Abnormal LFT’s in Asymptomatic Patients

FV Liver Care Pathway

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WSW Event 5th and 7th March 2013
Overview

• Liver disease in UK and Scotland
• Liver function tests - why bother?
• Liver function tests - the meaning of....
• Algorithms - explanation and discussion
2010 Liver Tsar  Prof. Martin Lombard
• Liver disease burden is rising
• Liver mortality rising as other major causes of mortality are declining
• Liver patients die younger than other major groups
• Huge and growing costs to the NHS
• Significant cost to the economy
PUTTING CHRONIC LIVER DISEASE ON THE PRIMARY CARE AGENDA

Chronic liver disease is a problem for all of us. It develops silently, often taking many years to cause sufficient damage to be detectable or cause signs or symptoms for which a patient would seek attention. Primary care has a central role in improving the prevention and early detection of chronic liver disease. This special issue of the British Journal of Primary Care Nursing (BJPCN) and Primary Care Cardiovascular Journal on chronic liver disease is full of step-by-step guides and informative articles to give you the key information and tools to get to grips with this important condition.

Training and education for health professionals, which historically has taken place in secondary care, tends to concentrate on the advanced spectrum of chronic liver disease, including cirrhosis and its subsequent complications of liver failure, variceal haemorrhage or hepatocellular carcinoma. Yet a lot of chronic liver disease is either preventable or its progression can be interrupted if only we could detect it earlier.

The emergence of health checks at 40-74 years, and emphasis on early detection of cancer provide some opportunities for primary care to detect liver disease at an earlier stage, particularly with the ubiquitous use of liver function tests (LFTs). However, there are two problems with this approach: the first is understanding how LFTs relate to liver disease at all and what should be done about it, and the second is that liver disease and its consequences are now appearing in younger age groups that do not often access primary care services.

Conversely, younger people who may have early signs of liver disease, or other subgroups who tend not to access ‘regular’ services, often present themselves with an unrelated acute episode to secondary care, where LFTs are often measured and found to be abnormal but no follow through is arranged. The cause of the abnormal LFTs is often obvious, and increasingly is due to fatty liver disease due to obesity or alcohol, but not always, so further tests must be done to exclude those particular liver diseases for which treatment is available (see the guide to LFTs on page 31 to help with this). For the remainder of people, our attitudes will need to adapt to the fact that we need to continually reinforce lifestyle messages over many years if we are to prevent progression to cirrhosis. This requires a robust system to monitor liver tests so that any signs of advanced disease can be detected, and a resilient workforce who will not give up on their patients (see Bev Bostock-Cox’s article on page 6 on how to monitor chronic liver disease) and will support them in lifestyle changes to reduce disease progression (see Andrew C’Shaughnessy’s article on page 35 on how to help patients reduce alcohol intake).

This special edition of BJPCN and PCJ is designed to help you face the challenges of liver disease in your practice. Browse or read at your own pace but we want you to understand the main causes of liver disease, how to spot patients at risk, what elevations of liver enzymes mean, why they are important in prompting you to check for specific liver diseases, the key functions of the liver, which function tests to monitor and how to prevent and treat liver disease effectively.

The back to basics annotated diagram (see page 22) provides a pictorial guide to the many essential functions the body carries out to keep the body healthy. And a second back to basics (see page 24) explains what goes wrong in chronic liver disease.

We would like you to appreciate that you can make a big difference not only to the patients you will see with liver disease but in a wider context to their relatives, friends and contacts by helping people to be more aware that they need a healthy liver for a healthy life!

“Primary care has a central role in improving the prevention and early detection of chronic liver disease”
Mortality rates at age 35-59 years for cirrhosis and selected other diseases: UK, 1952-2009

For Men:
- Lung cancer
- Stroke
- Cirrhosis
- Coronary heart disease

For Women:
- Coronary heart disease
- Breast cancer
- Stroke
- Cirrhosis
Liver Disease by Country.

**Men aged 45-64 years**

**Women aged 45-64 years**

Source: http://www.scotland.gov.uk/Topics/Health/health/Alcohol/health/chronic-liver-disease 2010
Movements in mortality 1971-2007
Deaths per million of population

% change vs 1971

Liver
Diabetes
Cancer
Respiratory
Road
Heart
Stroke
Chronic liver disease in Scotland: key points

• There are a variety of risk factors and diseases that cause chronic liver disease (CLD). The three commonest risk factors for CLD are excessive alcohol consumption; blood borne viruses, in particular Hepatitis B and C, and obesity.

• Between 1989 and 2010, there has been an approximate three-fold increase in chronic liver disease patient discharge rates in men, and a two-fold increase in rates among women.

• Men living in the most deprived areas are 12 times more likely to die from CLD and for women seven times more likely, than those living in least deprived areas.

• The CLD mortality rate in Scotland has been increasing steadily over the last 30 yrs which is in contrast to the majority of European countries where CLD death rates have been decreasing.

http://www.scotpho.org.uk/health-wellbeing-and-disease/chronic-liver-disease/key-points
Due to delivery error I regret to inform that this shop has no Buckfast at all. Please do not abuse the staff as it is not their fault. Thanks.
Chronic liver disease mortality rates (age-standardised, aggregated data for 2005 to 2009) in Scotland, by gender and SIMD decile

(Source: NRS; 1 = most deprived, 10 = least deprived; standardised to European population)

Increasing deprivation
Death rates chronic liver disease per LA

- **Stirling**
- **Falkirk**
- **Clackmannanshire**

Graphs showing EASR per 100,000 individuals for males and females from 1992-94 to 2008-10.
The liver

Superbly designed to maintain body’s chemical and metabolic homeostasis
Acute or Chronic Liver Disease

**Acute hepatitis** usually self-limiting – viruses, toxins, drugs

**Chronic hepatitis** – if changes persist for over 6 months

If continuing damage
– with cellular destruction
leads on to fibrosis and cirrhosis

**Chronic liver disease**
The challenge is to

- diagnose liver disease at an early stage
- determine aetiology
- modify disease if possible
- monitor and treat symptoms
- proactively deal with complications
Liver Function Tests

- **AST/ALT, GGT, Alk Phos**
  “Liver injury tests”
  Not a true reflection of hepatic functional reserve / capacity

- **PT, Fibrinogen, Albumin**
  Synthetic function -

- **Bilirubin**
  Excretory function
## Liver Function Tests

**Table 1: Key biochemical markers in hepatic systems and function**

<table>
<thead>
<tr>
<th>System or function</th>
<th>Marker</th>
<th>Site or significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte integrity</td>
<td>Aspartate aminotransferase</td>
<td>Liver, heart skeletal muscle, kidney, brain, red blood cell</td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase</td>
<td>Liver</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Alkaline phosphatase</td>
<td>Bone, intestine, liver, placenta</td>
</tr>
<tr>
<td></td>
<td>(\gamma)-Glutamyl-transpeptidase</td>
<td>Correlated levels with alkaline phosphatase indicate hepatobiliary origin</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>Elevations may indicate hepatic or extrahepatic disorder</td>
</tr>
<tr>
<td>Liver function mass</td>
<td>Serum albumin</td>
<td>Diet or liver</td>
</tr>
<tr>
<td></td>
<td>Prothrombin time</td>
<td>Liver synthesizes vitamin K-dependent clotting factors</td>
</tr>
</tbody>
</table>
In view of the statistical phenomenon of regression to mean, the principle of interval retesting to establish one-off from stable and progressive increases seems sound.

There is guidance, but limited evidence, on retesting intervals, although in the asymptomatic context and in view of the slow time course of the potential underlying diseases, the retesting interval of months rather than weeks seems reasonable for minor increases, commonly described as up to 3–5 times the upper limit of normal (ULN).

Indications for further investigation of persistent rises commonly refer to 1.5 x ULN.
Chronic liver disease with normal LFT’s
Is the normal range for tests for patients correct?

• Decrease in AST / ALT during treatment suggesting mild inflammation within normal range of test
How to determine severity of chronic liver disease

• **Liver biopsy** - Gold Standard - tells us as it is?

• **Bilirubin** - 
  Late change hepatocellular - can be normal till cirrhosis -
  Earlier change cholestatic

• **AST /ALT** - not always helpful guide to severity
  can be normal, intermittently raised or high

• **Alk Phos** - as bilirubin - can be normal throughout or early rise

• **Albumin** - progressive fall as liver damage more severe

• **PT / Clotting screen** - progressive rise as liver deteriorates

• **Platelets** - gradual fall as increasing cirrhosis
  as portal hypertension develops, spleen enlarges, fewer platelets

• **Hb / WCC** as spleen continues enlarging - drop in Hb, WCC
How to determine severity of chronic liver disease

- **Imaging**
  - **Ultrasound** can show coarse echotexture, fatty change, irregular liver edge, presence of ascites, varices, tumours
  - liver may be enlarged, normal or small
  - spleen tends to enlarge
  - **CT / MRI** - more information, more detail

- **Fibroscans** - measure of stiffness of liver
  - increased values with increasing fibrosis
  - Good at confirming normal liver or significant fibrosis cirrhosis but not as accurate in middle ground - mild to moderate fibrosis - problems if obese

- **“Fibrotests”** in-house or commercial kits - panel of serum markers used to produce an overall value of fibrosis
Jacob Jordaens, Der gefesselte Prometheus, um 1640
Investigation of an isolated rise in Bilirubin 1

Isolated increase in Bilirubin >25 (>1.5xULN)

Repeat test after 12hr fast
And check conjugated / unconjugated split
FBC and Film

Post fasting
if significant increase in Bilirubin
(up to 70umol/l )
predominantly unconjugated Diagnosis
is Gilberts Syndrome - reassurance and
no further Ix needed

Post fasting
if no increase in Bilirubin
But predominantly unconjugated consider
haemolysis or haematoma breakdown
Check FBC, blood Film
Reticulocytes and LDH

Check for potential Drug induced Liver Injury
If minor rise < 2xULN (34) recheck all LFT’s in 3months
If significant rise >2xULN recheck 1 month

Post fasting
if no increase in Bilirubin
but predominantly conjugated
Look for other evidence of
compensated chronic liver disease

Check for potential Drug induced Liver Injury
If minor rise < 2xULN (34) recheck all LFT’s in 3months
If significant rise >2xULN recheck 1 month

* Bilirubin Rising
Organise Abdo U/S
Check initial Liver screen

* Bilirubin falling
Repeat in 3 months then 6 months

Abdo-U/S Abnormal
Dilated Ducts
Abnormal liver mass
Urgent referral to
GI Medicine

Abdo U/S Normal
Await rest of results
And routine referral to
GI Medicine

Bilirubin normal
No further action
Investigation of Isolated Raised Alkaline Phosphatase 2

Rule out pregnancy, young age, post-prandial increase

If not already performed - check GGT

GGT Normal
- ALP likely bone origin
  - Test for bone disorders

GGT Increased
- ALP likely liver origin
  - Check for potential Drug induced Liver Injury
    - If minor rise < 2xULN (240) recheck 3 months
    - If significant rise > 2xULN recheck 1 month

ALP static or rising
- Organise Abdo U/S
  - Check initial liver screen
  - Abdo-U/S Abnormal
    - Dilated Ducts
    - Abnormal liver mass
    - Urgent referral to GI Medicine

ALP falling
- Repeat in 3 then 6 months

Fluctuating ALP
- But remains abnormal after 6 months
  - Abdo U/S Normal
    - Await rest of results, if abnormal perform extended liver screen and sent routine referral to GI Medicine
Causes of raised γ GT

**Hepatobiliary disease**
(often with other liver enzyme abnormalities).

Pancreatic disease.

Alcoholism (Sensitivity only 52-92% - low Specificity)

Chronic obstructive pulmonary disease.

Renal failure.

Diabetes.

Myocardial infarction.

**Drugs**
Enzyme inducers - eg, carbamazepine, phenytoin and barbiturates.
Serum aminotransferase levels in various liver diseases

- Acute on chronic alcoholic liver disease
- Liver cirrhosis
- Chronic hepatitis
- Autoimmune hepatitis
- Acute viral hepatitis
- Ischemic or toxic liver injury

Aminotransferase level, IU/L

Reference range
Non alcoholic fatty liver disease - NAFLD
NASH - non-alcoholic steatohepatitis

- Rapidly becoming disease of 21st century
- Metabolic syndrome – obesity, diabetes, IHD
“Patients with confirmed liver test abnormalities due to known significant alcohol excess, fatty liver or drug induced liver injury (eg statins) provided the appropriate algorithms and investigations detailed above have been followed, can be managed appropriately and safely within primary care.”

Importance of social / medication history
Investigation of Isolated Raised Transaminases 3

Isolated increase in AST/ALT

**Advise stop alcohol**
- Check for and stop any recently initiated hepatotoxic drugs
- Advise **stop all** over the counter herbal/alternative products
- If BMI > 25 or recent increase in wt - advise loss of 2-5kg
- Discuss if high risk - current/previous drug misuse/partner of drug misuser/from high prevalence area - check BBV
  - If <2xULN (<80) - recheck in 6 months
  - If >2xULN (>80) - recheck in 3 months
  - If >3xULN (>120) - recheck in 1 month

If persisting degree of abnormality or rising values at repeat testing
- Reinforce above advice
- Organise Abdo U/S
  - Examine for signs of liver disease
  - Check Initial Liver screen

If falling values at repeat test
- Repeat in 6-12 months

Abdo U/S - Abnormal
  - Dilated Ducts
  - Abnormal liver mass
  - Urgent referral to GI Medicine

Abdo U/S normal or abnormal texture
  - Initial liver screen positive
  - Send off extended liver screen as appropriate to clarify abnormality
  - And routine referral to GI Medicine

Abdo U/S Normal or fatty liver only
  - Initial liver screen negative - Reinforce advice re stopping alcohol/Drug/herbal meds, losing wt
    - If <2xULN (<80) - recheck in 6 months
    - If >2xULN (>80) - recheck in 3 months
    - If >3xULN (>120) - recheck in 1 month
  - if still abnormal - and full compliance with advice above
  - Consider routine referral to GI Medicine
  - See Triage pathway 6

Abdo U/S abnormal texture
  - Initial liver screen negative
  - Send off extended liver screen as appropriate
  - And routine referral to GI Medicine
Investigation of cluster of Abnormal LFT’s 4

**Predominantly Hepatocellular picture**
- Predominant increase in AST/ALT
- With raised GGT and +/- minor rise in Bil and ALP

**Predominantly Cholestatic picture**
- Predominant increase in Alkaline Phosphatase with elevated GGT +/- bilirubin and +/- minor rise in AST/ALT

**Advise stop alcohol**
- Check for and stop any recently initiated hepatotoxic drugs
- Advise **stop all** over the counter herbal /alternative products
- Discuss if high risk - current / previous drug misuse /partner of drug misuser /from area high prevalence - check for BBV
- Examine for signs of liver disease
  - If most deranged test <2xULN - recheck in 3 months
  - >2xULN - recheck in 2 months
  - >3xULN - recheck in 1 month

**Abdo U/S - Abnormal**
- Dilated Ducts
- Abnormal liver mass
- Urgent referral to GI Medicine

**Abdo U/S Normal or fatty liver only**
- Initial liver screen negative - Reinforce advice re stopping alcohol / Drug / herbal meds, losing wt
- If most deranged test <2xULN - recheck in 6 months
- If >2xULN - recheck in 3 months
- If >3xULN - recheck in 1 month
- if still abnormal - and full compliance with advice above
- Consider routine referral to GI Medicine
- See Triage pathway 6

**If falling values at repeat test**
- Repeat in 3 - 6 months

**Abdo U/S normal or abnormal texture**
- Initial liver screen positive
- Send off extended liver screen as appropriate to clarify abnormality
- And routine referral to GI Medicine

**If persisting degree of abnormality or rising values**
- Request abdo ultrasound and initial liver screen
- If rapidly deteriorating tests discuss with GI on Call
Follow previous algorithms to classify liver abnormality

If concerned about patient or with rapidly deteriorating condition
Discuss directly with consultant GI Medicine on Call via Switchboard FVRH

If evidence of significant alcohol excess or NAFLD (Fatty liver) and receptive to following lifestyle advice to address health issues. Only refer if adherent to advice with no improvement in LFT’s Routine referral via SciGateway to gastroenterology (A9)

If significant chronic Alcoholic liver disease or NAFLD (Fatty liver disease) Routine referral via Sci Gateway to gastroenterology (A9)

If evidence of Viral Hepatitis, genetic liver disease or autoimmune liver disease Routine referral via Sci Gateway to gastroenterology (A9)

If no clear diagnosis but persistent LFT abnormalities and monitored over time interval as per algorithms Routine referral via Sci Gateway to gastroenterology (A9)

Outside office hours in ill patient consider inpatient assessment via CAU

Emergency GI clinics for urgent OP referrals held twice week accessed via GI consultant on Call and Sci Gateway

If cholestatic jaundice with or without pain in a patient with no evidence of alcohol misuse. Discuss directly with Dr Dalziel's Sec for referral to the FastTrack Jaundice Pathway. For Urgent OP referral for rapid access to U/S and ERCP

Patients will be triaged by consultant on call to First available GI consultant routine OP slot

Patients will be triaged by consultant on call to First available Hepatology Service routine OP slot. Viral Hepatitis patients will be fast tracked to a Nurse Led assessment and harm reduction clinic

Patients will be triaged by consultant on call to First available GI consultant routine OP slot
FV Hepatology Service

• Based at Stirling Community Hospital
  clinics provided in FVRH, SCH, CCH, SPS, Addictions

• Previously the FV Hepatitis Service
  One consultant, three specialist hepatitis nurses, patient pathway co-ordinator, ( + medical secretary in FVRH)

• Now development of generic Hepatology nurse specialists
  Nurse led - Virtual Hepatoma screening clinics
  Administrator led - Varices recall databases
  Nurse led - Haemochromatosis maintenance clinics
  Nurse led - outreach HCV / HBV / Hepatology clinics
  Five consultant clinics per week

• Tasked to deliver on Government directives
• Respect and Responsibility / BBV/SH Framework / HIS Hepatitis Standards
• Sexual Health / HIV integration
Screening for significant fibrotic chronic liver disease

AST/ALT ratio = AST / ALT

• When greater than 2.0, it is more likely to be associated with 
  alcoholic hepatitis or hepatocellular carcinoma
• When greater than 1.0 but less than 2.0, it is likely to be associated with cirrhosis
• It is normally less than 1.0 with chronic hepatitis C and often becomes greater than 1.0 in cirrhotic HCV
• However, the AST/ALT ratio is less useful in scenarios where the liver enzymes are not elevated, or where multiple conditions co-exist
1-Recommendation: Clinicians should be aware that a minority of people with abnormal LFTs will have no liver disease. Evidence grade B.

2-Recommendation: Clinicians should be aware that normal LFTs do not mean an absence of significant liver disease. Evidence grade B.

3-Recommendation: Clinicians should be aware that the majority of asymptomatic patients with abnormal LFT’s will have liver disease and a proportion will have significant liver damage (fibrosis or cirrhosis). Evidence grade B.

4-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. Evidence grade B.

5-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. Evidence grade B.

6-Recommendation: Any degree of LFT abnormality should be considered for investigation as even minor abnormalities can be associated with significant liver disease. Evidence grade B.

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

8-Recommendation: The following tests comprise the initial liver screen and the subsequent more detailed extended liver screen
Initial ‘liver screen’
should include
Hepatitis Screen (hepatitis B surface antigen, hepatitis C antibody),
liver autoantibody screen (anti-mitochondrial antibody, anti-smooth muscle
antibody), anti-nuclear antibody (ANF), serum immunoglobulins,
serum ferritin, Thyroid function tests (TFT’s),
full clotting screen.
Also request Abdominal U/S

Extended ‘liver screen’
should include Tissue Transglutaminase (TTG) for coeliac disease
Anti-Neutrophil Cytotoxic Antibody (ANCA)
ceruloplasmin, *
α1 antitrypsin level *
Alpha Fetoprotein

✦ if HBV sAg positive - labs should check other HBV markers and Hep B DNA load
✦ If Ferritin raised above ULN range check Serum Iron / Total Iron Binding Capacity (Fe/TIBC) =
  transferrin Sat% If Transferrin Sat% above 55% male or 50% female -
  check HFE (haemochromatosis) gene assay
✦ If Ceruloplasmin below 0.15g/l - on referral Hepatology will organise 24hr urinary
copper excretion and ophthalmology review for Kayser Fleischer rings
Statins and Abnormal Liver function - for info -
Not really applicable to protocol as LFT monitoring following introduction of drug

0.5 to 3.0 percent occurrence of persistent elevations in aminotransferases in patients receiving statins. This occurs during the first three months of therapy and is dose-dependent. Several large trials with over 100,000 patient years of exposure have not shown any significant difference in the incidence or severity of persistently raised AST/ALT between statin and placebo treatment. A meta-analysis of 35 randomized trials found an excess risk of aminotransferase elevation with statin therapy versus placebo of 4.2 cases per 1000 patients. Rare episodes of more severe liver injury have also been seen, these predominantly occur three to four months after initiation of statin therapy. However, it appears these are sufficiently uncommon that overall the incidence of drug induced liver failure in patients taking statins appears to be no different from the low incidence in the general population.

US based knowledge base - UptoDate 2012 recommend changing medications or lowering the statin dose in patients who are found to have an alanine aminotransferase (ALT) level more than three times the upper limit of normal (>120 iu/ml), that is confirmed on a second occasion. The NHS Evidence Clinical Knowledge Summary 2012 - states that if liver function test’s are abnormal while on a statin: If less than three times the upper limit of normal: - Continue the statin, but recheck LFTs within 4–6 weeks to exclude further increases in transaminase levels. - No extra monitoring is required if values are stable. If transaminase levels are three times the upper limit of normal or more:- Stop the statin and recheck LFTs within 4–6 weeks to ensure that values settle (consider re-introducing the statin cautiously at a later date) or Reduce the statin dose and recheck LFTs within 4–6 weeks: Stop the statin if transaminase levels continue to be three times the upper limit of normal or more.

In Forth Valley we suggest that if there is no improvement to dose modification, then perform an initial liver screen, then if necessary, an extended liver screen should be carried out as per abnormal transaminase pathway above.