

## MANAGEMENT OF ABNORMAL LFT IN ADULT ASYMPTOMATIC PATIENTS

Based on BSG Guidelines (draft version, 2007)

These guidelines are aimed at Gastroenterologists and General Practitioners who manage patients with no symptoms, vague symptoms, or symptoms not attributable to liver disease who are found to have abnormal LFTs. They do not apply to children. The aetiology and investigation of abnormal LFTs in apparently asymptomatic infants and children are entirely different and require speedy referral to a paediatrician.

### WHAT ARE LIVER FUNCTION TESTS?

The term 'liver function tests' (LFTs) is usually used to describe a set of biochemical tests comprising of:

- Bilirubin
- Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT)
- Alkaline phosphatase

They may also include measurement of:

- Albumin
- Gammaglutamyl transferase
- Lactate dehydrogenase
- Prothombin time

A review of the sensitivity, specificity and performance characteristics of these individual tests is outside the scope of this document however they are extensively reviewed elsewhere (1).

#### **Bilirubin**

Bilirubin is formed from the breakdown of the haem component of red blood cells by the reticuloendothelial system. It is transported to the liver in its water insoluble unconjugated form where it is converted into the water soluble conjugated form, bilirubin glucuronide by UDP glucuronyltransferase. Normally it is the total serum bilirubin that is measured. A raised serum bilirubin may therefore reflect increased unconjugated bilirubin production (haemolysis), impaired conjugation in the liver (usually Gilbert's syndrome), impaired secretion of conjugated bilirubin into the bile (e.g. severe chronic liver disease) or extrahepatic biliary obstruction (e.g. common bile duct stones or carcinoma of the head of the pancreas). The commonest cause of an isolated raised bilirubin in an asymptomatic patient is likely to be Gilbert's syndrome which affects up to 5% of the population (2). In the absence of haemolysis (as manifest by a low haptoglobin and increased reticulocyte count) an increase in the bilirubin with fasting (or coincident illness) and confirmation of a predominant unconjugated hyperbilirubinaemia makes the diagnosis of Gilbert's syndrome virtually certain. This is not a disease, does not cause symptoms and therefore the patient can be reassured.

#### **Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)**

AST and ALT are enzymes present in hepatocytes that participate in gluconeogenesis. They are released into the blood stream in increased amounts during hepatocellular

injury or cell death. AST is also abundantly present in other tissues such as heart muscle, skeletal muscle and blood cells. AST was used historically as a 'cardiac enzyme' to detect myocardial infarction or may indicate myositis or haemolysis. ALT is often considered to be more liver specific as it is present in much lower concentrations in extrahepatic tissues, but it can still be elevated in conditions other than liver diseases such as myositis or muscular dystrophies.

AST and ALT are transiently raised in a variety of acute illnesses including acute hepatitis when a patient may or may not be symptomatic. The causes of elevated serum transaminases are shown in Table 1.

The ratio of AST to ALT can give a clue to the aetiology of the liver disorder. In most chronic liver diseases, ALT levels are higher than AST except when cirrhosis has developed (3, 4). However an AST to ALT ratio greater than 2 is suggestive of alcoholic liver disease (5).

### **Alkaline Phosphatase**

Alkaline phosphatase is produced mainly in the liver and bone but also in smaller quantities by the intestines, kidneys, and white blood cells. Levels are physiologically higher in childhood and pregnancy where it comes from the placenta. Pathologically increased levels occur mainly in bone disease (e.g. Paget's disease and fractures) and cholestatic liver disease e.g. primary biliary cirrhosis, primary sclerosing cholangitis, common bile duct obstruction, intrahepatic duct obstruction (metastases) or drug induced cholestasis. As with gamma glutamyltransferase, hepatic alkaline phosphatase can be induced by drugs, most commonly anticonvulsants. In elderly patients right heart failure can result in elevated alkaline phosphatase levels (6)

Gamma glutamyltransferase should be measured to establish the hepatic origin of the alkaline phosphatase. If doubt still exists, then differentiating a bone cause from a liver cause of a raised alkaline phosphatase can be aided by separation of the different isoenzymes by electrophoresis.

### **Gamma glutamyltransferase**

Gamma glutamyltransferase is abundant in the liver and other tissues such as kidney, intestine, prostate and pancreas. It is not present in bone, however, hence the usefulness of this enzyme in determining the source of an elevated alkaline phosphatase (8). A raised gamma glutamyltransferase is not confined to alcoholic liver disease as it can be induced by drugs (such as anticonvulsants, lipid lowering drugs, and oral contraceptives) and is also elevated in fatty liver disease. It is not always raised in chronic alcoholics (9), hence it is not sensitive for occult alcohol abuse.

In asymptomatic patients with a raised gamma glutamyltransferase alone who do not drink excessively, hepatic fibrosis is present only 5% of cases (10). Moreover patients drinking excess alcohol who have an isolated raised gamma glutamyltransferase are also unlikely to have significant liver damage (11)

Thus in isolation an elevated gamma glutamyltransferase is not a useful measurement and does not reflect significant underlying liver disease. It should only be requested if there is an isolated elevation of alkaline phosphatase in the presence of a normal ultrasound.

## DO LIVER FUNCTION TESTS OUTSIDE THE NORMAL RANGE ALWAYS INDICATE LIVER DISEASE?

By definition some healthy people will have abnormal LFTs. LFTs may vary for physiological reasons such as the elevation of alkaline phosphatase seen in pregnancy, be raised because of the lack of specificity of some of the LFTs for liver disease e.g. raised AST in muscle diseases and alkaline phosphatase in bone disease, or be falsely raised due to laboratory error, sample mishandling (haemolysis) or the presence of macroenzymes.

**Recommendation:** Clinicians should be aware that a minority of people with abnormal LFTs will have no liver disease.

## DO NORMAL LIVER FUNCTION TESTS INDICATE ABSENCE OF LIVER DISEASE?

Normal LFTs do not exclude the presence of significant liver disease therefore patients still need to be assessed if signs of liver disease are present or significant risk factors for chronic liver disease are present e.g. exposure to hepatitis C or family history of haemochromatosis. It is well established that certain liver disease patients can have normal LFTs and still have significant liver disease which might progress to cirrhosis e.g. chronic hepatitis C (16), haemochromatosis (17), and primary sclerosing cholangitis(18).

**Recommendation:** Clinicians should be aware that normal LFTs do not mean an absence of significant liver disease.

## HOW COMMON IS CHRONIC LIVER DISEASE IN ASYMPTOMATIC PATIENTS WITH ABNORMAL LFT?

No liver biopsy studies have been performed on people with abnormal LFTs on a single occasion in asymptomatic populations such as those shown in Table 3, so the true prevalence of liver disease in these populations is not known. Liver biopsy studies have been restricted to asymptomatic patients who have had abnormal LFTs for at least 6 months (standard practice) yet only 45-64% of patients identified in the studies in Table 3 may fit into this category (22,24)

Table 4 shows the studies which have reported liver biopsy findings in selected asymptomatic patients with abnormal LFTs.

These studies show that almost all asymptomatic patients with abnormal LFT do have liver disease. A small percentage of people however will have histologically normal livers, this percentage being similar (5-10%) in populations in which obvious causes of liver disease have been excluded by a comprehensive 'liver screen' and in those that have not (0-12%). Presumably these people are some of the 2.5% of the normal population whose LFTs lie above the normal range, have macroenzymes or non hepatic causes of raised LFTs.

In asymptomatic populations with abnormal LFTs the commonest pathology found on liver biopsy is fatty liver disease, whether it is alcoholic or non alcoholic fatty liver

disease (NAFLD). The proportion of other chronic liver diseases diagnosed on liver biopsy depends on the conditions diagnosed by a 'liver screen' and subsequently excluded from biopsy.

**Recommendation:** Clinicians should be aware that the majority of symptomatic patients with abnormal LFTs will have liver disease and a proportion will have significant liver damage (fibrosis or cirrhosis).

### **IS CHRONIC LIVER DISEASE LESS COMMON IN ASYMPTOMATIC COMPARED TO SYMPTOMATIC PATIENTS WITH ABNORMAL LFT?**

Only one study has compared the findings on liver biopsy of asymptomatic versus symptomatic patients with abnormal LFTs (30). This study was restricted to patients with a negative 'liver screen' and showed no difference in the number of patients with normal findings, steatosis, steatohepatitis, fibrosis and cirrhosis when comparing the two groups.

**Recommendation:** Abnormal LFTs in asymptomatic patients should be investigated in the same way as symptomatic patients as there is no difference in the severity of liver disease found.

### **IS CHRONIC LIVER DISEASE LESS COMMON IN ASYMPTOMATIC PATIENTS WITH AN ABSENCE OF STIGMATA OF LIVER DISEASE?**

Neither the presence or absence of stigmata of chronic liver disease (spider naevi, palmar erythema, Dupuytren's contracture, finger clubbing) influences the findings on liver biopsy. Hulcantz et al, 1986, Daniel et al, 1999, Mathiesen et al, 1999 and Skelly et al, 2001 only studied patients without stigmata of chronic liver disease. Mathiesen et al found that approximately half the patients studied had fibrosis including 4(2.7%) with cirrhosis and 19(12.7%) with near cirrhosis (bridging fibrosis). Skelly et al, found that a quarter of patients had some degree of fibrosis including 6% with cirrhosis and 8.5% with bridging fibrosis. Hay et al, 1989 compared findings of asymptomatic patients with abnormal LFTs in those with and without stigmata of chronic liver disease. 25% of cirrhotic patients and over 50% of chronic active hepatitis or steatohepatitis patients had no stigmata of liver disease. Although this study was conducted before the identification of hepatitis C and therefore the presumed aetiology of the liver biopsy findings may be erroneous, this doesn't alter the finding that the absence of stigmata of chronic liver disease does not mean an absence of liver disease let alone cirrhosis.

**Recommendation:** An absence of stigmata of chronic liver disease should not preclude investigation of abnormal LFTs as significant liver damage, including cirrhosis may still be present.

## IS THE DEGREE OF LFT ABNORMALITY IMPORTANT?

No single study has compared the clinical or histological diagnoses made at a certain degree of LFT abnormality to those at a different level of abnormality. From Table 4 it can be seen however that there is no great difference between the percentage of abnormal liver biopsies found when investigating patients with LFTs any degree above the normal range, above 1.5 times or twice the normal range. Investigating patients with a greater than threefold increase in transaminases may result in fewer normal liver biopsies i.e. fewer false positives but will clearly result in an under diagnosis of significant liver disease. The decision to perform liver biopsy in each individual patient must balance the small risk of the procedure against the potential to detect and treat any underlying liver disease. The decision should not simply be guided by the degree of biochemical abnormality. Sherwood et al, 2001 (32) investigated patients with abnormal LFTs > 2 times the reference range because lowering this threshold would have resulted in 6 times more patients to investigate, 'well beyond our means of investigation', and that of most gastroenterology or liver clinics.

**Recommendation:** Any degree of LFT abnormality should be considered for investigation as even minor abnormalities can be associated with significant liver disease.

## IS THE DURATION OF LFT ABNORMALITY IMPORTANT?

There is no data on the optimum time to investigate abnormal LFTs in asymptomatic patients. When liver biopsy has been used to investigate such patients, with or without a prior liver screen, all studies have used a minimum of 6 months duration of abnormality as the threshold of investigation. Even when a shorter minimum duration of LFT abnormality has been used as a criterion for performing liver biopsy in patients who may or may not have been asymptomatic, it is difficult to draw any conclusions as the mean duration of LFT abnormality in this study was 18 months (33). It has been suggested that LFTs should either be investigated after 3 months (34) or that there should be a staged approach to investigation over 0 to 6 months (35,36). Some expert reviews suggest treating the most likely cause of the abnormal LFTs i.e. alcohol (by abstinence), hepatotoxic drugs (by drug cessation) and NAFLD (by weight reduction and diabetes control) prior to more detailed investigation if LFTs remain abnormal after a period of observation (35,36)

**Recommendation:** Abnormal LFTs in asymptomatic patients should be investigated if the abnormalities have persisted for a minimum of 3-6 months.

## WHAT TESTS CONSTITUTE A 'LIVER SCREEN'?

Table 2 shows the tests that constitute a standard liver screen and also the additional or confirmatory tests that can be performed. There is no evidence base for the use of some or all of these tests as part of a liver screen but they have become accepted as standard practice. Serological screening tests for coeliac disease could also be included in a liver screen as this condition is recognised as causing asymptomatic elevation of transaminases, which subsequently normalise on a gluten free diet (15).

A thorough history should also be part of a 'liver screen' as not all chronic liver diseases can be diagnosed by blood tests alone as shown in table 1. The history should elicit the patients alcohol consumption, drug use (prescribed or otherwise) current and recently used, risk factors for viral hepatitis e.g intravenous drug use and blood transfusion prior to 1990, the presence of autoimmune diseases, family history of chronic liver disease and the presence of diabetes or obesity.

The suggested management of abnormal liver function test is summarised in Figure 1

**Recommendation:** A 'liver screen' should include hepatitis B surface antigen, hepatitis C antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-nuclear antibody, anti-liver kidney microsomal antibody, serum immunoglobulins, serum ferritin, transferrin saturation, copper and caeruloplasmin (under 40 years) and  $\alpha_1$  antitrypsin level. Imaging should consist of an ultrasound of the liver, biliary tree and pancreas.

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**Author** Dr Adam Stone, Consultant Gastroenterologist, St Richard's Hospital, Western Sussex NHS Foundation Trust, West Sussex.

**Others**

**Involved** Local Referral and Management Guidelines Committee.

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Table 1.

Common cause of elevated serum transaminases

<b>Elevation</b>	<b>Cause</b>
Minor (<100 IU/l)	Chronic hepatitis C Chronic hepatitis B Haemochromatosis NAFLD
Moderate (100-300 IU/l)	As above plus: Alcoholic hepatitis NAFLD Wilson's disease Autoimmune hepatitis
Major (>1000 IU/l)	Drug toxicity, paracetamol Acute viral hepatitis Ischaemic liver

**Table 2.** Laboratory tests to identify the cause of LFT abnormality

<b>Clinical Clue</b>	<b>Diagnosis</b>	<b>Initial test</b>	<b>Additional tests</b>
AST>ALT,MCV	Alcoholic liver disease		
Drug /herbal remedy history	Drug induced liver disease		
IVDU, blood transfusion	Chronic hepatitis B Chronic hepatitis C	HBsAg HCV antibody	HBeAg/eAb HBV DNA HCV RNA
Raised ALP	Primary biliary cirrhosis	AMA	
Inflammatory bowel disease	Primary sclerosing cholangitis		
Other autoimmune liver disease	Autoimmune hepatitis	ASMA,ANA,LKM Immunoglobulin	
Diabetes/joint pain	Haemochromatosis	Transferrin sat., ferritin	HFE gene test
Neurological signs	Wilson's disease	Caeruloplasmin	24hr urinary Copper
Lung disease	Alpha 1 antitrypsin	$\alpha_1$ antitrypsin level	$\alpha_1$ antitrypsin phenotype
Metabolic syndrome (BMI, diabetes, hypertension)	Non-alcoholic liver disease		
Malabsorption	Coeliac	Tissue Transglutaminase and/orEMA	

AMA = antimitochondrial antibody; ANA= antinuclear antibody; ASMA= smooth muscle antibody; LKM= liver kidney microsomal antibody;EMA = endomysial antibody

**Table 3.** Prevalence of abnormal LFTs in asymptomatic populations

POPULATION	SIZE	DEFINITION OF ABNORMAL	ABNORMAL (%)	LIKELY CLINICAL DISEASE (%)
NHAMES 111(20)	15676	ALT or AST > normal, 1 test	7.9	2.5
Health Screening (21*)	2294	AST > normal, 1 test	14.9	Unknown
	1309	AST or ALT > normal, 1 test	20.8	Unknown
	1309	AST or ALT > 2X normal	6.3	Unknown
Air force blood donors (22)	19877	ALT > 2X normal, 1 test	0.5	0.06 (pre HCV testing)
		ALT > 2X normal, 3 tests in 6 weeks	0.14	
Employee medicals (23)	235	AST,ALT, Bilirubin, Alk Phos, LDH > normal, 1 test	27.2	3.0 <sup>+</sup>
Civilian blood donors (24)	33780	ALT > normal, 3 tests / 6 weeks	0.5	Unkown (pre HCV testing)
Italian town (Dionysos study) (25)	6917	Elevated LFT (including GGT)	17.5	1 (cirrhosis)

\* exclude people with known existing liver disease therefore prevalence rates likely to be an underestimate

+ excludes Gilbert's syndrome and pregnancy as cause of abnormal LFTs

**Table 4.**

LIVER DISEASE EXCLUDED	DEFINITION OF ABNORMAL	STUDIED (EXCLUDE D)	ABNORMAL BIOPSIES %	FIBROSIS/ CIRRHOSIS	NORMAL BIOPSIES %	Reference
None	AST and ALT > 1.5X normal, > 6 months	149(0)	98.7	9 / 9	1.3	25
None	ALT>normal, >6months	150(0)	96.7	58-74 / 4	3.3	26
None	AST and ALT> normal	83	88	? / 14	12	27
HBV, alcohol, drug induced	AST 3-8X normal, > 6 months	47(131)	100	? / 16	0	28
HBV, HCV, alcohol, GH, AICAH, PBC, $\alpha_1$ AT, sarcoid Wilson's	AST or ALT >1.5X normal, > 6months	81(1043)	90	4 / 2	10	29
HBV, HCV, alcohol, GH, AICAH, PBC, $\alpha_1$ AT, Wilson's	AST or ALT or Alk Phos >1.5X normal, > 6months	36(445)	94.4	? / ?	5.6	30
HBV, HCV, alcohol, GH, AICAH, PBC, $\alpha_1$ AT, Wilson's	ALT, Alk Phos or GGT >2X normal, >6 months	354(?)	94	72 / 21	6	4*

\*Although not specifically stated in this paper all patients were asymptomatic (or had non specific symptoms) and had no stigmata of chronic liver disease (personal communication)

**Figure 1. Management of abnormal LFTs**

