

In addition, in patients not consuming excess alcohol, an AST:ALT ratio > 0.8 suggests advanced fibrosis and mandates referral to hepatology.
There are many causes of transient elevation of liver enzymes including intercurrent illness.

**A full liver screen IS NOT GENERALLY REQUIRED WITHIN THE FIRST 3 MONTHS if**
- IN SYMPTOMATIC PATIENT there is an alternative explanation—e.g. intercurrent illness or medication
- IN ASYMPTOMATIC PATIENTS the ALT < 120

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### Raised ALT (> 40 IU/L)

- **Asymptomatic isolated ALT > 120 IU/L?**
  - NO
    - Offer lifestyle advice (alcohol and weight) and recheck in 3 months. If Still Raised then arrange testing for:
  - Liver Ultrasound
  - AST
  - CK
  - TFT
  - Fasting Lipids
  - Coeliac Serology
  - Hepatitis serology (Hep B surface antigen, Hep C antibody)
  - Alpha-1-antitrypsin
  - Caeruloplasmin
  - Autoantibodies
  - Immunoglobulin
  - Ferritin

- YES
  - Patient Symptomatic?
    - Abnormal Platelets, Bilirubin, ALP, Albumin or PT

### Probable fatty liver disease
For asymptomatic patients age < 50y, ALT <120 and AST/ALT ratio < 0.8 the risk of significant fibrosis is minimal. Offer further diet, exercise and safe drinking advice and repeat LFT including AST in 3-5yrs. It is safe to prescribe a Statin where indicated for CV risk reduction. ALT rises < 2 fold from baseline do NOT require referral.


**Alkaline Phosphatase (ALP)**

The two main sources of ALP are liver and bone, although there are also intestinal and placental isoforms.

Elevations may be physiological or pathological.

Common causes for raised ALP:

**Physiological**

- Third trimester of pregnancy
- Adolescents, due to bone growth
- Benign, familial

**Pathological**

- Bile duct obstruction
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Drug induced cholestasis, e.g. anabolic steroids
- Metastatic liver disease
- Bone disease e.g Pagets
- Heart failure

**Gammaglutamyl transferase (GGT)**

GGT is a sensitive marker for hepatobiliary disease, but its use is limited by poor specificity.

Causes of raised GGT:

- Hepatobiliary disease (often with other liver enzyme abnormalities)
- Pancreatic disease
- Alcoholism
- Chronic obstructive pulmonary disease
- Renal failure
- Diabetes
- Myocardial infarction
- Drugs, e.g. carbamazepine, phenytoin and barbiturates and oral contraceptive pill

The use of GGT is in supporting a hepatobiliary source for other raised liver enzymes, e.g. ALP.
GGT Increased?

Yes

Persistent Significant Increase > 3 Months?

NO

Recheck in 12 months

NO

Liver Ultrasound
AST
CK
TFT
Fasting Lipids
Coeliac Serology
Hepatitis serology
   (Hep B surface antigen, Hep C antibody)
Alpha-1-antitrypsin
Caeruloplasmin (if < 50y)
Liver Autoantibodies
Immunoglobulins
Ferritin

&

HEPATOLOGY REFERRAL

ALP > 2 x ULN?
&/OR
Patient Symptomatic?
&/OR
ALT, Bilirubin, Albumin Abnormal

Yes

NO

Probably Not Liver Related
BUT
If ALT/Bili abnormal
OR
Liver Symptoms
Consider ALP Isoenzymes

Yes

NO

Raised ALP

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Albumin

Albumin synthesis is an important function of the liver. When the functioning capacity of the liver decreases, falls in plasma albumin can be seen. However, there are many other causes of decreasing albumin levels.

Causes of low albumin:

- Decreased Synthesis - severe liver disease, malabsorption, malnutrition, acute phase reaction
- Haemodilution - pregnancy, iv therapy, congestive cardiac failure, cirrhosis, antidiuresis
- Altered distribution - injury, infection, inflammation, malignancy, cirrhosis
- Loss from body - skin (burns), gut (protein losing enteropathy) and renal (nephrotic syndrome)
- Increased catabolism - acute/chronic illness, malignancy, pregnancy
Follow on Investigations

A detailed clinical assessment is very important for patient management and should include the following:

- Alcohol Consumption
- Medications
- Occupational exposure to toxins
- Risk factors for viral hepatitis:
  - intravenous drug use
  - travel history
  - non-sterile ear or body piercing
  - tattoos
  - health care intervention in developing nations
  - Country of birth

Second Line Tests:

- For alpha1-antitrypsin deficiency, when the serum alpha1-antitrypsin level is < 1200 mg/L samples will be referred for alpha1-antitrypsin phenotype analysis, if not previously carried out. In some instances alpha1-antitrypsin phenotype analysis may still be required when alpha1-antitrypsin levels are above 1200 mg/L, as transiently higher levels can be seen in the acute phase response. For more information please visit [http://ghr.nlm.nih.gov/condition/alpha-1-antitrypsin-deficiency](http://ghr.nlm.nih.gov/condition/alpha-1-antitrypsin-deficiency)

- For Wilson’s disease, if serum caeruloplasmin is < 200mg/L (< 0.2 g/L) in patients < 50 years of age then measurement of 24hr urine copper excretion should be carried out. If the patient is > 50 years of age then Wilson’s disease is very unlikely, however if there is a strong clinical suspicion still suggest a 24hr urine copper measurement, which requires a plain 24 hour urine container. Please note serum copper measurements are not useful when trying to diagnose Wilson’s disease. For more information please visit [http://www.wilsonsdisease.org/about-wilsondisease.php](http://www.wilsonsdisease.org/about-wilsondisease.php)

- For Haemochromatosis the first line screening test is Ferritin. When this is raised a Transferrin Saturation (TSAT) will be undertaken. If the TSAT is > 55 % in women and > 60 % in men this may be suggestive of Haemochromatosis. In these instances suggest repeat test, ensuring the patient has fasted and is not on iron supplements. After repeating tests, if results still over action limits, Hepatology referral and a genetic screen are recommended, irrespective whether the LFT’s are abnormal. In there is a family history of Haemochromatosis genetic screening is appropriate, even if the TSAT is normal. For more information please visit [http://www.haemochromatosis.org.uk/index.html](http://www.haemochromatosis.org.uk/index.html)
Summary

- Liver disease may be asymptomatic, and when symptoms are present they may be generalised and non-specific

- The first sign of liver disease may be a raised LFT result in an asymptomatic patient

- If there is a mild elevation in ALT, it is important to repeat the test to ensure it is not an acute injury

- Prior to referral with asymptomatic enzyme elevation is important to have first carried out an initial liver screen to aid efficient patient management.

Contacts

Duty Biochemist 01332 789383 (8.0am to 7.0 pm, Monday-Friday)
On Call Consultant Biochemist Via RDH switchboard, 01332 340131(24/7)

References

Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury. II. Recommendations for use of laboratory tests in screening, diagnosis, and monitoring. Clin Chem. 2000 Dec;46(12):2050-68


