Management of persistent minor elevations of ALT in adults

Definition
This guideline is directed towards an ALT that is raised, but less than three times the upper limit of normal, for greater than 3-6 months.

Minor transient elevations of ALT are common (up to 9% of asymptomatic patients) and to investigate all would expose patients to unnecessary investigation not to mention the cost burden. However, we do not want to miss those with early stages of treatable liver disease so guidelines suggest investigating if ALT is still raised after 3-6 months. Unfortunately the level of ALT does not correlate with the degree of liver disease so those with even minor elevations need investigating with a non-invasive liver screen (NILS).

This guideline only applies to isolated ALT elevations in asymptomatic patients. Those who have risk factors for chronic liver disease or symptoms should be managed according to the clinical presentation.

First ALT elevation
1. Assess patient to exclude any causes of acute hepatitis (including hepatitis A, glandular fever, medications, alcohol or paracetamol OD)
2. Assess medical history and symptoms (relevant co-morbidities such as malignancy or CCF)
3. Assess risk factors for chronic liver disease (IVDA, multiple sexual partners, high risk sexual behaviour, tattoos, non-sterile body piercing, transfusions, alcohol abuse, diabetes, obesity, hyperlipidaemia, autoimmune disease, IBD, travel or family history liver disease)
4. In low risk, asymptomatic patient repeat LFT in 3 months.
5. In the meantime it is important to address lifestyle issues including alcohol and metabolic features such as diet, weight, lipids and diabetes.
6. Do not stop statins unless ALT>X3 URL, or methotrexate unless ALT>X2.5 URL.
7. If risk factors, symptoms or clinical concern repeat LFT’s sooner or according to presentation.

Second ALT elevation
1. Consider investigations even if suspected alcohol abuse or presumed Non-alcoholic fatty liver disease (NAFLD).
2. A non-invasive liver screen (NILS) is indicated. This includes a liver ultrasound.

Non-invasive liver screen (NILS)

<table>
<thead>
<tr>
<th>ALL PATIENTS</th>
<th>PATIENTS WITH RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT</td>
<td>Alpha 1 antitrypsin</td>
</tr>
<tr>
<td>Clotting</td>
<td>Caeruloplasmin (under 40 year olds)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
</tr>
<tr>
<td>Fasting lipids</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
</tr>
<tr>
<td>Autoimmune profile</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td></td>
</tr>
<tr>
<td>Hepatitis serology</td>
<td></td>
</tr>
<tr>
<td>Liver ultrasound</td>
<td></td>
</tr>
</tbody>
</table>
NAFLD
NAFLD may be diagnosed when there is a negative liver screen and no history of alcohol excess in conjunction with;
Fatty liver seen on ultrasound plus 1 of the following;
   - Obesity
   - Impaired fasting glucose or Type 2 Diabetes Mellitus
   - Hypertension
   - Dyslipidaemia

NAFLD is increasingly common with 20% of the population estimated to have NAFLD and up to 70% of the obese and diabetic population. It is not always a benign disease. Up to 5% have steatohepatitis and can progress to liver fibrosis. Therefore, it is essential to actively manage these patients and repeat LFT’s at 3 monthly intervals for the first year to establish that there is no progression. It is also important to refer to the appropriate department if there are difficulties in managing any of the metabolic features such as the diabetes or lipid clinics.

General measures
- Weight loss by a combination of moderate calorie restriction and increased exercise aiming to lose 10% of body weight. More rapid weight loss may exacerbate liver damage.
  Diet should consist of a low saturated fat, “heart healthy” diet or standard diabetic diet if indicated.
- Smoking cessation
- Current recommended “sensible” alcohol limits (Men up to 21 units weekly, Women up to 14 units weekly)
- In Type 2 diabetic patients tight glycaemic control with metformin is recommended since this has been shown to reduce the risk of diabetes-related microvascular complications and death and all-cause mortality. Treatment with metformin may also be beneficial to the liver.
- Use statins for conventional indications including Type 2 diabetes and cardiovascular risk >20% over 10 years. There is no evidence that patients with NAFLD are at greater risk from statin-induced hepatotoxicity
  Consider using a fibrate first line if isolated raised triglycerides 5-10 mmol/l.
  Refer Lipid Clinic if triglycerides > 10mmol/l.
- Look for and treat hypertension particularly in patients with type 2 DM. Consider ACE Inhibitors or A2RA’s as first line therapies for hypertensive patients with NAFLD.

Referral
Patients should be referred to hepatology if;
   1. Persistent ALT >3x upper limit of normal
   2. INR raised
   3. No improvement in ALT after 12 months

Patients who do not meet NAFLD criteria
Patients who have a negative liver screen without fatty liver found on ultrasound OR have no additional metabolic features are less likely have severe fatty liver and LFT’s can be monitored annually. They should be referred if their ALT rises above 3 times the upper limit of normal or if they have a raised INR.
Raised ALT <3X URL

Stop Alcohol, review drugs
Recheck LFT’s in 3 months
If ALT remains abnormal, investigations are warranted.
Prioritise if risk factors for liver disease are present.

Non-invasive liver screen
Viral serology [HBV, HCV, HAV]
Autoimmune profile, immunoglobulins
Ferritin
Fasting lipid profile and glucose
Prothrombin time
USS Liver
If appropriate
Alpha-1-antitrypsin
Caeruloplasmin / copper [<40 years]

Discuss or Refer as appropriate if:
1. Abnormal investigations other than glucose, lipids or fatty liver on USS
2. Clinical suspicion chronic liver disease despite normal investigations

Probable NAFLD
USS suggestive of fatty liver
Alcohol intake within recommended limits and 1 or more of the following:
- Obesity
- Impaired fasting glucose or T2DM
- Hypertension
- Dyslipidaemia

Treat metabolic syndrome:
Lifestyle measures
Metformin for T2DM
Statins / fibrates if indicated
Control of blood pressure

Recheck LFT’s and prothrombin time at 3 months, 6 months then annually
Consider diabetic clinic referral if poor glycaemic control. Consider lipid clinic referral

Refer if:
- No improvement in ALT after 12 months
- ALT > 3X URL or abnormal PTT.

Raised ALT

ALT>3X URL on 2 separate occasions. Stop alcohol and hepatotoxic drugs.
Refer to hepatology

NAFLD criteria not met
Monitor LFT’s annually and refer if ALT >3X URL.
References:

1. Chalsani et al. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004: 128 1287-1292

2. Chalsani N. Statins and hepatotoxicity: Focus on patients with fatty liver. Hepatology Vol 41 No 4 April 2005

3. Tolman K. The Liver and Lovastatin. American Journal of Cardiology Vol 89;1374-1380


8. NHLBI-NIDDK Clinical Guidelines on the identification, evaluation and treatment of overweight and obese adults


10. AGA Technical review on NAFLD. Gastroenterology; 2002; 123: 1705-25


