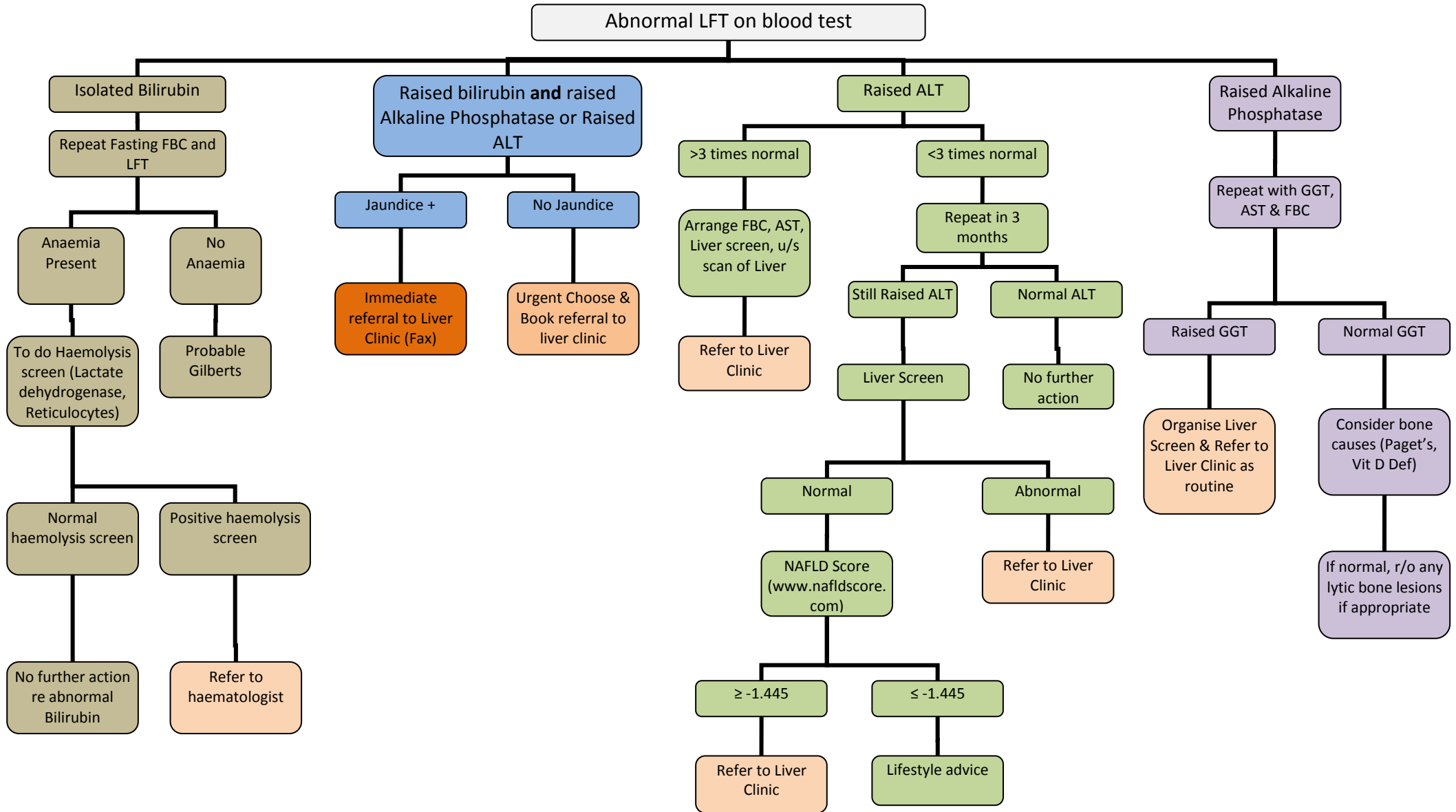


Management of Abnormal Liver Function Tests in Primary Care



Liver Screen (available on ICE system as Liver Screen)

HbSAg, HCV Ab, Auto-antibodies (ANA, AMA, ASMA), serum immunoglobulins, Coeliac Screen (TTg Ab), Ferritin, Iron saturations, Fasting Glucose, Fasting Lipids.

Consider U/S scan of liver, spleen and Pancreas.

1st Assessment with abnormal LFTs

(Think about Non-Alcoholic Fatty Liver Disease NAFLD), Careful Drug & Alcohol history (AUDIT score if appropriate), Drug causes (like NSAID), features of Metabolic Syndrome (HTN, Diabetes, Obesity and Abnormal Lipids), Repeat bloods.

When to repeat bloods-

- Isolated raised bilirubin – fasting sample when convenient
- Isolated raised Alkaline Phosphatase – no delay needed
- Isolated ALT – repeat in 3 months
- A raised ALT or Alkaline Phosphatase that is over 3x the upper limit of normal should have repeat LFTs including GGT and AST without delay at the same time as a liver screen and USS (step 3)
- A raised ALT or raised Alkaline Phosphatase, in combination with raised bilirubin should be referred routinely to a liver clinic or gastroenterologist. Please order an USS of liver / spleen / pancreas routinely at the same time.

2nd Assessment with abnormal LFT

If abnormality persists- Follow the algorithm.

Pattern Recognition-

- Isolated raised bilirubin- possible Gilberts.
- Cholestatic pattern- Alkaline Phosphatase more raised than ALT.
- Hepatic Pattern- raised ALT +/- Raised Alkaline Phosphatase.

Drugs Causing Abnormal LFTs

NSAIDs

Antibiotics (Flucloxacillin, Co-amoxiclav)

Antiepileptic Rx: Phenytoin, Carbamazepine, Sodium Valproate

Antituberculous Drugs: Rifampicin, Isoniazid, Ethambutol

Statin induced Hepatotoxicity is very rare (more often there might be underlying NAFLD).

Non-Alcoholic Fatty Liver Disease Management

Aim for BMI <25 (Orlistat if BMI >25 + exercise), optimise diabetes control, Rx HTN, reduce alcohol, start statin if appropriate, Annual CV check + Annual repeat FBC, LFT, Fasting Glucose/ Lipids & NAFLD fibrosis score (www.naflscore.com)

Full Clinical Guidelines for the Management of Adults with Asymptomatic Liver Function Abnormalities.

Introduction

This local guideline relates to adults with only vague or no symptoms or signs of liver disease, found to have abnormal LFTs. This guideline does not apply to children.

It is recognised that abnormal LFTs are an increasingly common presentation in primary care, in part due to the growing number of individuals with non-alcoholic fatty liver disease (NAFLD).

There are two main aims of these guidelines. The first is to improve our detection of significant liver disease to allow better care and prevent progression to cirrhosis. The second is to reduce the burden on primary and secondary care of unnecessary investigations and follow up.

PATTERN RECOGNITION

What sort of abnormality do the abnormal LFTs suggest?

a. **Isolated raised bilirubin** – most commonly due to Gilbert's syndrome. This is a benign condition and does not need referral. It occurs in about 5% of the population.

Repeat LFTs on a fasting sample with an FBC. The bilirubin should rise further and there should be no evidence of anaemia. If the patient is anaemic haemolysis needs to be excluded (reticulocyte count, LDH).

b. **Cholestatic pattern** – Alkaline phosphatase (Alkaline phosphatase) raised significantly more than ALT. Remember bone causes of raised Alkaline phosphatase e.g. Paget's Disease. Repeating LFTs with a GGT can help confirm a liver cause.

c. **Hepatitis pattern** – Most marked abnormality is a raised ALT (and AST if reported), though Alkaline phosphatase may also be raised. These can be short-lived, due to illness, reverting to normal a few weeks later. The bulk of this guidance refers to patients with this pattern of abnormality.

FIRST ASSESSMENT

Given that the most common causes of abnormal LFTs are NAFLD (commonly associated with other features of the metabolic syndrome), alcohol excess and adverse drug reactions, a careful drug/alcohol history should be taken and other features of the metabolic syndrome (hypertension, diabetes, obesity and abnormal lipids) should be sought.

Consider using the AUDIT questionnaire for detecting hazardous or harmful drinking. Patients should be given general advice as appropriate (reduction in alcohol intake, weight reduction by diet and exercise).

Any drugs known to be associated with drug induced liver injury should be stopped if possible. Of particular note are NSAIDs. These should be stopped and LFTs repeated after 3 months.

Many other drugs that cause abnormal LFTs are more difficult to stop (e.g. neuroleptics, anti-epileptics). Referral to a liver clinic for advice is appropriate in these circumstances. Patients with severe alcohol problems should be referred when appropriate.

Repeat the LFTs, requesting AST and GGT also, with an FBC.

When to repeat the LFTs?

- Isolated raised bilirubin – fasting sample along with FBC when convenient
- Isolated raised Alkaline phosphatase – no delay needed

- Isolated ALT – repeat in 3 months
- A raised ALT or Alkaline phosphatase > 3x the upper limit of normal should have Fasting sample with GGT, AST, liver screen and USS (step 3); without delay.
- A raised ALT or raised Alkaline phosphatase, in combination with raised bilirubin should be referred routinely to a liver clinic or gastroenterologist.

Please order an USS of liver / spleen / pancreas routinely at the same time.

SECOND ASSESSMENT (PERSISTENTLY ABNORMAL LFTs)

If the abnormalities have persisted for 3 months despite the above measures, then a Liver screen should be arranged:

- a. Viral screen (HBsAg, HCVAb)
- b. Autoantibodies – ANA, AMA, ASMA
- c. Coeliac screen (TTG Ab)
- d. Ferritin (and Transferrin Saturation if Ferritin raised)
- e. Fasting blood glucose, fasting lipids
- f. USS – liver, biliary tree, pancreas

WHO TO REFER

The history taken and results so far should point to possible pathologies causing the abnormal LFTs. Most of the list below will need referral for further assessment and management.

Chronic viral hepatitis – history of risk behaviours, blood transfusion and positive markers.

Primary biliary cirrhosis – raised Alkaline phosphatase (cholestatic pattern), positive anti-mitochondrial antibody.

Primary sclerosing cholangitis – history of inflammatory bowel disease, cholestatic pattern on LFTs.

Autoimmune hepatitis – positive autoantibodies (smooth muscle, antinuclear antibodies), might have history of other autoimmune diseases,

Haemochromatosis – raised ferritin and transferrin saturation (>45%). Might have history of diabetes and joint pain.

USS – the presence of dilated bile ducts requires further assessment and URGENT hospital referral. (62 Day Target) Any reported dilation of the biliary tree is significant.

The presence of unexplained clinical jaundice should lead to immediate referral. (62 Day target Referral)

Alcohol

Alcoholic fatty liver disease – from history, raised MCV, fatty liver on USS. Consider referral to Well Liver Clinic.

Advanced alcoholic liver disease- features that suggest underlying cirrhosis include portal hypertension on USS or low platelets. These patients should be referred routinely.

Patients with features of decompensated cirrhosis i.e. above plus any of ascites, jaundice, low albumin raised INR or encephalopathy (fluctuating consciousness) should be referred urgently.

The hazardous drinker without evidence of cirrhosis or decompensated liver disease require advice, regular counselling and, where appropriate, referral to secondary alcohol specialists. (E.g. COOPs or Kennedy House). Consider referring these patients to the nurse led Well Liver Clinic.

NAFLD

– USS shows fatty liver only, remainder of screen is negative. Patients likely to have raised BMI or increased waist circumference, hypertension, impaired fasting glucose (IFG) or diabetes, raised fasting triglyceride and low HDL cholesterol.

RISK STRATIFICATION OF PATIENTS WITH NAFLD

NAFLD represents a spectrum of metabolic syndrome-associated liver disease progressing from simple steatosis (fat but no inflammation or hepatocellular injury), through non-alcoholic steatohepatitis (NASH = fat + inflammation+ hepatocellular injury) and fibrosis to cirrhosis. Estimates suggest that up to a third of the population has NAFLD. The majority of patients with NAFLD have simple steatosis which is not associated with liver-related mortality. However, 10–30% of patients with NAFLD has NASH and are at risk of developing progressive fibrosis resulting in cirrhosis and subsequent life threatening liver related complications such as hepatocellular carcinoma, portal hypertension and liver failure.

There are no simple blood tests that can differentiate patients with NASH from simple steatosis, but there are algorithms based on simple blood tests and clinical parameters that can accurately exclude advanced fibrosis, and these can be used to triage patients who require referral to secondary care for further investigation and management. The NAFLD fibrosis score has been well validated for this purpose.

For all patients with a clinical diagnosis of NAFLD who have had other causes of liver disease excluded the NAFLD fibrosis score should be calculated.

To calculate the NAFLD fibrosis score you need

- Age
- AST
- ALT
- Platelets
- Albumin
- Presence of DM or IFG

An online calculator for this is available at www.naflscore.com

If the NAFLD fibrosis score is less than minus 1.455 (e.g. minus 1.66) advanced fibrosis is excluded with >90% accuracy. These patients can be managed in primary care.

If the score is greater than minus 1.455 (e.g. minus 0.8) patients have a significant probability of having advanced fibrosis (30-52% chance) and 90% will have the potentially progressive form of fatty liver, steatohepatitis. Referral to a liver clinic is recommended for these patients for further investigation and management as these are at the highest risk of liver related complications.

MANAGE PATIENTS WITH LOWER RISK NAFLD

Currently the mainstay of management for patients with NAFLD without advanced fibrosis is lifestyle modification and optimisation of diabetes and cardiovascular risk factors.

- Lose weight if BMI >25 or raised waist circumference
- Aim for at least a loss of 10% of body weight.

- Consider Orlistat as per NICE guidance
 - Advise exercise at least 30 minutes 3 times per week (both cardiovascular and resistance exercise are beneficial even independent of weight loss)
 - Optimize control of diabetes
 - Use metformin, Glitazone or GLP analogue where possible
 - Treat hypertension - Use ACEI or ARB first line (these might be anti-fibrotic)
 - Drink sensibly – within current limits. There is no evidence at present to recommend abstinence.
 - Reduce other risk factors for vascular disease. Statins are safe in patients with NAFLD
 - Undertake an annual vascular disease risk score as patients with NAFLD are more at risk from this than from direct effects on the liver.
 - Monitor FBC, LFTs (including AST), FBG and lipids annually.
- Calculate NAFLD score annually and refer if the NAFLD score become greater than minus 1.455.

APPENDIX 1

After consideration, screening for Wilson’s disease and alpha-1-antitrypsin deficiency has been left out of our recommended liver screen (Step 3). This is due to the rarity of these conditions and the significant cost of the relevant tests. However you may want to consider these conditions in patients presenting with atypical features at a young age.

Wilson’s disease

An autosomal recessive disorder of hepatic copper metabolism. Wilson’s disease most commonly presents in the teenage years and should always be considered in this context particularly in the presence of neuropsychiatric features. However, Wilson’s disease can be very difficult to diagnose and there is no single diagnostic test that can exclude or confirm Wilson’s disease with 100% certainty. Suspicion should be alerted in the patient with a low alkaline phosphatase level or Coomb’s negative haemolytic anaemia. A low serum Caeruloplasmin level is a useful screen but can be normal.

Alpha 1 antitrypsin deficiency (AAT)

AAT is a proteinase inhibitor and mainly produced in the liver. AAT disease of the liver is rare in adults. Most commonly presenting within the first week of birth with jaundice. AAT deficiency is particularly important in the lungs, especially with a history of smoking. Be suspicious in the patient with COPD who has evidence of chronic liver disease but in the absence of obvious risk factors. It remains uncertain whether heterozygous carriers have an increased susceptibility to liver injury in the presence of a “second hit” on the liver as with excessive alcohol consumption.

However, patients should be advised not to smoke and keep alcohol intake within recommended safe drinking limits.

Coeliac disease

Coeliac disease can present with cryptogenic liver disease with persistent “transaminitis” in up to 5 – 10% patients. This will often resolve with a gluten free diet but may persist and can be associated with autoimmune liver disease. There is a reported increased association with haemochromatosis and a three-fold higher incidence of coeliac disease in NAFLD as compared to the general population. However, be aware that in the presence of chronic liver disease tissue transglutaminase (TTG) antibodies can be falsely elevated.

Hereditary Haemochromatosis

Hereditary haemochromatosis is a common inherited (recessive) disorder of iron absorption. This can result in iron deposition in tissues, mainly the liver but also other organs including the pancreas and heart. The C282Y and H36D mutations within the HFE gene account for > 90% cases seen in our region. There are at least 4 other mutations that have been identified that account for the remaining 10% of cases but the tests are not widely available for clinical use. Generally speaking we recommend Genotyping if the Transferrin saturation is

> 45% in the presence of a raised serum ferritin. It should be born in mind that ferritin is an acute phase reactant and can be raised in a wide series of inflammatory conditions. In addition a raised serum ferritin is often seen in other liver conditions such as alcoholic liver disease, hepatitis C and non-alcoholic steatohepatitis. Hereditary haemochromatosis is an important condition to diagnose as it is readily treatable (venesection) and has implications for other family members. Those parents, siblings and children over the age of 20 years will require screening. Some patients ask for dietary advice. They should avoid iron – rich foods and vitamin C supplements, minimize alcohol to within recommended safe drinking limits and advise weight loss in patients with central obesity.

APPENDIX 2

Adverse drug effects on the liver are important and should be considered when assessing patients with liver function abnormalities. This is not a comprehensive list but some of the commonest culprits are:

NSAIDs

Antibiotics: Flucloxacillin, Co-amoxiclav

Antiepileptics: Phenytoin, Carbamazepine, Sodium Valproate

Antituberculous drugs: Rifampicin, Isoniazid, Ethambutol

NB: Statin induced hepatotoxicity is very rare and most abnormal LFTs in the setting of statin use are due to underlying non-alcoholic fatty liver disease.