Clinical Guidelines

Revised Newcastle, North Tyneside and Northumberland Guidelines for the Management of Adults with Asymptomatic Liver Function Abnormalities.

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Dr Mark Hudson
Dr Stuart McPherson
On behalf of the North East & North Cumbria Hepatology Network

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ORIGINAL GUIDELINE DEVELOPMENT GROUP MEMBERSHIP

Professor C Day, Consultant Hepatologist, Newcastle Upon Tyne Hospitals NHS Foundation Trust

Mr A Hodge, Clinical Governance, NHS North of Tyne

Dr M Hudson, Consultant Hepatologist, Newcastle Upon Tyne Hospitals NHS Foundation Trust

Dr P McKenna, Consultant Chemical Pathologist, Northumbria Healthcare NHS Foundation Trust

Dr S McPherson, Consultant Hepatologist, Newcastle Upon Tyne Hospitals NHS Foundation Trust

Dr D Neely, Consultant in Chemical Biochemistry and Metabolic Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr E Phillips, Consultant Gastroenterologist, Northumbria Healthcare NHS Foundation Trust

Dr G Pilkington, GP, CCG Clinical Chair, Newcastle West CCG

Dr C Robson, GP North Tyneside.

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Introduction

This local guideline is revised from the Newcastle, North Tyneside and Northumberland guidelines based on previous Newcastle West PCT guidance. It 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).

This guideline makes recommendations for the diagnosis and management of adults with abnormal liver function tests with little or no symptoms, and is intended for use by all clinicians in Newcastle, North Tyneside and Northumberland involved in the diagnosis and management of these patients. The interventions should be offered to all people who are likely to benefit, irrespective of race, disability, gender, age, sexual orientation or religion. Information should be provided to patients in an accessible format and consideration should be given to mobility and communication issues, and being aware of sensitive and cultural issues.

STEP 1 – 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 (Alk phos) raised significantly more than ALT. Remember bone causes of raised Alk phos e.g. Paget's Disease. Repeating LFTs with a γGT can help confirm a liver cause.

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

STEP 2 – 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 or FAST 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) and 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 γGT** also, with an FBC.

When to repeat the LFTs?

a. Isolated raised bilirubin – **fasting sample** when convenient
b. Isolated raised Alk phos – no delay needed
c. Isolated ALT – repeat in 3 months
d. A raised ALT or Alk phos that is over 3x the upper limit of normal should have the above done without delay at the same time as a liver screen and USS (step 3)
e. A raised ALT or raised Alk phos, 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.

The presence of unexplained clinical jaundice should lead to immediate referral.

STEP 3 – 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

STEP 4 – DECIDE 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 Alk phos (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. Any reported dilation of the biliary tree is significant.

Many of these patients in the list below will not require referral. Low risk patients with Fatty Liver can be managed in primary care.

- Alcoholic fatty liver disease – from history, raised MCV, fatty liver on USS. Advanced alcoholic liver disease is indicated by splenomegaly or other signs of portal hypertension on USS, low platelets, low albumin or raised bilirubin
- 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.

The hazardous drinker without evidence of decompensated liver disease requires advice, regular counselling and, where appropriate, referral to secondary alcohol specialists. These patients should not be referred to liver clinics.

STEP 5 – 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 have 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.

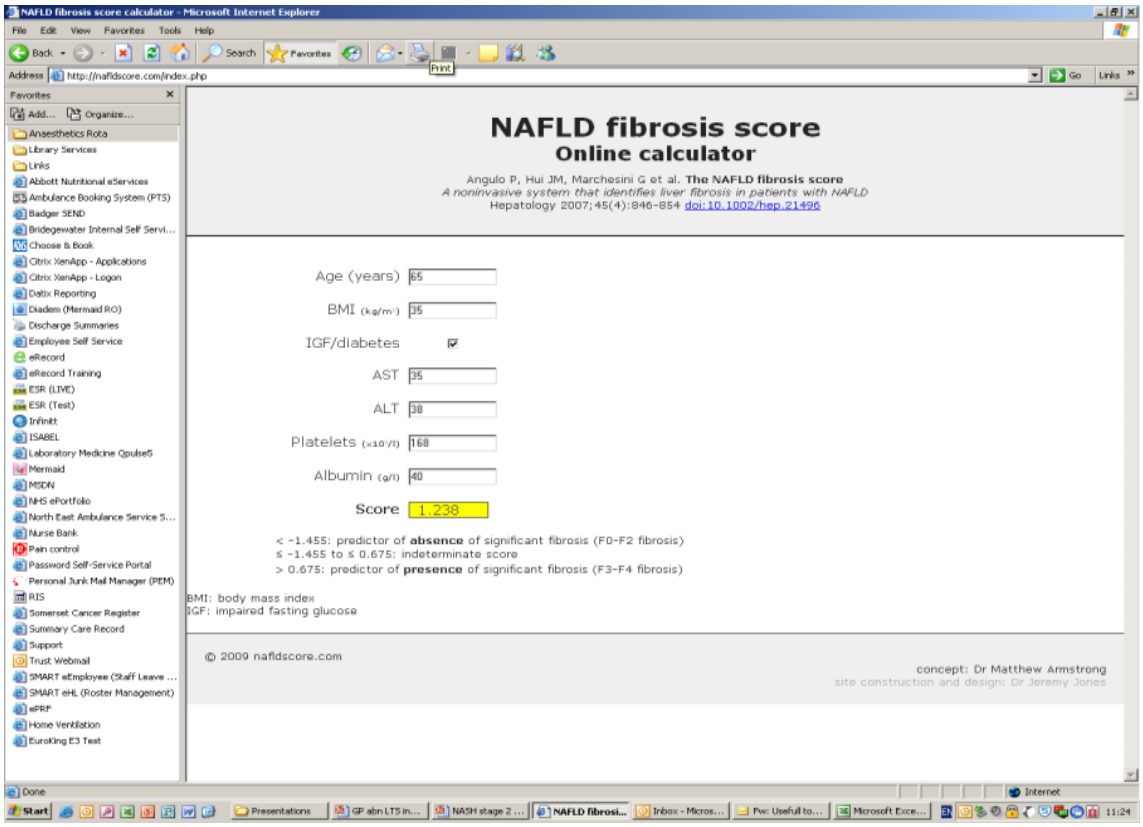
There are no simple blood tests that can differentiate patients with NASH from simple steatosis, but there are algorithms based on simple blood tests and clinical parameters that can accurately exclude advanced fibrosis, and these can be used to triage patients who require referral to secondary care 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.nafldscore.com



- If the NAFLD fibrosis score is less than **minus** 1.455 (eg 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** (eg 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.

STEP 6 – 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 (e.g. FATS6). 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.

REFERENCES

Ratziu V, Bellentani S, Cortez-Pinto H, Day C & Marchesini G. A position statement on NAFLD/ NASH based on the EASL 2009 special conference. Journal of Hepatology. **2010**; 53; 372-384.

APPENDIX 1

Testing for Gilbert's syndrome

A solitary abnormal raised bilirubin result is likely to be due to Gilbert's. Repeat testing should confirm that none of the other LFTs are abnormal. A repeat **fasting** sample should show a further isolated rise in bilirubin.

If you wish to confirm that the rise in bilirubin is unconjugated, send the sample wrapped (e.g. in a small envelope) within the usual pathology bag. This will reduce light exposure (which leads to conjugation). At low levels of bilirubin, testing for conjugation is unreliable (e.g. up to 25µmol/L).

Confirm there is no evidence of haemolysis – reticulocytes and LDH will be normal (raised retics/LDH seen in haemolysis). There is no need to test the urine.

Samples required to confirm Gilbert's:

1 x SST 11 (gold top) wrapped
1 x EDTA (lavender top)

APPENDIX 2

Samples required for full liver screen (Step 3)

3x SST 11 (gold top)
1 x Fluoride oxalate (grey top)
1 x EDTA (lavender top)

In addition to tick boxes for FBC, FBG, fasting lipids, ferritin, Ig and autoantibodies, you will need to request Transferrin saturation in the biochemistry section and for Microbiology/Virology request HBsAg and HCVAb.

APPENDIX 3

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 4

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

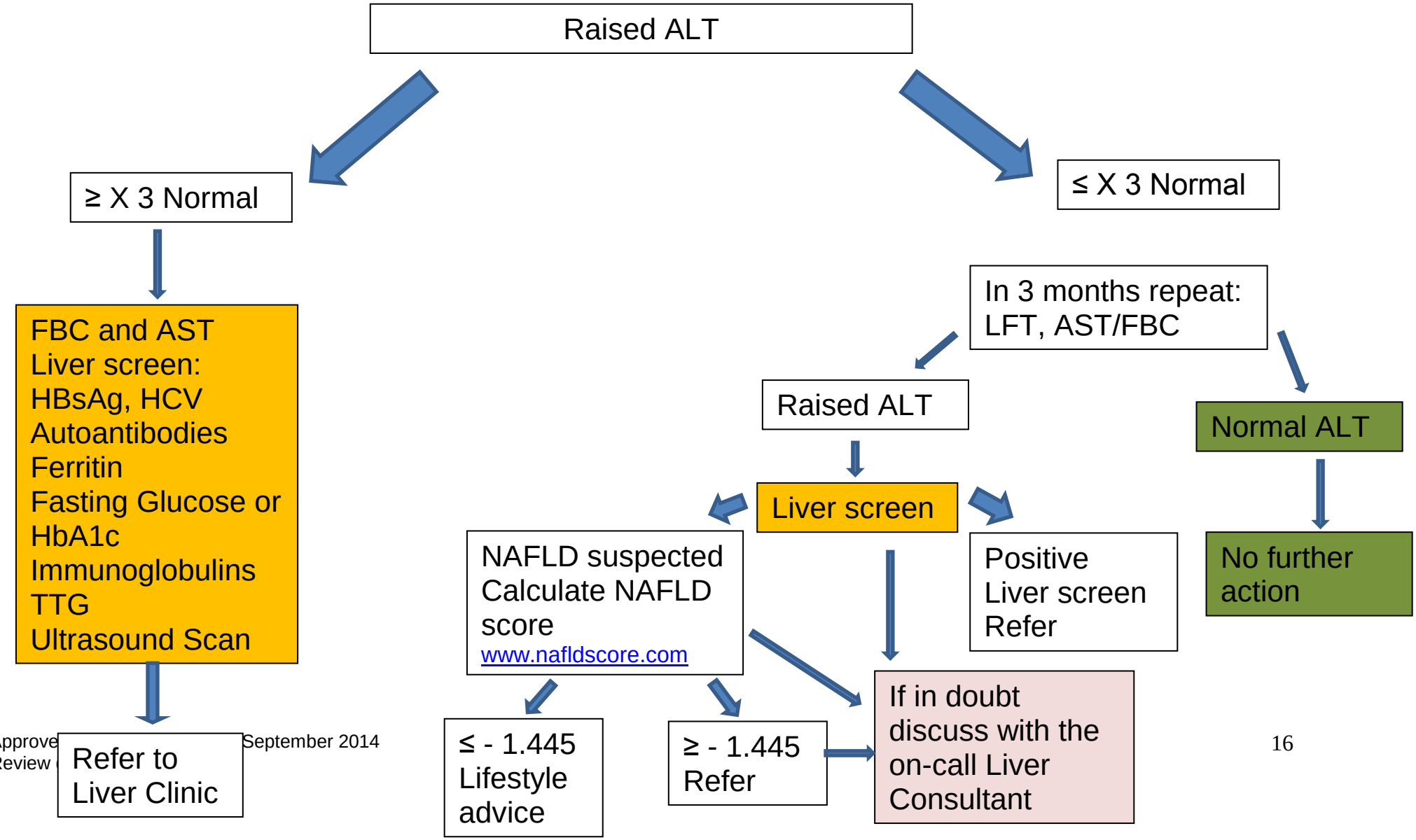
Antibiotics: Flucloxacillin, Co-amoxiclav

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.

Asymptomatic Liver Function Abnormalities (ALFA)
Raised ALT



Asymptomatic Liver Function Abnormalities (ALFA)