2016 SGNA Fall Conference

Hepatology- A Clinical Review

George Nikias MD
Hackensack Gastroenterology Associates

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

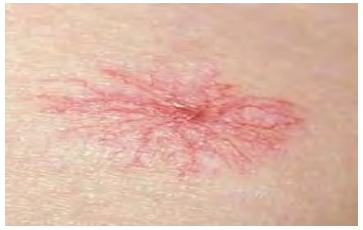
  Acute or Chronic? Hospital or Community acquired?

  Context (Coexistent diseases – Autoimmune/IBD)

  Risk factors (Transfusion/Prior recreational drug use/EtOH)

  Symptoms (Pain/Distention/Confusion)

  Findings (Jaundice/Ascites/Asterixis/Spider Angiomata)



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 antibotic) (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!

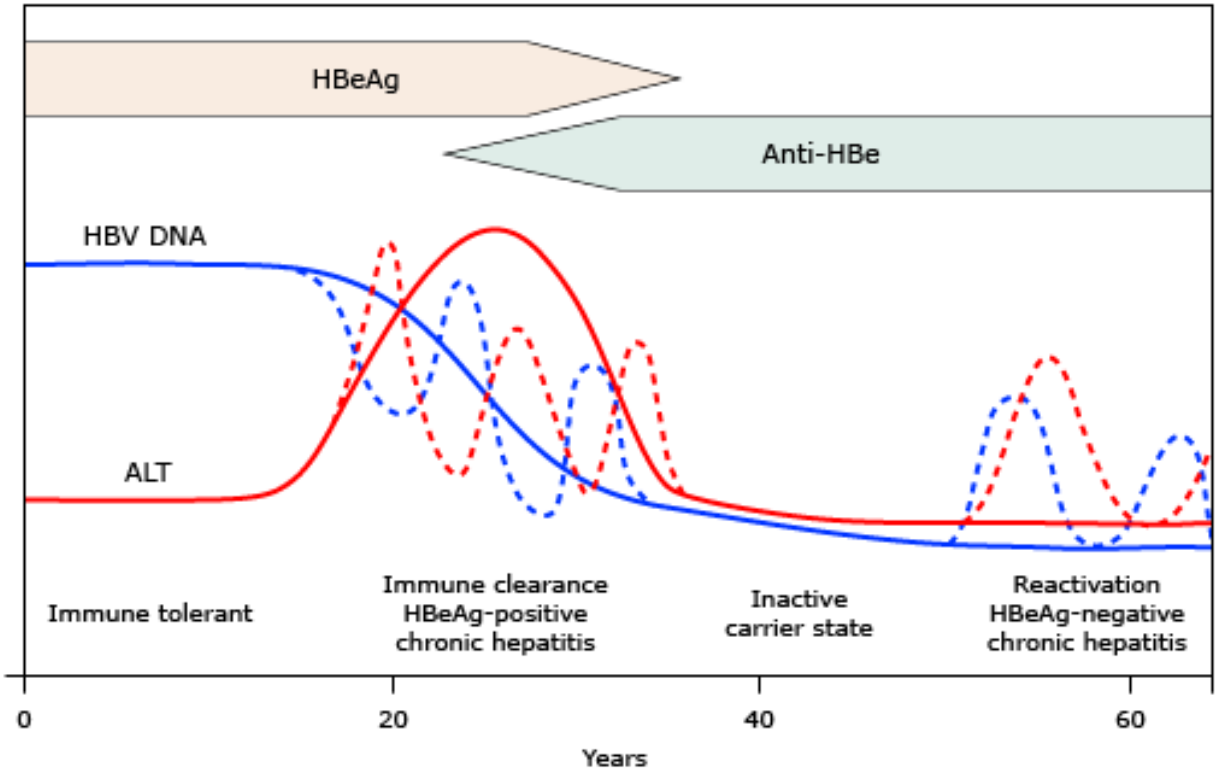
Hepatitis B

- 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

Course of chronic HBV infection



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.

Reproduced with permission from: Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006; 43:S173. Copyright © 2006 John Wiley & Sons, Inc.

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Hepatitis B

- Presentations in host (Chronic states)

- Inactive - HBsAg pos HBeAg neg HBV DNA low ALT Nl No treatment
- Immune tolerant – HBsAg pos HBEAg pos HBV DNA high ALT Nl 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 ?

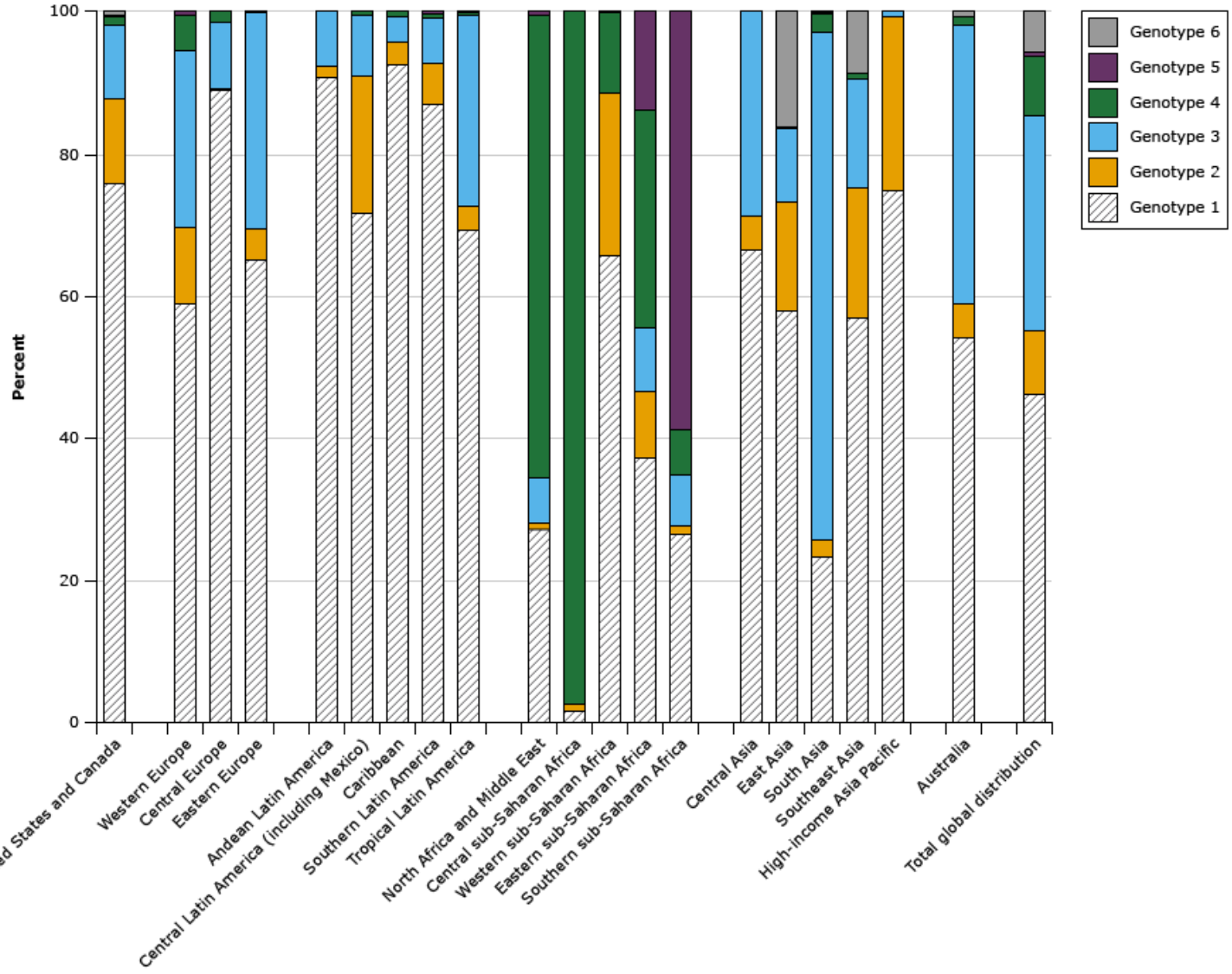
- Decision re treatment based on degree of activity (ALT) viral load (DNA) and degree of liver disease (fibrosis)

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

Carroll KC et al. Hepatitis Viruses. In: Carroll KC et al. eds. *Jawetz, Melnick, & Adelberg's Medical Microbiology, 27e.* New York, NY: McGraw-Hill; 2015.

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



HCV: hepatitis C virus

Data from: Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015; 61:77.

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

Carroll KC et al. Hepatitis Viruses. In: Carroll KC et al. eds. *Jawetz, Melnick, & Adelberg's Medical Microbiology, 27e.* New York, NY: McGraw-Hill; 2015.

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!

Krawitt EL. *N Engl J Med*. 2006;354:54-66.

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

Krawitt EL. *N Engl J Med*. 2006;354:54-66.

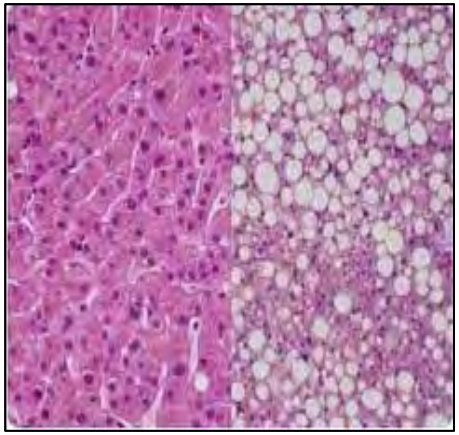
Non-alcoholic Fatty Liver Disease (NAFLD)

- 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)

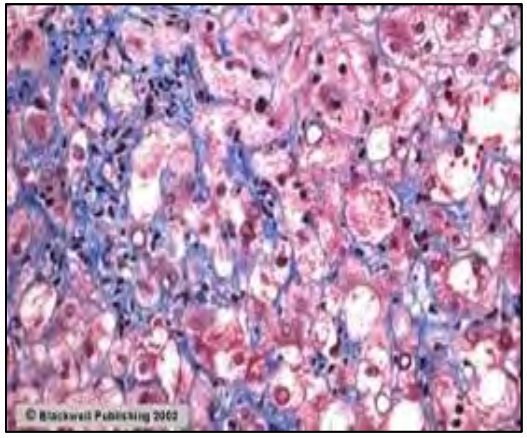
Rinella ME. *JAMA*. 2015;313:2263-2273.

Non-alcoholic Fatty Liver Disease (NAFLD)

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



Normal liver Fatty liver



NASH/Fibrosis

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)

1. Rinella ME. *JAMA*. 2015;313:2263-2273; 2. Neuschwander-Tetri BA et al. *Lancet*. 2015;385:956-965.

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

Das SK, Ray K. *Nature Clin Pract Neurol*. 2006;2:482-493.

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

Das SK, Ray K. *Nature Clin Pract Neurol*. 2006;2:482-493.

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

Bacon BR et al. Available at: https://www.aasld.org/sites/default/files/guideline_documents/Hemochromatosis2011.pdf. Accessed April 20, 2016.

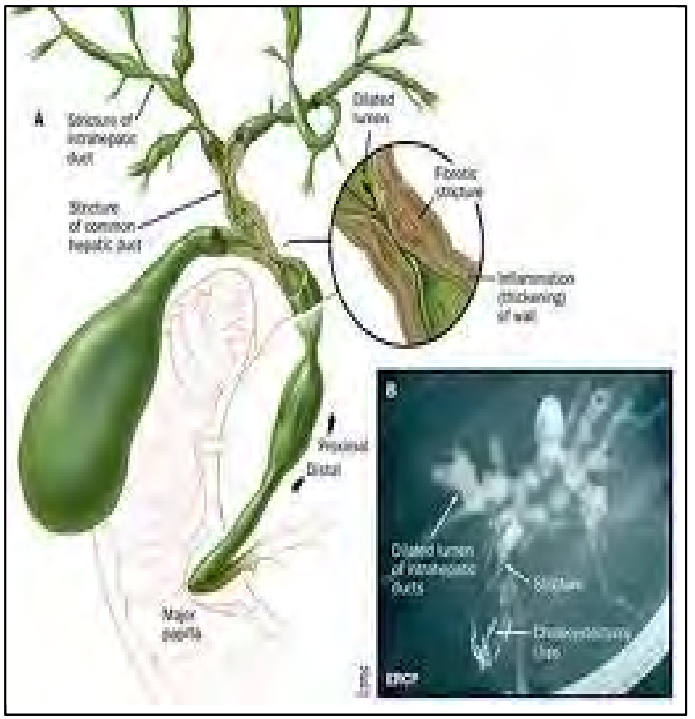
Genetic Hemochromatosis

- 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

Bacon BR et al. Available at: https://www.aasld.org/sites/default/files/guideline_documents/Hemochromatosis2011.pdf. Accessed April 20, 2016.

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

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

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

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)

Carey EJ et al. *Lancet*. 2015;386:1565-1575.

Hemolysis, **E**levated **L**iver Enzymes, **L**ow **P**latelets (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

Haram K et al. *BMC Pregnancy Childbirth.* 2009;9:8-15.

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

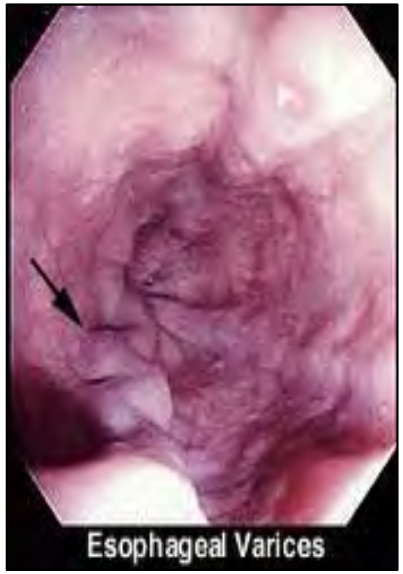
Complications of Liver Disease: Cirrhosis

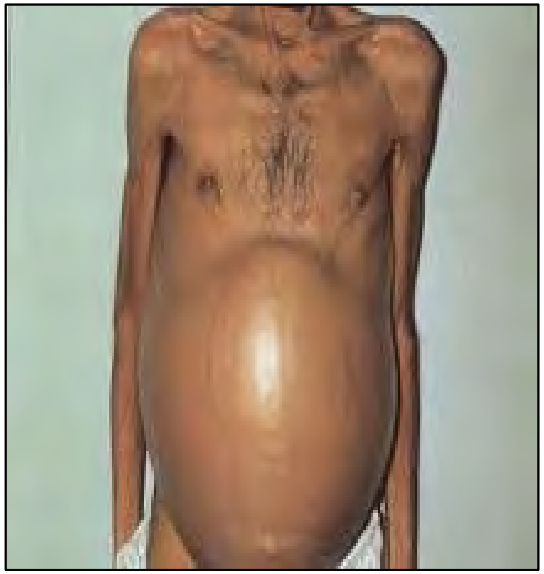
- Hepatocellular carcinoma (rising incidence): 80% in cirrhosis[1,2]
  - Ultrasound screening twice yearly
  - Alpha-fetoprotein not sensitive
  - Orthotopic liver transplant only curative option in cirrhosis
  - Ablation if orthotopic liver transplant not an option or as bridge to transplant
  - Resection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

1. Sherman M et al. *Hepatology.* 2012;56:793-796; 2. Bruix J et al. *Hepatology.* 2011;53:1020-1022.

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)

Bloom S et al. *Intern Med J.* 2015;45:16-26.

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 cm^2
- Cardiac issues[3]:
  - Hepatopulmonary syndrome: hypoxia/orthodeoxia (AV shunting)
  - Portopulmonary hypertension: right heart failure (arteriopathy)
  - Cirrhotic cardiomyopathy (systolic/diastolic dysfunction)

1. Angeli P, Gines P. *J* Hepatol. 2012;57:1135-1150; 2. Bruix J et al. *Hepatology.* 2011;53:1020-1022; 3. Meller S, Henriksen JH. *Gut*. 2008;57:268-278.

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

Gotthardt D et al. *Nephrol Dial Transplant.* 2007;22 (Suppl 8):viii5-viii8.

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

Gotthardt D et al. *Nephrol Dial Transplant.* 2007;22 (Suppl 8):viii5-viii8.

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

Case

-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 ?