Continued elevation of liver tests following HCV Eradication

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Objectives

• Define what true normal ranges are and what levels are safe to monitor

• Demonstrate a stepwise approach to elevated liver tests based on pattern of injury and degree of elevation

• Identify tests indicated for common causes of elevated liver tests
Pre DAA era

• Everyone underwent work up for other causes of liver disease
  • Autoimmune hepatitis in particular
• Everyone underwent a liver biopsy
DAA era

• Noninvasive fibrosis staging
  • Limiting factor – no path

• Liver tests elevated but in line with HCV infection
  • Wait and reassess following eradication

• **What levels are safe to monitor?**
  • Borderline elevations \( \leq 2 \times \text{ULN} \)
  • Mild elevations 2-5 \times \text{ULN}
    • Moderate elevations 5-15 \times \text{ULN}
  • Severe elevations >15 \times \text{ULN}
  • Massive elevations ALT >10,000 U/L
When and how often should you monitor liver tests following treatment?

• From the AASLD simplified guidelines for non cirrhotics
• Post-Treatment Assessment of Cure (SVR)

• Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.

• Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.
True normal values for transaminase

• Female below 20-25
• Male below 30-35
I checked them at SVR 12 and they are still elevated!

- What is the pattern of injury
- What is the degree of injury
- HBcAb positive?
- Any ongoing alcohol use?
- Metabolic syndrome?
- Concerning medications or supplements?
- Toxins?
Causes of elevated transaminase elevations (hepatocellular injury)

- AST > ALT
  - Alcohol
  - Cirrhosis
  - Congestive hepatopathy
  - Ischemic hepatitis

- ALT > AST
  - Steatotic liver disease (SLD)
  - Viral hepatitis
  - Medications/supplements
  - Toxins
  - Hemochromatosis
  - Autoimmune hepatitis
  - Wilsons Disease
  - Alpha 1 antitrypsin deficiency
Non hepatic causes of elevated transaminase

- Skeletal muscle damage
- Cardiac muscle damage
- **Thyroid disease**
- Hemolysis
New nomenclature for NAFL

• Metabolic dysfunction – associated steatotic liver disease (MASLD)
• Metabolic dysfunction-associated steatohepatitis (MASH)
• MetALD – MASLD with alcohol overuse (140 g/week and 210g/week for females and males respectively)
Steatotic Liver Disease Sub-classification

Steatotic Liver Disease (SLD)

- Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)
- MetALD (MASLD and increased alcohol intake*)
  - MASLD predominant
  - ALD predominant
  - Weekly alcohol intake (g)
    - 140/210
    - 210
    - 280
    - 350/420
  - Average daily alcohol intake (g)
    - 20/30
    - 30
    - 40
    - 50/60
- Alcohol-Associated (Alcohol-related) Liver Disease (ALD)
- Specific aetiology SLD
- Cryptogenic SLD
  - Drug-Induced Liver Injury (DILI)
  - Monogenic diseases**
  - Miscellaneous***

*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinaemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

This depicts the schema for Steatotic Liver Disease (SLD) and its sub-categories. SLD, diagnosed histologically or by imaging, has many potential etiologies. MASLD, defined as the presence of hepatic steatosis in conjunction with one CMRF and no other discernable cause, ALD, and an overlap of the two (MetALD), comprise the most common causes of SLD. Within the MetALD group there exists a continuum across which the contribution of MASLD and ALD will vary. To align with current literature, limits have been set accordingly for weekly and daily consumption, understanding that the impact of varying levels of alcohol intake are evolving. Other causes of SLD need be considered separately, as is already done in clinical practice, given their distinct pathophysiology. Multiple etiologies of steatosis can coexist. If there is uncertainty and the clinician strongly suspects metabolic dysfunction despite the absence of CMRF then the term possible MASLD can be considered pending additional testing (e.g., HOMA-IR, OGTT). Those with no identifiable cause (cryptogenic SLD) may be recategorized in the future pending developments in our understanding of disease pathophysiology. Lastly, the ability to provide an affirmative diagnosis allows for the coexistence of other forms of liver disease with MASLD, e.g., MASLD + autoimmune hepatitis or viral hepatitis.

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Autoimmune hepatitis

- Anti-nuclear antibody (ANA)
- Smooth muscle antibody (ASMA)
- Immunoglobulin G total (IgG total)
Hemochromatosis

- Ferritin
- Iron panel (want iron sat)
- Ferritin elevated or iron sat over 45%
  - HFE gene mutation analysis
    - C282Y homozygotes
Alpha 1 antitrypsin deficiency

• Alpha 1 antitrypsin level
  • Low check genotype (PiZZ and PiMZ)
Wilson's disease

- Ceruloplasmin
  - Low then get 24 hour urine copper, serum copper, slit lamp exam for Kayser-Fleischer rings
ACG Guideline for the work up for borderline to mild transaminase elevations

<table>
<thead>
<tr>
<th>Borderline elevation</th>
<th>Mild elevation</th>
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<tbody>
<tr>
<td>&lt;2x ULN</td>
<td>2-5x ULN</td>
</tr>
</tbody>
</table>

### Borderline elevation:

- History and physical exam
- Discontinue hepatotoxic meds
- Discontinue alcohol consumption
- Assess for risk factors for fatty liver and viral hepatitis

- CBC/platelet count, AST/ALT, Ak Phos, TB, albumin, PT/INR
  - HBsAg, HBcAb, HBeAb, HCV Ab with PCR confirmation if +, iron panel, abdominal ultrasound

- If negative, consider observation for 3–6 months with repeat AST/ALT, Ak Phos, TB or ...

- If persistently elevated, continue investigation: ANA, ASMA, gamma-globulin, ceruloplasmin, alpha-1 antitrypsin phenotype and may consider additional tests based on history (e.g., celiac sprue, tick-borne disease, thyroid disease, and muscle disorders)

- If normal, further testing at discretion of clinician or refer to hepatologist for consideration of liver biopsy

### Mild elevation:

- History and physical exam
- Discontinue hepatotoxic meds
- Discontinue alcohol consumption
- Assess for risk factors for fatty liver and viral hepatitis

- CBC/platelet count, AST/ALT, Ak Phos, TB, albumin, PT/INR
  - HBsAg, HBcAb, HBeAb, HCV Ab with PCR confirmation if +, iron panel
  - Abdominal ultrasound

- If negative, consider observation for 3 months with repeat AST/ALT, Ak Phos, TB or continue investigation

- If persistently elevated, continue investigation:
  - ANA, ASMA, gamma-globulin, ceruloplasmin, alpha-1 antitrypsin phenotype and may consider additional tests based on history (e.g., celiac sprue, tick-borne disease, thyroid disease and muscle disorders)
  - If no diagnosis, consider diagnostic liver biopsy
# ACG guidelines for moderate transaminase elevations

<table>
<thead>
<tr>
<th>Moderate elevation</th>
<th>5-15x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical exam</td>
<td></td>
</tr>
<tr>
<td>Discontinue hepatotoxic meds and alcohol</td>
<td></td>
</tr>
<tr>
<td>Evaluate for signs of acute liver failure</td>
<td></td>
</tr>
<tr>
<td>CBC/platelet count, AST/ALT, Alk Phos, TB, albumin, PT/INR, HAV IgM, HAV IgG, HBsAg, HbcAb IgM, HbcAb IgG, HBsAb, HCV Ab with PCR confirmation if +, iron panel, ceruloplasmin, ANA, SMA, and gamma-globulin</td>
<td></td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td></td>
</tr>
<tr>
<td>If signs of acute liver failure --&gt; urgent liver consultation with consideration of referral to a liver transplant center</td>
<td></td>
</tr>
<tr>
<td>If diagnostic evaluation negative --&gt; consideration for diagnostic liver biopsy if medically stable</td>
<td></td>
</tr>
</tbody>
</table>
ACG Guidelines for severe and massive transaminase elevations

**Severe elevation**

- ALT > 5x ULN

  - History and physical exam
  - Discontinue hepatotoxic meds and alcohol
  - Evaluate for signs of acute liver failure

  - CBC/platelet count, AST/ALT, A1C, albumin, PT/INR, HAV IgM, HBsAg, HBeAg, HBV, HCV, HCV Ab, HSV, EBV, CMV, ceruloplasmin, ANA, ASMA, Anti-LKM, IgG, serum drug panel, and urine toxicology panel
  - Consider n-acetyl cysteine if any evidence of acetaminophen ingestion

  - If signs of acute liver failure -> urgent liver consultation with consideration of referral to a liver transplant center

  - If diagnostic evaluation negative -> consideration for diagnostic liver biopsy if medically stable

**Massive elevation**

- ALT > 10,000 ULN

  - History and physical exam
  - Discontinue hepatotoxic meds and alcohol
  - Assess for toxic ingestions, ischemia, and rhabdomyolysis
  - Evaluate for signs of acute liver failure

  - CBC/platelet count, AST/ALT, A1C, albumin, PT/INR, HAV IgM, HBsAg, HBeAg, HBV, HCV, HCV Ab, HSV, EBV, CMV, ceruloplasmin, ANA, ASMA, Anti-LKM, IgG, serum drug panel, and urine toxicology panel
  - Doppler abdominal ultrasound
  - Consider n-acetyl cysteine if any evidence of acetaminophen ingestion

  - If signs of acute liver failure -> urgent liver consultation with consideration of referral to a liver transplant center

  - If diagnostic evaluation negative -> consideration for diagnostic liver biopsy if medically stable
Causes of elevated alk phos

- **Hepatobiliary**
  - Choledocholithiasis
  - Malignancy (obstruction of infiltration)
  - Bile duct fluke
  - Primary sclerosis cholangitis (PSC)
  - Primary Billiary cholangitis (PBC)

- **Medications**
  - Infiltrative
    - Sarcoidosis
    - Amyloidosis
    - TB
  - Viral hepatitis

- **Cirrhosis**

- **Alcohol**

- **CHF**

- **Non hepatic causes**
  - Bone disease
  - Hyperthyroid
  - Chronic renal failure
  - Gastric ulcer
  - Blood type O and B
  - Extrahepatic malignancy
  - Influx of alk phos after a fatty meal
Isolated alk phos elevation?

• Alk phos isoenzymes vs GGT
  • Isoenzymes provide origin
  • GGT – also elevated with alcohol overuse
PBC

• Antimitochondrial antibody
• Immunoglobulin M total (IgM total)
PSC

- No specific serologies
- Diagnosed with MRCP or ERCP
**Figure 4.**

Algorithm for evaluation of elevated serum alkaline phosphatase.

Kwo, Paul Y; Cohen, Stanley M; Lim, Joseph K
doi: 10.1038/ajg.2016.517
Causes of elevated bilirubin

• Unconjugated
  • **Gilberts syndrome**
  • Crigler-Najjar syndrome
  • **Hemolysis**
  • **Medications**
  • Hyperthyroidism

• **Conjugated**
  • **Bile duct obstruction**
  • Bile duct stricture
  • Viral hepatitis
  • **Medications**
  • Cirrhosis
  • **PSC**
  • **PBC**
  • **Infiltrative disease**
  • **Malignancy**
  • Wilsons
  • Autoimmune hepatitis
  • **Dubin-Johnson syndrome**
  • Rotor Syndrome
Figure 5.

Algorithm for evaluation of elevated serum total bilirubin.

Kwo, Paul Y; Cohen, Stanley M; Lim, Joseph K

doi: 10.1038/ajg.2016.517