Evaluation of Abnormal Liver Tests

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Disclosures

- Speaker’s Bureau for Abbvie
- I will not discuss off label use and/or investigational use in this presentation
Educational Objectives

- Distinguish the differential diagnosis and subsequent workup for liver disease
- Evaluate the different laboratory and radiographic markers for liver disease
- Summarize the major liver diseases and treatments

“Liver Function Tests”

LFT’s Do Not measure “function”

AST/ALT = “activity”
Albumin/PT/Glucose = “function”
Bilirubin = hepatic transport capability
Alkaline Phosphatase = bile duct injury
ALT and AST

- Enzymes, found in Hepatocytes
  Released when liver cells damaged
- ALT is specific for liver injury
- AST (SGOT) is also found in skeletal and cardiac muscle

Function Tests

- Albumin
- Prothrombin time
- Bilirubin
- (Platelets)
  - Pancytopenia
PROTHROMBIN TIME/INR

- Measure of the Vitamin K dependent clotting factors ie. II, VII, IX and X.
- The liver is involved in activating Vitamin K. With liver damage, these clotting factors cannot be produced.
- Make sure the patient has adequate Vitamin K by giving 10mg sc.
- Giving Vitamin K has no effect on INR if patient has impaired synthetic function.

ALBUMIN

- Albumin has a half life of 21 days, so the drop that occurs with hepatic dysfunction does not occur acutely
- Acute illness can cause albumin to drop rapidly due to cytokines increasing the rate of albumin metabolism
- HOWEVER, don’t forget that low albumin also occurs in NEPHROTIC syndrome, so always check the urine for protein.
• The key to finding the cause of abnormal liver tests is in the process of the evaluation
• Many answers are in the H&P

History
• Chief complaint vs Asymptomatic
• Medical History
  ◦ Associated Medical Conditions
  ◦ Surgeries
• Medications
  ◦ Include otc and herbal remedies
  ◦ New medications
History

- Risk Factors/Social History
  - Alcohol
  - Drugs
  - Tattoos
  - Piercings
  - Transfusions
  - Sexual History
  - Nationality/Place of Birth
  - Pregnancy
- Old labs

Physical Examination
Ascites

Caput Medusa
Spider Angioma

Esophageal Varices

Normal esophagus
Gastric Varices
Portal Hypertensive Gastropathy

Pattern of Abnormality

- Hepatocellular
- Isolated Hyperbilirubinemia
- Cholestatic
- Mixed Pattern
Hepatocellular

- Alcohol
- Viral hepatitis
- Non Alcoholic Steatohepatitis (NASH)
- Wilson’s Disease
- Hemochromatosis
- Drug Induced Liver Disease
- Ischemic Hepatitis
- Vascular
- Autoimmune Hepatitis
- Alpha-1 Antitrypsin Deficiency
- Celiac Sprue
- Malignancy

Alcohol

- Significant alcohol consumption is defined as an average consumption of >210 grams of alcohol per week in men or >140 grams of alcohol per week in women over at least a two-year period
- A standard drink (360 mL [12 oz] of beer, 150 mL [5 oz] of wine, or 45 mL 1.5 oz] of 80-proof spirits) contains approximately 14 grams of alcohol
  - 15 drinks/week for a man
  - 10 drinks/week for a woman
Alcoholic Liver Disease

- Labs
- Alcoholic Hepatitis vs. Cirrhosis
- Alcohol as a confounding factor in other causes of liver disease
- Abstinence!
- Prognosis

Viral Hepatitis

- Acute viral hepatitis
  - Hepatitis A
  - Hepatitis B
    - Hepatitis D
  - Hepatitis E
  - CMV, EBV, etc
- Chronic viral hepatitis
  - Hepatitis B
    - Hepatitis D
  - Hepatitis C
### Acute Viral Hepatitis

- Hepatitis A IgM
- Hepatitis B Surface Ag
- Hepatitis B Core IgM Ab
- Hepatitis C PCR
- CMV IgM
- EBV panel
- HSV IgM

### Hepatitis A

- Fever, malaise, fatigue, anorexia, nausea, vomiting, RUQ pain and hepatosplenomegaly
- Jaundice, dark urine, clay colored stools follow later
- Tender enlarged liver
- Transaminases >500 U/L (typically in 1000's)
- Bilirubin <10 mg/dL
- Rare extrahepatic manifestations
- Outbreaks
CHRONIC VIRAL HEPATITIS

Exposure history

Hepatitis B: Surface Ag/Ab, Core Ab, E Ag, DNA positive
Hepatitis C: Ab and PCR RNA positive

Chronic Hepatitis B Is a Global Health Problem

An estimated 240 million people worldwide are living with chronic hepatitis B (CHB).


HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen.
Hepatitis B Serology

<table>
<thead>
<tr>
<th>Interpretation of Hepatitis B Serology Test Results</th>
<th>HBsAg</th>
<th>HBV DNA</th>
<th>HBeAb (IgM)</th>
<th>HBeAb (IgG)</th>
<th>HbeAg</th>
<th>HBeAb</th>
<th>HBsAb</th>
<th>Interpretation</th>
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<td>Chronic HBV (&gt; 6 months)</td>
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<td>Immune to HBV (past infection)</td>
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<td>Immune to HBV (vaccinated)</td>
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</table>
Current Screening Guidelines for Hepatitis C

- Screening based on risk factors alone was not optimal
  - Many patients have no known exposure risk
  - Baby boomers (born between 1945 and 1965) account for 75% of all HCV patients
- The CDC, USPSTF, and AASLD issued updated guidelines to include the one-time screening of all baby boomers
- This age cohort should be screened regardless of symptoms or other risk factors
- Along with baby boomers, other high-risk groups to screen include people who currently inject or ever injected drugs, those who received a tattoo in an unregulated setting, and those who had a blood transfusion before 1992

AASLD=American Association for the Study of Liver Diseases; CDC=US Centers for Disease Control and Prevention; USPSTF=US Preventive Services Task Force.

WHO TO SCREEN?
The CDC, USPSTF, and AASLD recommend screening all high-risk populations, including a one-time screening of all baby boomers.

- Baby boomers (born 1945–1965)
- Persons who ever injected illegal drugs
- HIV-infected patients
- Persons who have received tattoos from unlicensed or unregulated environments
- Those with certain medical conditions, including:
  - Persons who received clotting factor concentrates produced before 1987
  - Persons who were ever on long-term hemodialysis
  - Persons with persistently abnormal alanine aminotransferase levels
- Prior recipients of transfusions or organ transplants, including:
  - Persons who were notified that they received blood from a donor who later tested positive for HCV infection
  - Persons who received a blood transfusion, blood components, or an organ transplant before July 1992
- Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-positive blood
- Children born to an HCV-positive mother
Recommendations for One-Time Hepatitis C Testing

- One-time, opt out HCV testing is recommended for all individuals aged 18 years and older
- One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures or conditions or circumstances associated with an increased risk of HCV
- Periodic repeat HCV testing should be offered to all persons with behaviors, exposure or conditions or circumstances associated with an increased risk of HCV exposure
- Annual HCV testing is recommended for all persons who inject drugs and HIV-infected men who have unprotected sex with men
- JAMA March 2, 2020- The USPSTF recommends screening for HCV in all adults aged 18-79 years

HCVGuidelines.org- American Association for the Study of Liver Disease and Infectious Disease Society of America (Updated November 6, 2019)
JAMA.2020; 323(10):970-975

HCV IS UNDERDIAGNOSED AND UNDERTREATED

The problem of HCV is widespread, with as many as half of those with chronic HCV being unaware they are infected.¹

~3.5 MILLION
Americans have chronic HCV infection¹

50% UNDIAGNOSED¹

ONLY 9% HAVE BEEN SUCCESSFULLY TREATED¹

Meta-analysis from articles published between January 2003 and July 2013.

Non-Alcoholic Fatty Liver Disease

- **Prevalence in United States**
  - NAFLD 34%(43 million adults), NASH 12%

- **Risk Factors**
  - Obesity
  - DM/Insulin resistance
  - Hypercholesterolemia
  - Family History

Chicken or Egg?

Liver Biopsy


Detecting NASH, Fibrosis With Liver Biopsy

- **Benefits**
  - Establish diagnosis of NASH
  - Rule out other processes: alpha-1 antitrypsin, iron overload, autoimmune component
  - Assess early fibrosis

- **Limitations**
  - Risk of bleeding, pain
  - Sampling variability (especially with IR biopsies if they are small)
### Natural History of NAFLD

- **NAFLD**
  - 80% Isolated Fatty Liver
  - 20% Fatty Liver with Mild Inflammation

- **NASH**
  - ~11% over 15 years, but significant variability

- **NASH Cirrhosis**
  - ~7% over 6.5 years

- **HCC**
  - ~31% over 8 years

- **Decompensation**
  - Possible sampling variability with some risk of progression

- **↑ risk of death compared with general population**
  - Cardiovascular, malignancy, liver-related
  - NASH with fibrosis portends worse prognosis
  - Fibrosis progression associated with diabetes, severe IR, weight gain >5 kg, rising ALT, AST

- **None to very minimal progression to fibrosis**
  - No ↑ risk of death compared with the general population

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### AASLD Guidance: Nonpharmacologic Approaches

- **Weight loss**
  - 3% to 5% to improve steatosis, but 7% to 10% to improve the majority of the histopathologic features of NASH, including fibrosis

- **Exercise**
  - Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown

- **Bariatric surgery**
  - Can be considered in otherwise eligible obese individuals with NAFLD or NASH
  - Premature to consider bariatric surgery as an established option to treat NASH
  - The type, safety, and efficacy of bariatric surgery are not established in obese individuals with cirrhosis from NAFLD
  - In patients with compensated NASH or cryptogenic cirrhosis, bariatric surgery may be considered on a case-by-case basis by an experienced bariatric surgery program
**An Integrated Approach to Obesity, Diabetes, and NAFLD**

- **Multidisciplinary:** hepatologist, endocrinologist, nutritionist
  - Also psychologist, clinical pharmacist, physical therapist
- **Cardiovascular risk reduction is essential**
  - Manage dyslipidemia, hypertension, smoking cessation, antiplatelet therapy
- **Screen and treat other comorbid conditions**
  - Obstructive sleep apnea, degenerative joint disease
- **Lifestyle interventions for all; add obesity pharmacotherapy and bariatric surgery when appropriate**
- **Individualize antihyperglycemic medications, targeting CV risk and body weight reduction when appropriate**
- **In patients with advanced liver disease, choose or dose drugs for diabetes or weight management appropriately**

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**AASLD Guidance on CV Risk: Statins in Patients With NASH**

- “Patients with NAFLD are at high risk for cardiovascular morbidity and mortality. Thus, aggressive modification of CVD risk factors should be considered in all patients with NAFLD”
- “Patients with NAFLD or NASH are not at higher risk for serious liver injury from statins. Thus, statins can be used to treat dyslipidemia in patients with NAFLD and NASH”

Statins recommended for reducing CV risk, not for resolving NASH
Drug/Toxin Induced Hepatitis

Thorough history/timing

Labs: AST/ALT 100-3000
Bilirubin nl-marked elevation
Eosinophilia

Environmental toxins

vinyl chloride, herbal preparations with pyrrolizidine alkaloids (Jamaica bush tea), Amanita phalloides mushrooms

Drugs implicated in idiosyncratic liver injury

<table>
<thead>
<tr>
<th>Infrequent But Not Rare</th>
<th>Rare</th>
<th>Combination Agents with Enhanced Toxicity</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>Didanosine</td>
<td>Ethanol-acetaminophen</td>
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<tr>
<td>Sulfonamides</td>
<td>Sustiva</td>
<td>Trimethoprim-sulfamethoxazole</td>
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<tr>
<td>Phenytoin</td>
<td>Metformin</td>
<td>Rifampin-isoniazid</td>
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<td>&quot;Statins&quot;</td>
<td>Ofloxacin</td>
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<td>Propylthiouracil</td>
<td>Ketoconazole</td>
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<td>Amiodarone</td>
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<td>Dapsone</td>
<td>Isosulfurane</td>
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<td>Herbals</td>
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<td>Flutamide</td>
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Autoimmune Hepatitis

- History
- Young females
- Varied presentation
- Elevated ANA, auto-antibodies and gamma globulins
- Liver Biopsy
- Scoring system

Hemochromatosis

- Genetic mutation leading to increased intestinal iron absorption
  - Most common autosomal recessive genetic disorder
- Secondary iron overload
- Buzzword?
  - Cardiac disease, impotence and arthopathy
- Labs
  - Ferritin
  - Transferrin saturation (iron/transferrin ratio)
    - >60% in men, >50% in women
  - Genetic testing- HFE gene (C282Y)
Wilson’s Disease

- Liver Disease with neurologic and psychiatric features
- Impaired biliary copper excretion (genetic)
- Acute hepatitis with liver failure vs chronic liver disease with cirrhosis
  - Low Ceruloplasmin
  - Elevated Urinary copper excretion
  - Classic examination finding?

Kayser-Fleischer Rings
Alpha 1 Anti-trypsin

Associated with emphysema

Low A-1A levels
Neutrophil elastase
Check Phenotype/Alleles (MM,MS,ZZ)

Hepatic Malignancies

- Primary vs Metastatic disease
- Not always a prior known primary malignancy
  - Breast, colorectal, esophageal, lung, melanoma,
    pancreatic, gastric, bladder, ovary, prostate, uterine
- Underlying cirrhosis
  - Suspect in a newly decompensated patient
- Screening
  - Imaging
  - AFP
  - Biopsy
Hepatic Ischemia

- Hepatic Ischemia
  - Acute hypoperfusion
  - Usually self-limited
  - Typically liver function is preserved
- Hepatic Infarction
  - Focal ischemia not diffuse
  - Hepatic arterial occlusion
    - Iatrogenic ligation
    - Atherosclerosis or hypercoagulable disorder

Hepatic Vascular Disease

- Hepatic Vein Thrombosis (Budd-Chiari)
  - Acute (less common)
  - Subacute/chronic- cirrhosis
- Portal Vein Thrombosis
  - Prehepatic, intrahepatic, posthepatic
  - Hypercoagulable state
  - Procedure related
  - Associated conditions
    - Cirrhosis
    - Pancreatitis
Hyperbilirubinemia

Classification of jaundice according to type of bile pigment and mechanism

**Unconjugated hyperbilirubinemia**
- Increased bilirubin production
  - Extracanalicular hemolysis
  - Intra-vascular hemolysis
  - Bone marrow failure

**Impaired hepatic bilirubin uptake**
- Hemolysis
- Hepatocellular cholestasis
- Some patients with Gilbert’s syndrome
- Certain drugs: rifampin, phenobarbital, fenurapride and sodium

**Crigler-Najjar congenital**
- Crigler-Najjar syndrome types I and II
- Gilbert’s syndrome
- Neonates

**Gilbert’s disease**
- Drug effect

**Conjugated hyperbilirubinemia**
- A biliary cholobast os biliary obstruction
  - Cholecystolithiasis
  - Tumors and periradicular lesions
  - Papillary stenosis
  - Primary sclerosing cholangitis
  - Biliary dysplasia

**Obstructive jaundice**
- Duodenal and chronic pancreatitis
- Strictures after invasive procedures
- Certain paracolic infections — e.g., Acet’s syndrome, liver fluke

**Intrahepatic cholestasis**
- Virus hepatitis
- Antibiotics
- Acetominophen
- Primary biliary cirrhosis
- Drugs and toxins — eg, nitrofurantoin, fluoroquinolones, herbal medications (e.g., banaba, echinacea)
- Septic and hemorrhage states
- Infiltrative diseases — eg, sarcoidosis, lymphoma, carcinoids, tuberculosis
- Total parenteral nutrition
- Postoperative cholestasis
- Following organ transplantation
- Hepatitis virus in cirrhotic disease
- Pregnancy
- End-stage liver disease

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**Hyperbilirubinemia**

- **Unconjugated bilirubin**
  - Overproduction
    - hemolysis
    - Ineffective erythropoiesis
  - Impaired uptake/conjugation of bilirubin
  - Crigler-Najjar
    - Neonatal jaundice with neurologic impairment
  - Gilbert’s
  - Drug effect
Hyperbilirubinemia

- Conjugated bilirubin
  - decreased excretion into the bile ductules or leakage of the pigment from hepatocytes into serum
  - Dubin-Johnson
  - Rotor’s
    - Both are benign, rare, genetic conditions

Cholestasis

- Extrahepatic
- Intrahepatic
Extrahepatic Cholestasis

Choledocholithiasis (most common)

Malignancies
- pancreatic head, ampullary, cholangiocarcinoma

Primary Sclerosing Cholangitis (PSC)

Chronic pancreatitis

AIDs cholangiopathy (CMV, cryptosporidium)

Extrahepatic Cholestasis

Right upper quadrant pain, fever
Mild elevation of transaminases
++ Alk phos elevation
Elevated Bilirubin
MRCP/EUS/ERCP
Magnetic Resonance CholangioPancreatography (MRCP)

Endoscopic Ultrasound
Endoscopic Retrograde CholangioPancreatography (ERCP)

Ampulla of Vater
Choledocholithiasis
Endoscopic Sphincterotomy

Endoscopic Stone Extraction
Biliary Stricture

Pancreatic and Biliary Cancer
Cholangitis

- Charcot's Triad is present in 60% of cases
  - Reynold's Pentad adds hypotension and altered mental status
- Klebsiella, E. Coli, Enterococcus
- Need abx AND drainage
  - One of the few biliary emergencies
- Rare with malignant obstruction
Choledochal Cysts

- Congenital anomalies characterized by cystic dilation of variable portions of the intrahepatic and extrahepatic bile ducts
- More common in Asians
  - F>M
  - Primarily affects children and young adults
- Present with pain, jaundice, fever and a palpable abdominal mass

![Diagram of Choledochal Cysts]
Intrahepatic Cholestasis

- Drug Induced
- Sepsis/Bacteremia
- Alcoholic hepatitis
- Viral hepatitis
- PSC
- PBC
- TPN
- Cholestasis of pregnancy
- Hereditary Cholestasis

Primary Sclerosing Cholangitis (PSC)

- Chronic cholestatic disease of the liver and bile ducts that is frequently progressive and can lead to end-stage liver disease
- Characterized by progressive inflammation, fibrosis, and stricturing of the intrahepatic and extrahepatic bile ducts
- Predominantly a disease of middle aged, white males
- UC has been reported in up to 90 percent of patients with PSC
  - PSC occurs in approximately 5 percent of patients with ulcerative colitis
Primary Sclerosing Cholangitis
Primary Sclerosing Cholangitis

Portal bile duct with periductal sclerosis associated with degeneration of the bile duct epithelium

Complications include
- Cholestasis associated problems
  - fatigue, pruritus, steatorrhea, fat-soluble vitamin deficiencies (A, D, E, and K), and metabolic bone disease
- Dominant biliary stricture
- Cholangitis and cholelithiasis
- Cholangiocarcinoma
  - 10 to 15 percent lifetime risk of developing cholangiocarcinoma
- Colon cancer- risk is greater than with UC alone
Primary Biliary Cholangitis

- Characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts
  - Continued loss of intralobular bile ducts causes the signs and symptoms of cholestasis and eventually results in cirrhosis and liver failure
- 95% female predominance
- Disease typically affects middle aged women

Main symptoms are fatigue and pruritis
- May develop typical symptoms of cholestasis
- Dermatologic manifestations
  - Skin hyperpigmentation due to melanin deposition
  - Xanthomata and xanthelasma (eyes)
  - Xerosis and dermatographism
- Rheumatic Symptoms
  - Rheumatoid arthritis, Sjogren’s syndrome, cutaneous Scleroderma or CREST
- Thyroid disease
  - 20 percent of patients with PBC have or will develop hypothyroidism
- Malabsorption
  - Vitamin deficiency
  - Metabolic bone disease
Primary Biliary Cholangitis

- Elevated alkaline phosphatase with minimal elevation in transaminases
- 95% AMA+
  - ANA + in up to 70%
- Elevated lipids
  - Cholesterol may exceed 1000mg/dL
- Liver biopsy
- Treatment
  - UDCA
  - Obeticholic acid

Non-Hepatic Causes of Elevated Liver Tests

- Transaminases
  - Acute pancreatitis
  - Intestinal injury
  - Pulmonary/cerebral/myocardial infarction
  - Burns
  - Rhabdomyolysis/muscular injury

- Alkaline Phosphatase
  - Bone disease
  - Intestinal origin
  - Placental origin
  - Ectopic neoplastic production
  - Hodgkin’s disease
  - Anti-convulsant use
Thank you