Abnormal Liver Function Tests Considerations

- Not all tests of liver function - AST ALT Alk Phos GGT 5’NT LDH Bili Alb
- Not always reflective of liver injury (heart skeletal muscle gut)

Aminotransferases (AST/ALT)  
Hepatocyte injury  
Viral/drug

Alkaline Phosphatase (AlkPhos) Cholestasis  
Obstructive/Nonobstructive

GGT/5NT/LDH – Not as useful (Can confirm hepatic source of elevation)

Albumin – Low in synthetic dysfunction  
Bilirubin (Direct/Indirect) – Measure of “metabolic capacity” of liver
Abnormal Liver Function Tests Considerations

- Cholestatic liver disease causes increased alkaline phosphatase values
- International normalized ratio (INR) and serum albumin values are markers of synthetic liver function
  - INR most sensitive (if vitamin K is replaced)

- Diagnostic considerations
  Acute or Chronic? Hospital or Community acquired?
  Context (Coexistent diseases – Autoimmune/IBD)
  Risk factors (Transfusion/Prior recreational drug use/EtOH)
  Symptoms (Pain/Distention/Confusion)
  Findings (Jaundice/Ascites/Asterixis/Spider Angioma)
Abnormal Liver Function Tests

- Hepatitis causes increased serum aminotransferase (ALT, AST) values
  - If >10-20x ULN differential diagnosis is drug, toxin, virus, Budd-Chiari syndrome
  - >5x ULN: autoimmune disease
  - Any systemic illness can cause a mixed hepatocellular-cholestatic picture
- Symptoms: fatigue, nausea, upper abdominal pain, and jaundice
- Bilirubin:
  - If indirect predominates: Gilbert’s syndrome
  - If direct predominates:
    - Obstruction
    - Viral hepatitis
    - If with elevated AST/ALT - hepatocellular dysfunction
Hepatitis, Acute Causes

- Hepatitis A: Fecal oral Self-Limited (rare prolonged illness or autoimmune trigger)
- Hepatitis B
- Hepatitis C
- Hepatitis D/E
- EBV
- CMV
- HSV 1/2 – Immune-compromised (Very high ALT – Bili minimal elevation)
- Drugs (hospital-acquired ie antibiotic) (EtOH) (Acetaminophen)
- Autoimmune Hepatitis
- Budd-Chiari Syndrome
- Wilson’s Disease
Hepatitis Chronic

- Hepatitis B/C/D
- Alcohol
- NAFLD
- Autoimmune Hepatitis
- Hemochromatosis
- A1AT deficiency
- Wilson’s Disease
- Tumor infiltration of Liver
- Drugs/Toxin
Alcoholic Liver Disease

- 6-8 glasses/day alcohol for men and 3-4 glasses/day for women over a 5-year period may result in cirrhosis
- Discriminant function = 4.6 (PT patient – PT control) + bilirubin
- Discriminant function >32 may benefit from steroids if no sepsis
  - Steroid use is controversial—may reduce short-term mortality, but not long-term mortality
- Orthotopic liver transplantation is an option after 6 months of sobriety
- Management:
  - Pentoxifylline is not effective in treating alcoholic liver disease
  - Maybe steroids?
  - Nutritional support!
Hepatitis B

- DNA virus (Lifelong infection)
- Risk factors – sexual transmission, IDU, perinatal infection
- Lots of tests that make things confusing (HBsAg/HBcAb/HBsAb, etc.)

- HBsAg = Infection, acute or chronic
- HBcAb = Prior infection (total) or new or recurrent (IgM)

- HBV DNA - corresponds to viremia
- Test can be qualitative or quantitative
- Level of virus important in some cases to make treatment decisions
The course of chronic HBV infection is considered to consist of four phases: immune tolerance, immune clearance (HBeAg-positive chronic hepatitis), inactive carrier, and reactivation (HBeAg-negative chronic hepatitis), although not all patients go through every phase. HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg; HBV, hepatitis B virus; ALT, alanine aminotransferase.

Hepatitis B

• Presentations in host (Chronic states)

• Inactive - HBsAg pos HBeAg neg HBV DNA low ALT NI No treatment
• Immune tolerant – HBsAg pos HBEAg pos HBV DNA high ALT NI No treatment
• Immune active HBV DNA high HBeAg pos ALT very high may watch or treat if chronic
• Chronic active HBV DNA high HBeAg pos ALT high Treat
• Chronic (precore mutation) HBeAg neg HBV DNA varies ALT varies Treat ?

• Decision re treatment based on degree of activity (ALT) viral load (DNA) and degree of liver disease (fibrosis)
Hepatitis C

- Common (1.7% of population)
- RNA virus
- Risk factors – IDU, Transfusion (before 1992)
- Screen with HCV Ab – Confirm viremia with RNA study (Qual/Quant)
- Multiple genotypes (Most common GT1 in US)
- CDC recommends one-time screen for all baby boomers (born 1945-1965)
- No more interferon; all-oral regimens are highly effective (cure rates >90%) but extremely expensive
  - Treatment choices influenced by genotype and presence of cirrhosis

Proportion of HCV infections caused by the six major genotypes, by geographic region

Hepatitis C

- Risk for liver-related complications in HCV affected by:
  - Cirrhosis (low platelet count)
  - Alcohol overconsumption
  - Hepatitis A/B coinfection (vaccinate)
- No link to HCV viral load and risk
- No link to genotype and risk
- No link to ALT level and risk

Autoimmune Hepatitis

- Autoimmune hepatitis is an inflammatory condition of the liver of unknown cause
- Female predominance; many have other autoimmune disease – thyroid/joint, etc.
- Symptoms: fatigue most common; also jaundice, anorexia, myalgias
- Increased gamma globulin is the key!

Autoimmune Hepatitis

• Labs: Elevated liver related tests, hypergammaglobulinemia, elevated autoantibodies
• Liver biopsy: interface hepatitis with portal plasma cell infiltrate
• Think autoimmune hepatitis if you see a female with jaundice, negative viral markers, and thyroid disease
• Steroid-responsive
  – Relapse occurs in >50% of patients within 6 months of withdrawal
• Orthotopic liver transplant for refractory patients

Non-alcoholic Fatty Liver Disease (NAFLD)

- Spectrum of histologic change as a result of fat deposition
- Non-alcoholic steatohepatitis represents necroinflammatory change which can lead to cirrhosis
- Most common liver disease (75-100 million in US)

Rinella ME. JAMA. 2015;313:2263-2273.
Non-alcoholic Fatty Liver Disease (NAFLD)

- More prevalent in obese patients, dyslipidemias, diabetics, and those with glucose intolerance
  - Drugs (estrogen, tamoxifen, amiodarone)
- Labs: AST/ALT 2-5 x ULN

Rinella ME. JAMA. 2015;313:2263-2273.
Non-alcoholic Fatty Liver Disease (NAFLD)

- Biopsy:
  - Steatosis, inflammatory changes, fibrosis, cirrhosis
- Indications for biopsy:
  - Obese
  - Diabetes mellitus
  - AST:ALT >1
  - Low platelet count
- Consider hypoglycemic agents (pioglitazone, rosiglitazone)
- 1%-2% of patients will develop end-stage liver disease requiring orthotopic liver transplantation

Rinella ME. JAMA. 2015;313:2263-2273.
Non-alcoholic Fatty Liver Disease (NAFLD)

Treatment

• Current:
  – Weight loss
  – Exercise
  – Insulin sensitizers (pioglitazone)
  – Vitamin E

• Drugs on horizon:
  – Farnesoid X receptor agonist (bile acid analog: obeticholic acid improved histology)

Wilson’s Disease

• Etiology:
  – Autosomal recessive disorder of copper metabolism
  – Reduced biliary excretion of copper results in copper deposition throughout the body including brain, liver, cornea, kidney

• Presentation:
  – 50% present with liver disease (ranging from abnormal liver function tests to fulminant hepatic failure)
  – 30% neurologic disease
  – 10% psychiatric symptoms

• Physical exam:
  – Kayser-Fleischer rings on slit lamp exam

Wilson’s Disease

• Labs:
  – Low alkaline phosphatase
  – Low ceruloplasmin
  – Elevated urine copper on 24-hour collection (perform liver biopsy for copper quantitation)
  – If total bilirubin is higher than alkaline phosphatase, it’s Wilson’s disease

• Treatment:
  – Penicillamine
  – Orthotopic liver transplant for fulminant hepatic failure

Genetic Hemochromatosis

• Etiology:
  – Autosomal recessive disorder
  – Increased hepatic absorption in the intestine with resulting increased deposition in liver, heart, joints, thyroid, and hypothalamus

• Presentation:
  – Classic triad: cirrhosis, diabetes mellitus, skin hyperpigmentation
  – Fatigue, impotence, destructive arthropathy or simply abnormal lab values

• Screen for hereditary hemochromatosis in all patients with chronic liver disease

Genetic Hemochromatosis

• Diagnosis:
  – High iron saturation/ferritin
  – Liver biopsy: hemosiderin in hepatocytes; elevated iron index
  – Genetic test (C282y or H63D mutations)—homozygous or compound heterozygote

• Treatment:
  – Phlebotomy around every 3 months
  – Goal is to keep ferritin <50 ng/mL

• Risk for cirrhosis and hepatocellular carcinoma in 30% of patients

Primary Sclerosing Cholangitis (PSC)

- Chronic cholestatic illness of unknown cause
- Male predominance (20s to 30s)
- Up to 80% have IBD (although <5% of patients with UC have PSC)
- Alkaline phosphatase predominates; jaundice/pain (right upper quadrant)
- Characteristic appearance at ERCP/MRCP

ERCP=endoscopic retrograde cholangiopancreatography; MCRP=magnetic resonance cholangiopancreatography.
Primary Sclerosing Cholangitis (PSC)

• 30% lifetime risk for cholangiocarcinoma; also at increased risk for hepatocellular carcinoma
• Patients with PSC and UC are at higher risk for colorectal cancer than patients with UC alone
• Management:
  – Assessment for dominant strictures
  – Treatment of cholangitis
  – Symptomatic management

Primary Sclerosing Cholangitis (PSC)

- Orthotopic liver transplant is the only intervention to offer overall survival benefit
- No medical therapy is effective
- No good screening strategy for cholangiocarcinoma

Karlsen TH, Boberg KM. *J Hepatol*. 2013;59:571-582.
Primary Biliary Cholangitis

- Most common symptoms:
  - Fatigue
  - Localized or generalized pruritus often develops

- Other autoimmune diseases; metabolic bone disease, hypercholesterolemia, and fat-soluble vitamin deficiencies

- Diagnosis
  - Alkaline phosphatase >10 x ULN
  - Positive AMA (98% diagnostic!)
  - Non-suppurative cholangitis on liver biopsy

- Treatment:
  - Ursodeoxycholic acid improves the biochemical profile, reduces pruritus, decreases progression to cirrhosis, and delays the need for liver transplantation
  - Therapy usually continued indefinitely
  - Liver transplant for intractable pruritis or liver failure (disease can recur following transplant)

**Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) Syndrome**

- Unique to pregnant women
  - More common in preeclampsia and multiple pregnancies
- Usually third trimester but may occur up to 48 hours postpartum
- Labs:
  - Hemolytic anemia with abnormal smear
  - Low haptoglobin
  - Elevated serum indirect bilirubin
  - Elevated lactate dehydrogenase
  - AST >2 x ULN
  - Platelets <100,000/µL

- Differential diagnosis:
  - Acute fatty liver of pregnancy (AFLP) but not associated preeclampsia
  - Usually other coagulation defects present

- Treatment:
  - Stabilize patient
  - Prompt delivery
  - HELLP resolves in 48 hours

Hepatic Tumors/Lesions

- Simple cysts: most common benign hepatic mass
- Hemangioma: Common, no risk for malignancy
- Hepatocellular carcinoma
  - Rising incidence
  - Consequence of chronic liver disease
- Hepatic adenomas
  - Estrogen-sensitive and are premalignant
  - Rupture risk is high with large adenomas
  - Treatment for large adenomas: surgery
- Focal nodule hyperplasia
  - Radiology features central scar
  - More common in women than men
  - No malignant risk
- Hepatic abscess
  - Usually related to cholangitis diverticulitis or appendicitis with hematogenous seeding or direct spread
Complications of Liver Disease: Cirrhosis

- Hepatocellular carcinoma (rising incidence): 80% in cirrhosis\(^1,2\)
  - Ultrasound screening twice yearly
  - Alpha-fetoprotein not sensitive
  - Orthotopic liver transplant only curative option in cirrhosis
  - Ablation if orthotopic liver transplant not an option or as bridge to transplant
  - Resection if no portal hypertension

Complications of Liver Disease: Cirrhosis

- Infection (SBP)
- Cardiopulmonary complications
Complications of Liver Disease
Cirrhosis: Portal HTN

- Portal hypertension
  - Associated with bleeding/ascites/wasting syndrome/renal failure

- Varices:
  - Large esophageal varices should receive a nonselective β-blocker or band ligation as prophylaxis against bleeding

- Ascites:
  - Sodium restriction
  - Diuretics (spironolactone [Lasix] escalating treatment)

Complications of Liver Disease
Cirrhosis: Portal HTN

- Patients with suspected spontaneous bacterial peritonitis: Diagnostic paracentesis with cell counts/culture of ascitic fluid
  - 250 PMNs/cc = spontaneous bacterial peritonitis
- Patients who have had 1 episode of spontaneous bacterial peritonitis should receive long-term antibiotics to prevent future episodes
- In advanced liver disease, beta-blockers may increase mortality (precipitation of hepatorenal syndrome?)
- Advanced cirrhosis:
  - Physiology of sepsis syndrome ie, low systemic vascular resistance, high cardiac output
Complications of Liver Disease
Cirrhosis

• Almost all patients with hepatorenal syndrome will require liver transplantation (Type I-rapid/Type II-slow)
• Liver transplantation is an option for patients with hepatocellular carcinoma who have ≤3 lesions (the largest of which is <3 cm) or a single lesion <5 cm²
• Cardiac issues³:
  – Hepatopulmonary syndrome: hypoxia/orthodeoxia (AV shunting)
  – Portopulmonary hypertension: right heart failure (arteriopathy)
  – Cirrhotic cardiomyopathy (systolic/diastolic dysfunction)

Fulminant Hepatic Failure

- No preexisting liver disease → Hepatic failure and encephalopathy
  - Increased intracranial pressure (elevated INR)
- Distinguish from cirrhosis – fulminant hepatic failure is potentially reversible (advanced cirrhosis is not)
- Most common causes:
  - Acetaminophen toxicity (intentional or unintentional)
  - Idiosyncratic drug reaction (often antibiotics/NSAIDs)
  - Hepatitis A/B/E, CMV, EBV, HSV
  - Ischemic liver disease (occurring as a complication of shock)
  - Budd Chiari Syndrome
  - Autoimmune liver disease

Fulminant Hepatic Failure

• Hepatic encephalopathy may progress to cerebral edema which is the most common cause of death
  – Differs from portal-systemic encephalopathy in cirrhosis
• No contraindication to transplant? Transfer patient to center where orthotopic liver transplant is performed
  – Spontaneous recovery is possible

Case

• 55-year-old male with HCV

• No other medical conditions

• Physical exam unremarkable

• Labs
  – AST 35 U/L
  – ALT 32 U/L
  – Platelet count 87,000/µL
  – HCV quant 10 log6

• Genotype 1a
Case

What lab study is most predictive of a poor outcome without therapy?
Case

- Platelet count
  - Low platelet count predicts cirrhosis until proven otherwise
Case

*What are appropriate measures for his subsequent care? (Pick 3 of 4 below)*

a) HCV viral load monitoring  
b) HCC surveillance  
c) Hepatitis A/B vaccination  
d) HCV therapy
- No value to viral monitoring in HCV as no link to disease severity (in contradistinction to HBV)
- HCC surveillance is appropriate – Typically Ultrasonography every 6 months
- Vaccination for Hep A/B recommended for all HCV infected individuals
- HCV therapy indicated given advanced fibrosis (Uniform recommendation for therapy of all infected individuals regardless of fibrosis stage ?)
THANK YOU! --- QUESTIONS?