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
- 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

- AST 289 IU/L
- ALT 311 IU/L
- Alk. Phos. 343 IU/L
- GGTP 360 IU/L
- T. bilirubin 3.0 mg/dl

- 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
Portal Triad

Common Liver Chemistries

- Liver chemistry test
- Alanine aminotransferase
- Aspartate aminotransferase
- Bilirubin
- Alkaline phosphatase
- Prothrombin time
- Albumin
- Gamma-glutamyltransferase
- 5-Nucleotidase
- Lactate dehydrogenase

Clinical Implication
- Hepatocellular damage
- Hepatocellular damage
- Cholestasis, Impaired conjugation, or Biliary obstruction
- Cholestasis, Infiltrative Dx, or Biliary Obstruction
- Synthetic Function
- Synthetic Function
- Cholestasis or Biliary obstruction
- Cholestasis or Biliary obstruction
- Cholestasis or Biliary obstruction
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
Hepatocellular Injury

- **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
Hepatocellular Injury
ALT or AST <5x Normal

- **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

- **Non-Hepatic Causes**
  - Hemolysis
  - Myopathy
  - Thyroid Dx
  - Strenuous Exercise
### Hepatocellular Injury

#### Common Drugs

- Acetaminophen
- NSAIDs
- Statins
- Augmentin
- Amiodarone
- Fluconazole
- INH
- PTU
- Protease Inhibitors
- Trazadone
- Labetolol
- Methyldopa
- Carbamazepine
- Glyburide
- Cipro
- Halothane
- Nitrofurantoin
- Phenytoin
- Zafirlukast
- Dantrolene
- Heparin
- Valproic acid

#### 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**

- 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

**Extrahepatic 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
Elevated Alkaline Phosphatase

- **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
- Serum iron, 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 C

- Initial screening test is Hepatitis C IgG
- A reactive antibody should be followed by HCV RNA testing
  - If positive, diagnosis is confirmed
  - If negative - past HCV infection vs false positive
- Once diagnosis is established, genotype should be tested along with metavir score
CDC screening guidelines - HCV

- Adults born from 1945-1965
- IVDA
- Clotting factor prior to 1987
- Long-term hemodialysis
- Persistently elevated transaminases
- HIV
- Transfusions prior to 1992
- Exposure in healthcare professional

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
Hepatitis B

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Susceptible (vaccinate)</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Resolved HBV infection</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Vaccinated</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>Active HBV infection (usually chronic)</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Various possibilities:</td>
</tr>
<tr>
<td>HBeAg</td>
<td>positive</td>
<td>distant resolved infection (most common)</td>
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<tr>
<td>HBcAb</td>
<td>positive</td>
<td>recovering from acute infection</td>
</tr>
<tr>
<td>HBsAb</td>
<td>negative</td>
<td>false positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>occult hepatitis B</td>
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</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-Smooth Ab
  - 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
PBC
Introduction

- Diagnosis
  - Cholestasis (elevated alkaline phosphatase and bilirubin)
  - Antimitochondrial antibodies (AMA)
  - Histology
- UDCA for all patients
- Transplantation
  - Marginal liver reserve
  - Poor quality of life
  - Prognostic models

Primary Sclerosing Cholangitis

- right hepatic duct
- left hepatic duct
- common hepatic duct
- common bile duct
- pancreas
- pancreatic duct
- duodenum
- gallbladder
- cystic duct
- sphincter of Oddi
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
Alcoholic Hepatitis

- 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
Assessing Disease Severity

- **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
Management

- Mild to Moderate
  - ETOH abstinence
  - Supportive care

- Severe Alcoholic Hepatitis (DF ≥ 32)
  - Glucocorticoids
    - 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
**Ascites**

- Portal hypertension leads to increase nitric oxide
- Vasodilation
- Renal sodium retention
- Increase intravascular volume to overflow
- Treatment with furosemide and spironolactone keeping patient eukalemic

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**SAAG**

<table>
<thead>
<tr>
<th>&gt;1.1g/dL</th>
<th>&lt; 1.1 g/dL</th>
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<tbody>
<tr>
<td>Cirrhosis</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Tuberculous peritonitis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Biliary</td>
</tr>
<tr>
<td>Liver mets</td>
<td>Nephrotic</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>Leak</td>
</tr>
<tr>
<td>Budd-Chiari</td>
<td></td>
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<tr>
<td>Portal vein thrombosis</td>
<td></td>
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</tbody>
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Spontaneous Bacterial Peritonitis

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

Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0: Minimal HE</td>
<td>No clinical manifestations, but some abnormalities on psychometric testing</td>
</tr>
<tr>
<td>Grade 1: Mild HE</td>
<td>Alterations in behavior, mild confusion, slurred speech, disordered sleep</td>
</tr>
<tr>
<td>Grade 2: Moderate HE</td>
<td>Lethargy, moderate confusion</td>
</tr>
<tr>
<td>Grade 3: Severe HE</td>
<td>Stupor, incoherent speech, sleeping</td>
</tr>
<tr>
<td>Grade 4: Coma</td>
<td>Coma, unresponsiveness</td>
</tr>
</tbody>
</table>
Hepatic Encephalopathy

- Ammonia - not a marker of severity
  - Clinical diagnosis

- Treatment
  - Lactulose - titrate to 2-3 soft BMs daily
  - Xifaxin

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