




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


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



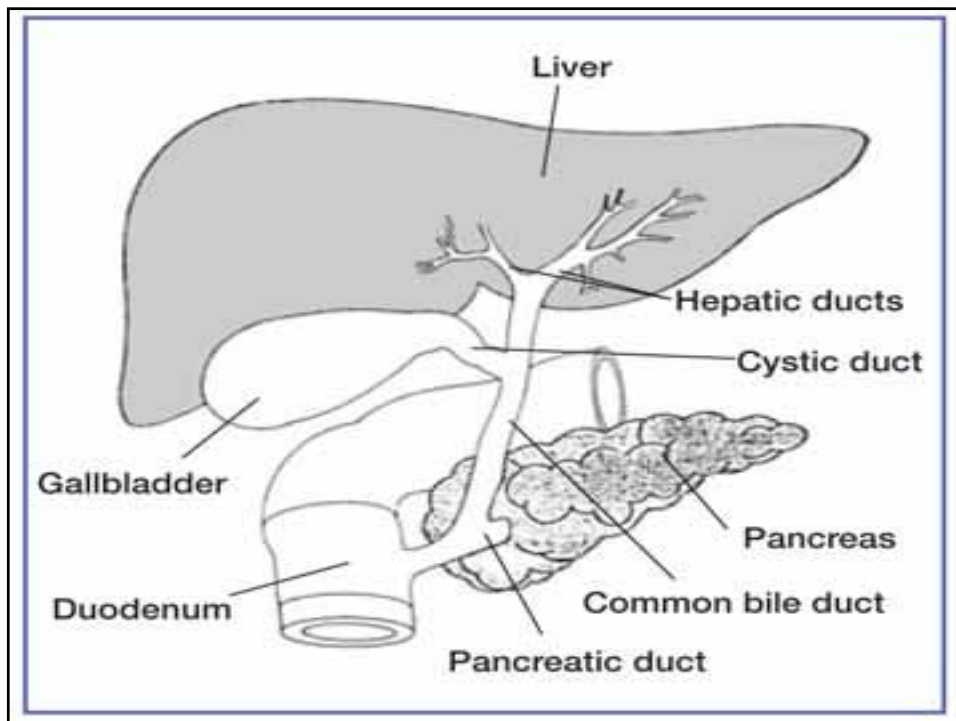
Pattern of Liver Injury


- Hepatocellular
- Cholestatic
- Hyperbilirubinemia
 - Conjugated
 - Unconjugated
- Mixed
- Hepatic Synthetic Function



Common Liver Chemistries


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





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



Hepatocellular Injury

ALT or AST <5x Normal

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



Hepatocellular Injury

Common Drugs

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



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
- Hydrochlorofluorocarbons
- 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



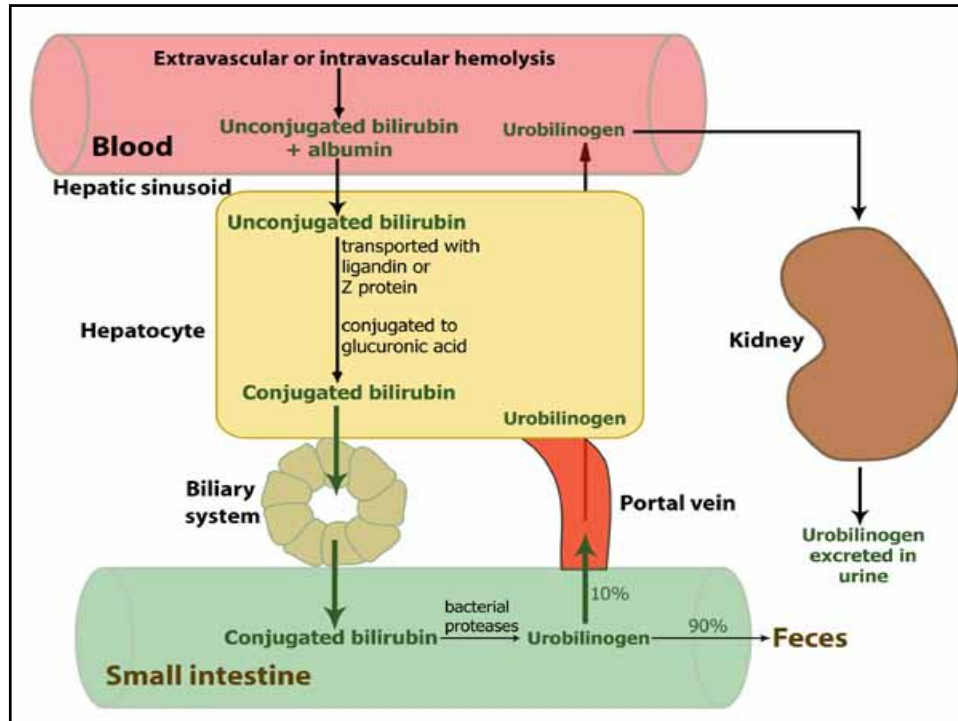
Hepatocellular Injury

- 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




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
- 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

Hepatitis B


Test	Result	Interpretation
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible (vaccinate)
HBsAg anti-HBc anti-HBs	negative positive positive	Resolved HBV infection
HBsAg anti-HBc anti-HBs	negative negative positive	Vaccinated
HBsAg anti-HBc anti-HBs	positive positive negative	Active HBV infection (usually chronic) *If anti-HBc IgM present, may represent acute infection.
HBsAg HBcAb HBsAb	negative positive negative	Various possibilities: distant resolved infection (most common) recovering from acute infection false positive occult hepatitis B



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

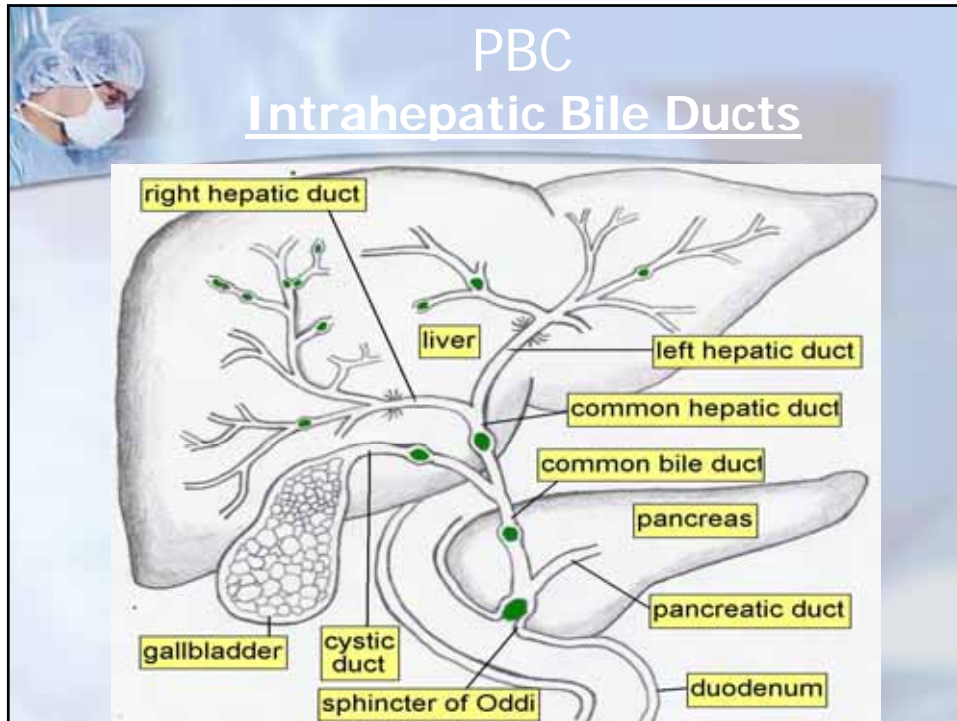
- Dx: Type I: ANA, Anti-SMA, p-anc
 - Adult
 - Responds best to treatment
- Type II: Anti-liver-kidney microsomal antibodies
 - usually children (2-14y/o)
- Type III: Soluble liver antigen associated with HCV




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




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 \geq 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 Aldactone keeping patient eukalemic




SAAG

- $>1.1\text{g/dL}$
 - Cirrhosis
 - Alcoholic hepatitis
 - Cardiac
 - Liver mets
 - Fulminant hepatic failure
 - Budd-Chiari
 - Portal vein thrombosis
- $< 1.1 \text{ g/dL}$
 - 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

Dunn W et al. Utility of a new model to diagnose an alcohol basis for steatohepatitis. *Gastroenterology*. 2006;131(4):1057.


Sheth M, Riggs M, Patel T. Utility of the Mayo End-Stage Liver Disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. *BMC Gastroenterol*. 2002;2:2.

Dunn W et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology*. 2005;41(2):353.

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.

Forrest EH et al The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. *Gut*. 2007;56(12):1743.

UptoDate



References

- Green RM and Flamm S. AGA Technical Review on the Evaluation of Liver Chemistry Tests. *Gastroenterology* 2002;123:1367-1384.
- Wallach J. Interpretation of Diagnostic Tests: 8th Ed. Lippincott Williams and Wilkins. 2007:223-302.
- Guardino JM. Primo Gastro: The Pocket GI/Liver Companion. Lippincott Williams and Wilkins. 2008:220-222.
- MKSAP 15. GI Questions