The Primary Care Physician’s Approach to Abnormal Liver Tests
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Objectives
- Define LFT’s
- Define Pattern of Liver Injury
- Review Common LFT’s
- Identify what tests are appropriate in different patients with elevated liver tests
- Cost
- Questions
Case Presentation

Mr. Steel is a 59 year old male that presents for wellness exam. He has not followed with a physician for over 10 years. He has no complaints. Physical exam is benign except dark skin and a palpable spleen. He admits to drinking 2 bourbon’s with dinner and sometimes more on weekend. Family history includes two brothers with diabetes mellitus.

Routine blood work

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>289 IU/L</td>
</tr>
<tr>
<td>ALT</td>
<td>311 IU/L</td>
</tr>
<tr>
<td>Alk. Phos.</td>
<td>343 IU/L</td>
</tr>
<tr>
<td>GGTP</td>
<td>360 IU/L</td>
</tr>
<tr>
<td>T. bilirubin</td>
<td>3.0 mg/dl</td>
</tr>
</tbody>
</table>

What is next best step?
Liver Function Tests

- Liver “Function” Tests is a Misnomer
  - Liver “Chemistry” Tests more correct

- Normal Lab test values defined as occurring within 2 SD from the mean
  - 2.5% therefore have a high false positive

- AGA guidelines: 1-4% of asymptomatic people have elevated liver chemistries

Pattern of Liver Injury

- Hepatocellular

- Cholestatic

- Hyperbilirubinemia
  - Conjugated
  - Unconjugated

- Mixed

- Hepatic Synthetic Function
<table>
<thead>
<tr>
<th>Liver chemistry test</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase</td>
<td>Hepatocellular damage</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>Hepatocellular damage</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Cholestasis, Impaired conjugation, or Biliary obstruction</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Cholestasis, Infiltrative Dx, or Biliary Obstruction</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Synthetic Function</td>
</tr>
<tr>
<td>Albumin</td>
<td>Synthetic Function</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase</td>
<td>Cholestasis or Biliary obstruction</td>
</tr>
<tr>
<td>5-Nucleotidase</td>
<td>Cholestasis or Biliary obstruction</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Cholestasis or Biliary obstruction</td>
</tr>
</tbody>
</table>

![Liver and Biliary System Diagram](image)
**Hepatocellular Injury**

- **ALT (SGPT) or Alanine Aminotransferase**
  - Predominantly in Hepatocyte Cytoplasm; injury causes rise
  - LOW amount found in skeletal and cardiac muscle
  - Most specific for Hepatocellular Injury
  - Diurnal Variation:
    - Highest in Afternoon
    - Lowest at Night
  - Can have less than or equal to 30% Day to Day Variation
  - Serum Half Life is ~48 hours

- **AST (SGOT) or Aspartate Aminotransferase**
  - Abundantly expressed in cardiac and skeletal muscle and blood
  - 15% Higher in African American Males
  - Can Increase up to 3x with Exercise
  - Less than 10% Day to Day Variation
  - Serum Half Life is ~18 hours
Hepatocellular Injury
ALT or AST <5x Normal

**AST Predominant**
- AST: ALT > 2:1
  - Alcohol Related Liver Injury
  - *Acute EtOH Hepatitis almost never has AST/ALT >400!*
- Steatosis/Steatohepatitis
- Cirrhosis

**ALT Predominant**
- Chronic Hep C
- Chronic Hep B
- Acute Viral Hep (A-E, EBV, CMV)
- Hemochromatosis
- Medications/Toxins
- Autoimmune hepatitis
- Alpha 1 Antitrypsin Deficiency
- Wilson’s Dx
- Celiac Dx
Hepatocellular Injury
ALT or AST <5x Normal

- **Non-Hepatic Causes**
  - Hemolysis
  - Myopathy
  - Thyroid Dx
  - Strenuous Exercise

Hepatocellular Injury
Common Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Labetolol</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Statins</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Augmentin</td>
<td>Glyburide</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Cipro</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Halothane</td>
</tr>
<tr>
<td>INH</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>PTU</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Trazadone</td>
<td>Dantrolene</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
</tr>
</tbody>
</table>
Hepatocellular Injury
Herbs/CAM

- Chaparral leaf
- Ephedra
- Gentian
- Germander
- Jin Bu Huan
- Senna, Kavakava
- Scutellaria
- Shark Cartilage
- Vit A

Hepatocellular Injury
Illicit Drugs

- Anabolic Steroids
- Cocaine
- Ecstasy (MDMA)
- Phencyclidine (PCP)
Hepatocellular Injury
Toxins

- Carbon tetrachloride
- Chloroform
- Dimethylformamide
- Hydrazine
- Hydrochlorofluorcarbons
- 2-Nitropropane
- Trichloroethylene
- Toluene
- *Amanita phalloides*

Hepatocellular Injury
ALT or AST >15x Normal

- Acute Viral Hep (A-E, Herpes)
- Medications/Toxins
- Ischemic (Shock) Liver
- Autoimmune hepatitis
- Wilson’s Dx
- **Acute Bile Duct Obstruction**
- Acute Budd-Chiari Syndrome
- Hepatic Artery Ligation
Hepatocellular Injury

- Most Common Cause of Fulminant Hepatic Failure?
  - Acetaminophen OD
  - Rumack-Matthew Nomogram
- Hep E most likely to be fulminant in?
  - Pregnant Female
- Hep D can occur only if what is present?
  - Hep B infection (co-infection or subsequent superinfection)

Bilirubin

- **Bilirubin**
  - Heme degradation product
  - Unconjugated (Indirect) Insoluble
  - Conjugated (Direct) Water Soluble
- Urine – Urobilinogen (Dark Amber Urine)
- Stool – Stercobilinogen (Clay Stool)
- What level will lead to Jaundice?
  - >2.5
Elevated Bilirubin

- **Normal Lab Values**
  - Total Bilirubin: 0.3-1.9 mg/dl
  - Direct Bilirubin: 0-0.3 mg/dl

- **<20% Conjugated**
  - Gilbert Syndrome
  - Crigler-Najjar Syndrome
  - Hemolytic State

- **20-40% Conjugated**
  - Favors Hepatocellular Disease
  - Dubin-Johnson
  - Rotor Syndrome

- **40-60% Conjugated**
  - Either Hepatocellular or Extrahepatic Obstruction
  - (>50% Conjugated Favors Extrahepatic Obstruction)
Unconjugated Hyperbilirubinemia

- **Overproduction**
  - Hemolysis
  - Ineffective Erythropoiesis
  - Resorption of Large Hematoma

- **Impaired Uptake**
  - CHF - congestive hepatopathy
  - Portosystemic Shunt (TIPS)
  - Medications (Rifampin, Probenecid)

Unconjugated Hyperbilirubinemia

- **Defective Conjugation**
  - Gilbert’s syndrome (~5% Population)
  - Crigler-Najjar Syndrome
  - Neonatal Jaundice
  - Advanced Cirrhosis
  - Wilson’s Dx
  - Ethinyl estradiol
Conjugated Hyperbilirubinemia

- **Hepatocellular Disease**
  - Hepatitis
  - Cirrhosis
  - EtOH
  - Medications/Toxins (Acetaminophen, Arsenic, etc)
  - Sepsis/Ischemia
  - HCC
  - Cystic Fibrosis
  - TPN
  - Infectious (Bacterial/Fungal/Parasitic)

- **Defective Excretion**
  - Dubin-Johnson Syndrome
  - Rotor Syndrome
  - Alagille Syndrome

Conjugated Hyperbilirubinemia

- **Intrahepatic Cholestasis**
  - Primary Biliary Cirrhosis
  - Primary Sclerosing Cholangitis
  - NASH
  - Sarcoid/Amyloid
  - Lymphoma
  - Cholangiocarcinoma
  - Biliary Atresia
  - Intrahepatic Cholestasis of Pregnancy
Conjugated Hyperbilirubinemia

- **Extraheptic Cholestasis**
  - Bile Duct Obstruction
    - Stones
    - PSC
    - Cholangiocarcinoma
    - Pancreatic Cancer
    - Acute/Chronic Pancreatitis
    - Ampullary Neoplasm/Stenosis/Sphincter of Oddi Dysfunction
  - Parasite (Ascaris/Flukes)
  - AIDS Cholangiopathy
  - Post Op Stricture

Alkaline Phosphatase

- **Alkaline Phosphatase**
  - Enzyme bound in Hepatic Canicular Membrane
  - Also found in Bone, Intestines, and Placenta
  - How do you confirm source?
    - Isoenzymes
    - GGT or 5’ nucleotidase correlates with biliary
  - Increased by:
    - Biliary Obstruction
    - Cholestasis
    - Infiltrative Disease
  - Increased in Pregnancy and OCP
  - Can be up to 2x ULN Post-Prandial
Elevated Alkaline Phosphatase

**Hepatobiliary**
- Bile Duct Obstruction (same as prior list)
- Primary Biliary Cirrhosis
- Primary Sclerosing Cholangitis
- Medications (Separate Slide)
- Infiltrative Disease of Liver
- Hepatic Metastasis
- Hepatitis
- Cirrhosis
- Vanishing Bile Duct Syndrome
- Benign Recurrent Cholestasis

**Non-Hepatic**
- Bone Disease
- Pregnancy
- Chronic Renal Failure
- Lymphoma and other Malignancies
- CHF
- Infection/Inflammation of Liver
- Childhood Growth
Elevated Alkaline Phosphatase

- **Infiltrative Liver Disease**
  - Metastatic Malignancy
  - Lymphoma
  - Sarcoidosis
  - Amyloidosis
  - Tuberculosis
  - HCC
  - Fungal Infection
  - Other Granulomatous Disease
- **AST/ALT/Bili may be normal or slightly elevated**

Clues of Synthetic Function

- Albumin
  - Serum Half Life ~20 days
  - Prealbumin Half Life ~2 days
- PT/INR
  - What factor not synthesized in the liver?
    - Factor 8 synthesized in Vascular Endothelium
Other Tests

- Ammonia
- Platelets

Hereditary Hemochromatosis

- Autosomal recessive
- Ferritin, transferrin saturation
- HFE gene (C282Y, H63D)
- Increased intestinal iron absorption
- Excessive iron deposition in tissues
  - Especially the liver, heart, pancreas, pituitary, thyroid, gonads
  - “Bronze Diabetes”
- Hepatic iron index (HII); value 1.9 is consistent with disease
- Treatment: Phlebotomy
Hepatitis B

- Hepatitis B surface Antigen (HbsAg)
  - Presence in the blood indicates infection
- HepBsAb- immunity
- HepBcAb- prior exposure with clearance
- Spectrum of disease
  - Mild subclinical resolving cases to fulminant hepatitis to persistent chronic infection
  - Acquired from blood and secretions of infected individuals
  - The carriers with viral replication activity which is indicated by Hb eAg and HBV-DNA are the most dangerous

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<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>HbAg anti-Hbc anti-HBs</td>
<td>negative</td>
<td>Susceptible (vaccinate)</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>HbAg anti-Hbc anti-HBs</td>
<td>positive</td>
<td>Resolved HBV infection</td>
</tr>
<tr>
<td></td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>HbAg anti-Hbc anti-HBs</td>
<td>negative</td>
<td>Vaccinated</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>HbAg anti-Hbc anti-HBs</td>
<td>positive</td>
<td>Active HBV infection (usually chronic)</td>
</tr>
<tr>
<td></td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>*If anti-Hbc IgM present, may represent acute infection.</td>
</tr>
<tr>
<td>HbAb HbcAb HbsAb</td>
<td>negative</td>
<td>Various possibilities: distant resolved infection (most common) recovering from acute infection false positive occult hepatitis B</td>
</tr>
</tbody>
</table>
Hepatitis B Treatment

- Interferon- alpha
- Lamivudine
- Entecavir

- Typically don’t treat unless chronic
- Elevated AST/ALT for 3-6 months
- Viral DNA > 20,000

Autoimmune Hepatitis

- 3.6 times more frequent in women
- usually early adulthood
- 40% associated with CUC, autoimmune thyroiditis, Coomb’s-positive hemolytic anemia, diabetes, vitiligo, rheumatoid arthritis, interstitial pneumonitis, or myositis (all autoimmune diseases)
- Etiology: viral illness, drugs?
Autoimmune Hepatitis

- **Dx:** Type I: ANA, Anti-SMA, p-anc
  - Adult
  - Responds best to treatment
- **Type II:** Anti-liver-kidney microsomal antibodies
  - Usually children (2-14y/o)
- **Type III:** Soluble liver antigen associated with HCV

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PBC

**Introduction**

- **Diagnosis**
  - Cholestasis (elevated alkaline phosphatase and bili)
  - Antimitochondrial antibodies (AMA)
  - Histology
- **UDCA for all patients**
- **Transplantation**
  - Marginal liver reserve
  - Poor quality of life
  - Prognostic models
Non-alcoholic Fatty Liver Disease (NAFLD)

- Most common liver disease in U.S.
- Associated with insulin resistance, type II DM, obesity, hyperlipidemia, DM, hypothyroidism
- No serological marker for this disease- clinical
Stages of NAFLD

- Stage I: fatty liver (steatosis)
- Stage II: fatty liver + inflammation (Non-alcoholic steatohepatitis or NASH)
- Stage III: NASH + septal fibrosis
- Stage IV: cirrhosis

In 10 yrs., will be #1 reason for transplant.

Treatment of NASH

- 10% weight loss at 1-2 lbs/week
- Vitamin E has anti-oxidant effect; commonly used now
- Pioglitzaone decrease AST/ALT in patient with NASH without cirrhosis
Drug induced liver injury

- Only way to diagnose is careful review of new medications and stop highest probability
- If unsure, reintroduce medications one at a time with careful monitoring of liver tests

Diagnosis & Work-Up

- Clinical and laboratory features are often adequate for establishing the diagnosis of alcoholic hepatitis in a patient with a long history of heavy alcohol use (typically >100 g/day for more than 20 years)
  - Jaundice
  - Moderately elevated LFTs (<300 units/mL)
  - AST:ALT ≥ 2
  - Elevated serum bilirubin (>5 mg/dL)
  - Elevated INR
  - Presence of fever / leukocytosis supports the dx

- No laboratory or radiologic tests currently being used that are specific for alcoholic hepatitis
Assessing Disease Severity

- **Maddrey Discriminant Function**
  - Variables: PT / Bilirubin
  - Interpretation:
    - DF value ≥32 have high short-term mortality and may benefit from treatment with glucocorticoids

- **MELD**
  - Variables: Bilirubin / INR / Cr
  - Interpretation:
    - MELD score of ≥21 had a sensitivity of 75 percent and a specificity of 75 percent for predicting 90-day mortality
    - Increase in the MELD score of ≥2 points in the first week of hospitalization may independently predict in-hospital mortality
### Management

- **Social Work consult for aid with alcohol abstinence**
- **Treatment of alcohol withdrawal**
- **Nutritional support & electrolyte repletion**
- **FFP is NOT recommended in the absence of procedure**
- **PPx against gastric mucosal bleeding (PPI) if receiving glucocorticoid therapy**

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### Management

- **Mild to Moderate**
  - ETOH abstinence
  - Supportive care

- **Severe Alcoholic Hepatitis (DF > 32)**
  - **Gluocorticoids**
    - Dose: Prednisolone 40 mg/day x 28 days → taper
    - CI: Active bacterial or fungal infection / chronic HCV or HBV
  - **Pentoxifylline**
    - Alternative to glucocorticoids
    - Dose: 400 mg TID (adjust for renal fxn) x 28 days
    - Not effective in patients who have failed glucocorticoid therapy
Cirrhosis Management

- Hepatocellular carcinoma
  - US q 6months +/- AFP
  - CT liver protocol if lesion present

- Esophageal varices - Screen with EGD yearly
  - Prophylaxis with band ligation or non-selective beta blocker

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Ascites

- Portal hypertension leads to increase nitric oxide
- Vasodilation
- Renal sodium retention
- Increase intravascular volume to overflow

- Treatment with furosemide and Aldactone keeping patient eukalemic
SAAG

- >1.1 g/dL
  - Cirrhosis
  - Alcoholic hepatitis
  - Cardiac
  - Liver mets
  - Fulminant hepatic failure
  - Budd-Chiari
  - Portal vein thrombosis

- < 1.1 g/dL
  - Peritoneal carcinomatosis
  - Tuberculous peritonitis
  - Biliary
  - Nephrotic
  - Leak

Spontaneous Bacterial Peritonitis

- Positive culture
- Elevated PMN > 250
- No evidence of surgically treatable source of infection- i.e. abscess
- Typically caused by gram-
References


Srikureja W, Kyulo NL, Runyon BA, Hu KQ. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. J Hepatol. 2005;42(5):700.


UptoDate

References

- MKSAP 15. GI Questions