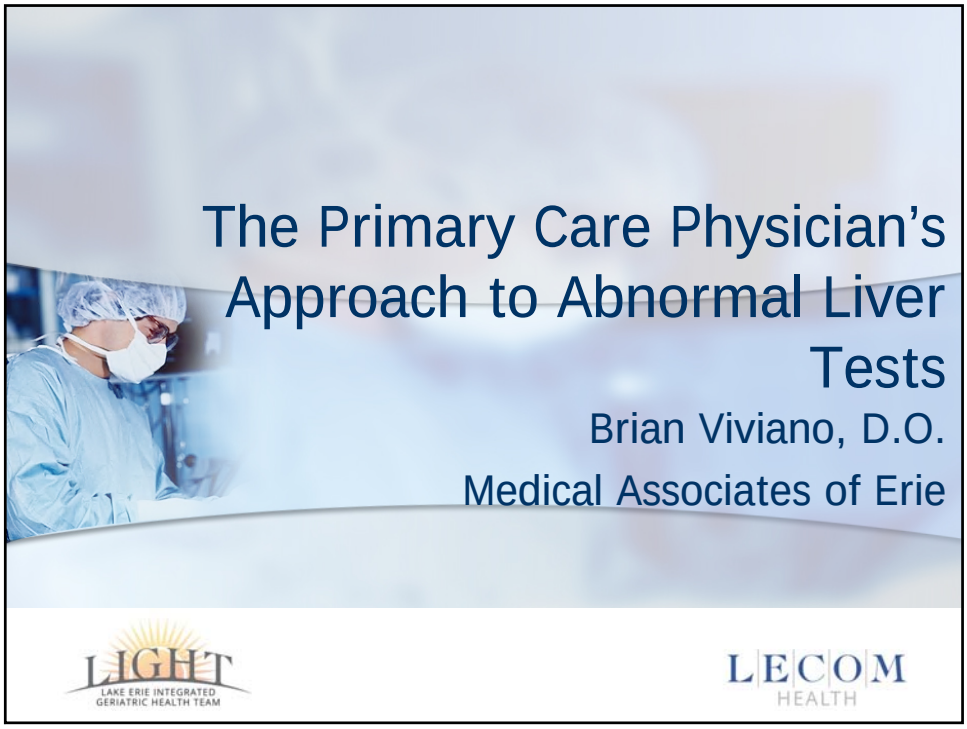

The Primary Care Physician's Approach to Abnormal Liver Tests
Brian Viviano, D.O.
Medical Associates of Erie
LIGHT
LAKE ERIE INTEGRATED GERIATRIC HEALTH TEAM
LECOM HEALTH


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

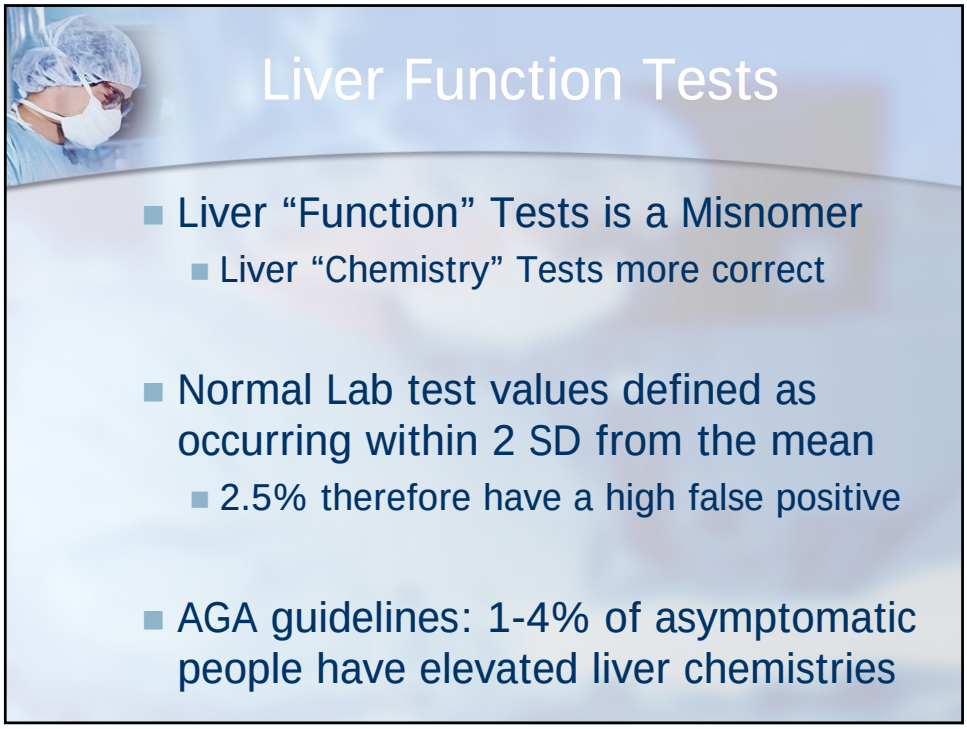
## Case Presentation

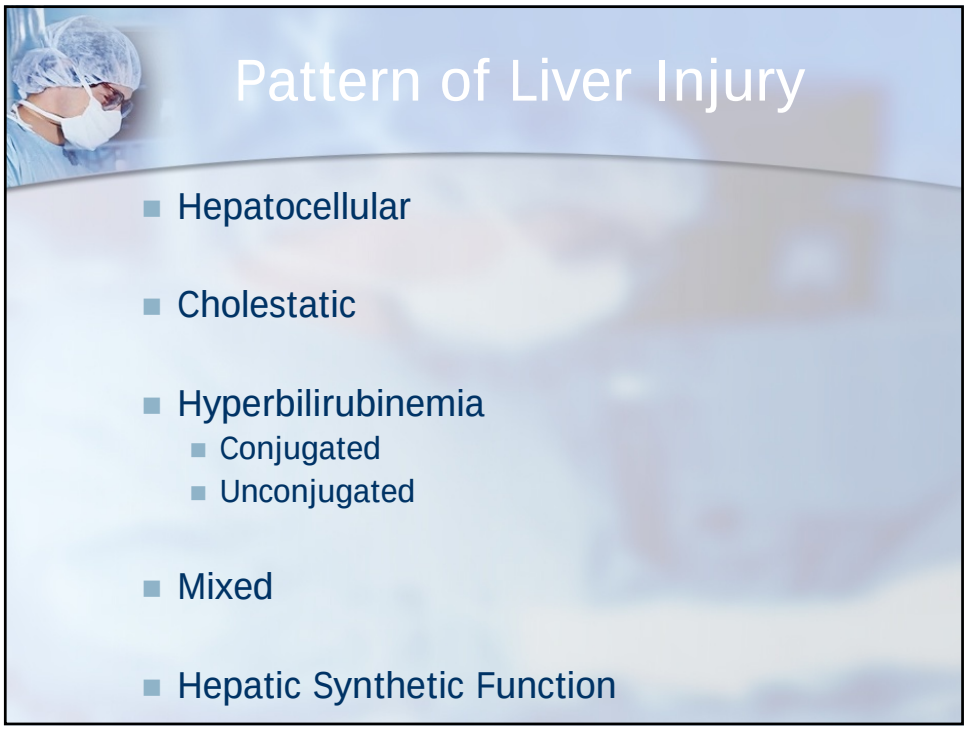
- Mr. Steel is a 59 year old male that presents for wellness exam. He has not followed with a physician for over 10 years. He has no complaints. Physical exam is benign except dark skin and a palpable spleen. He admits to drinking 2 bourbon's with dinner and sometimes more on weekend. Family history includes two brothers with diabetes mellitus.

## Routine blood work

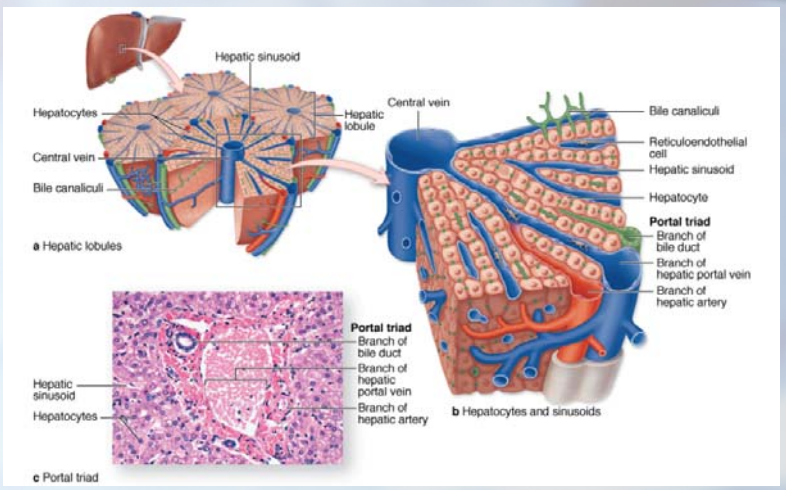
| | |
|---|---|
| AST | 289 IU/L |
| ALT | 311 IU/L |
| Alk. Phos. | 343 IU/L |
| GGTP | 360 IU/L |
| T. bilirubin | 3.0 mg/dl |

- 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

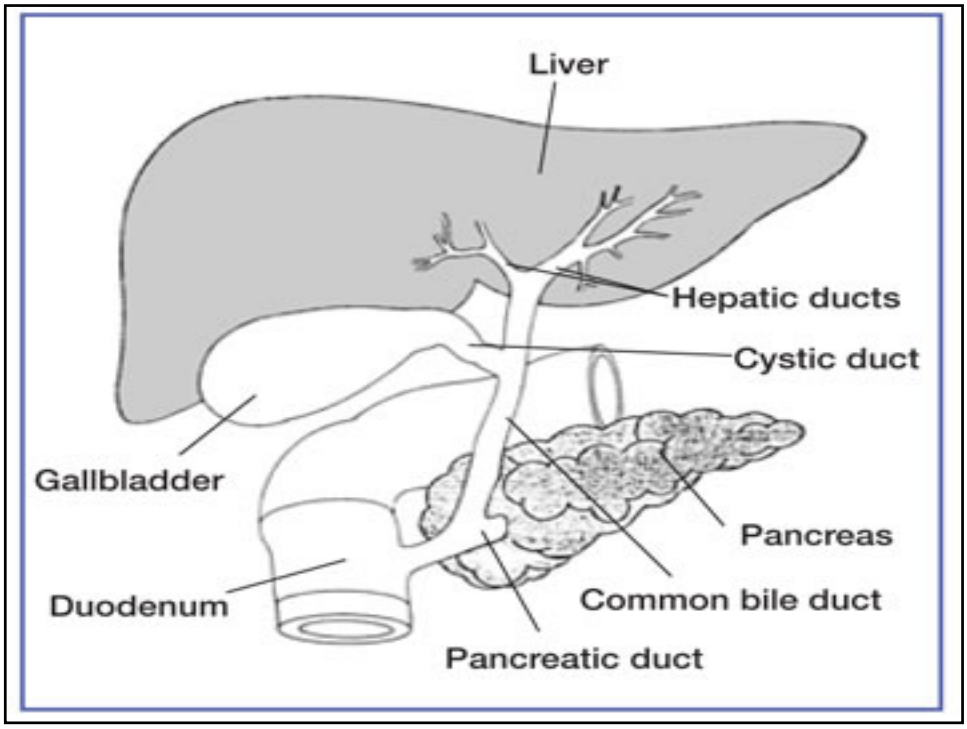

Pattern of Liver Injury
Hepatocellular
Cholestatic
Hyperbilirubinemia
Conjugated
Unconjugated
Mixed
Hepatic Synthetic Function

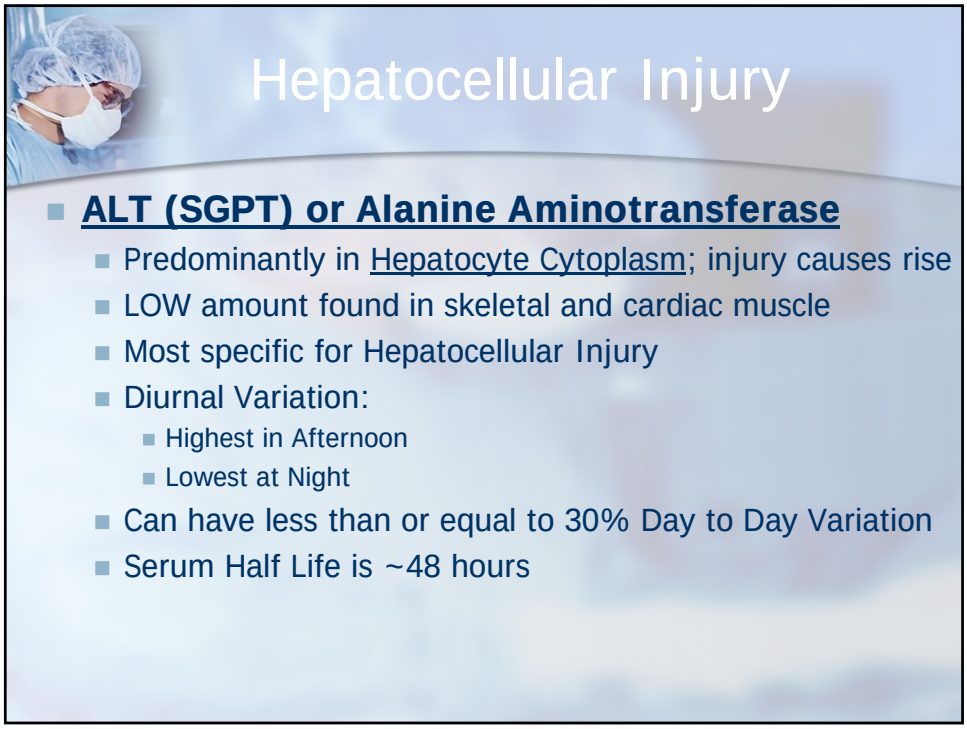
# Portal Triad

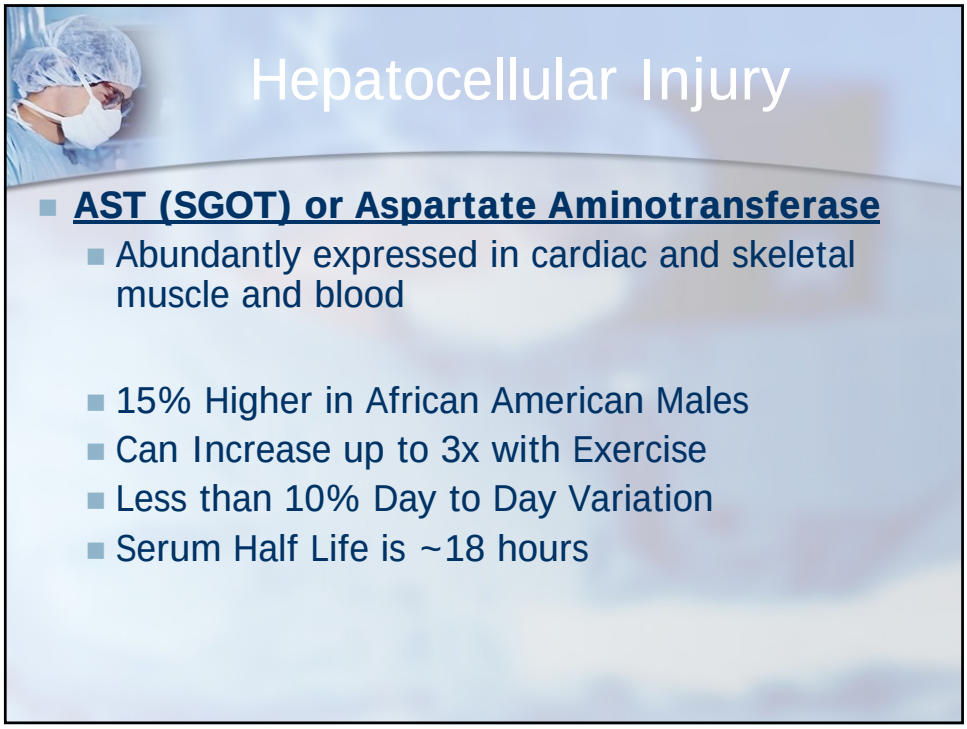


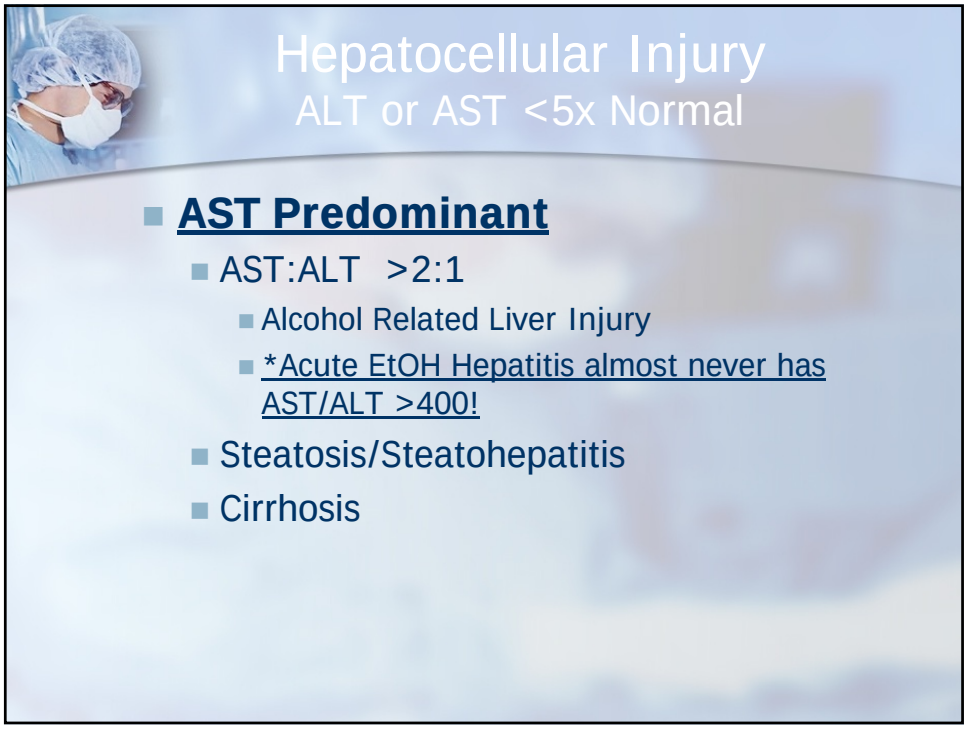

# Common Liver Chemistries

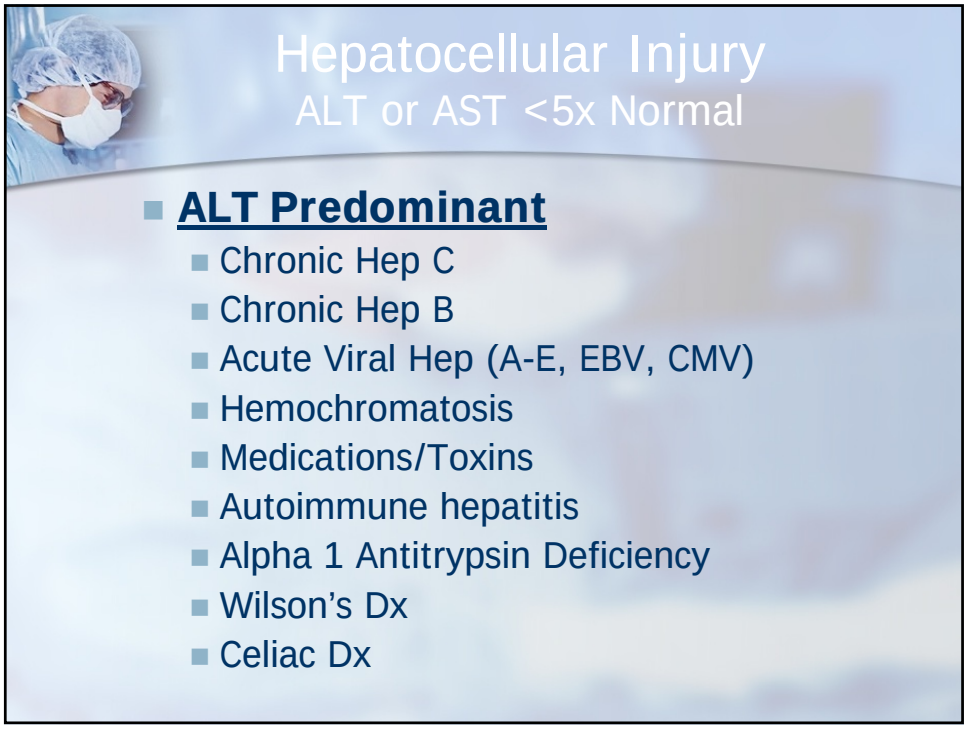
| Liver chemistry test | Clinical Implication |
|---|---|
| Alanine aminotransferase | Hepatocellular damage |
| Aspartate aminotransferase | Hepatocellular damage |
| Bilirubin | Cholestasis, Impaired conjugation, or Biliary obstruction |
| Alkaline phosphatase | Cholestasis, Infiltrative Dx, or Biliary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

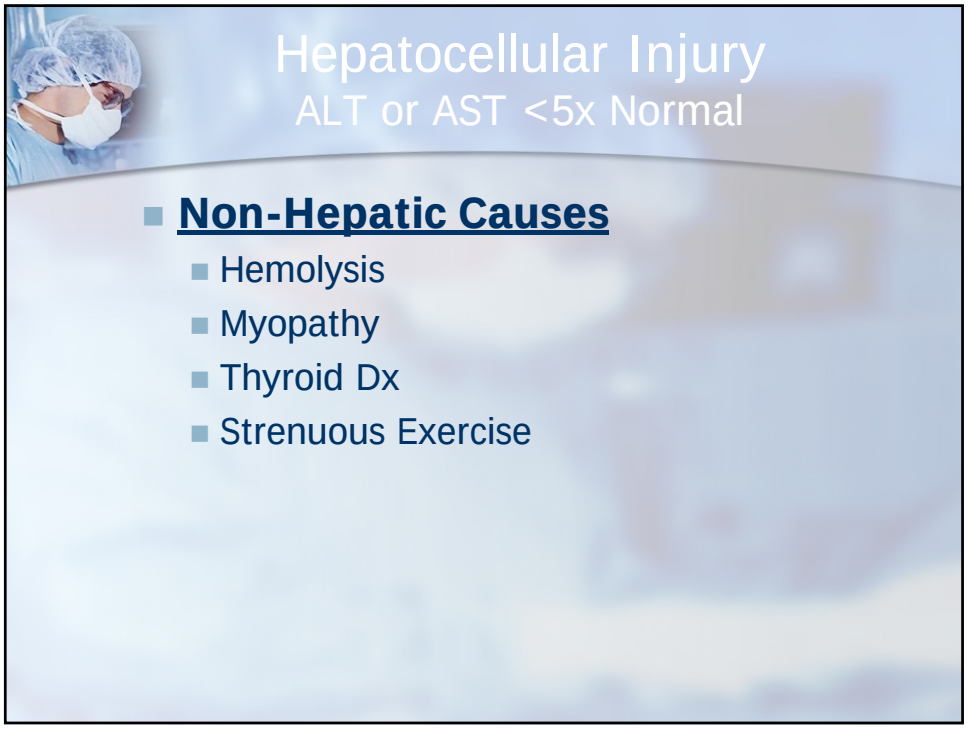

Liver
Hepatic ducts
Cystic duct
Gallbladder
Pancreas
Duodenum
Common bile duct
Pancreatic duct

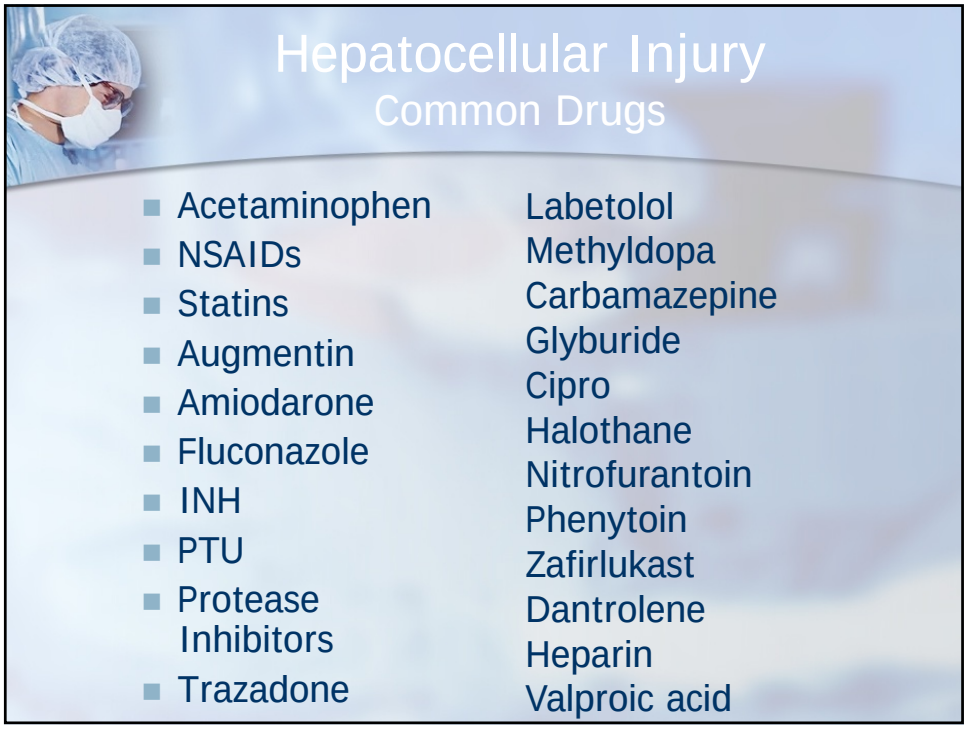

Hepatocellular Injury
ALT (SGPT) or Alanine Aminotransferase
Predominantly in Hepatocyte Cytoplasm; injury causes rise
LOW amount found in skeletal and cardiac muscle
Most specific for Hepatocellular Injury
Diurnal Variation:
Highest in Afternoon
Lowest at Night
Can have less than or equal to 30% Day to Day Variation
Serum Half Life is ~48 hours

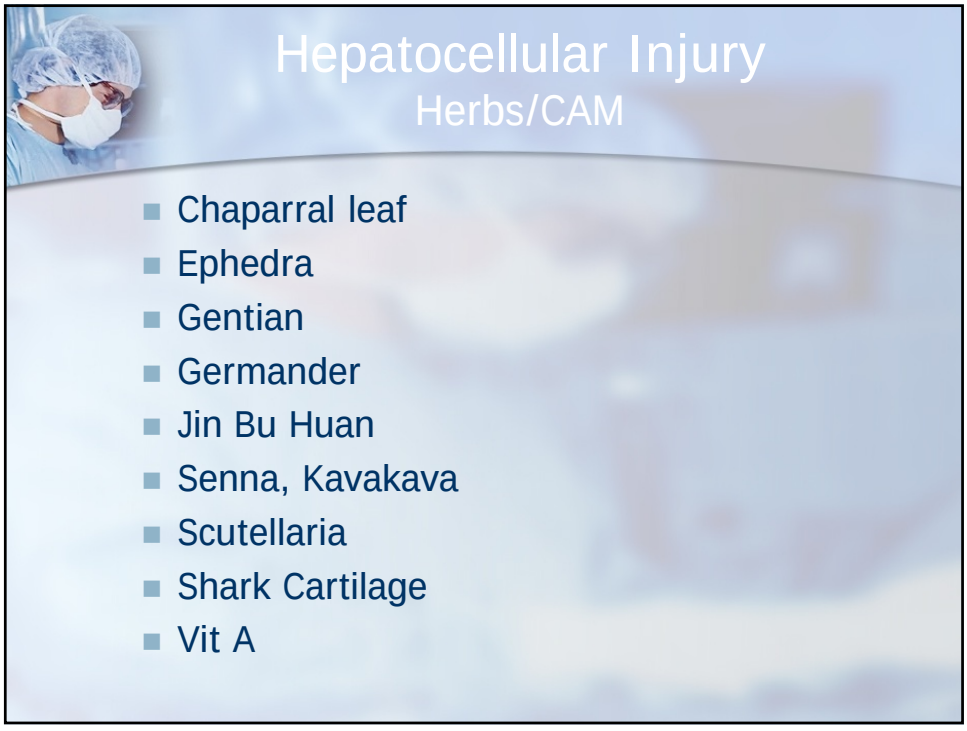

Hepatocellular Injury
AST (SGOT) or Aspartate Aminotransferase
Abundantly expressed in cardiac and skeletal muscle and blood
15% Higher in African American Males
Can Increase up to 3x with Exercise
Less than 10% Day to Day Variation
Serum Half Life is ~18 hours


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

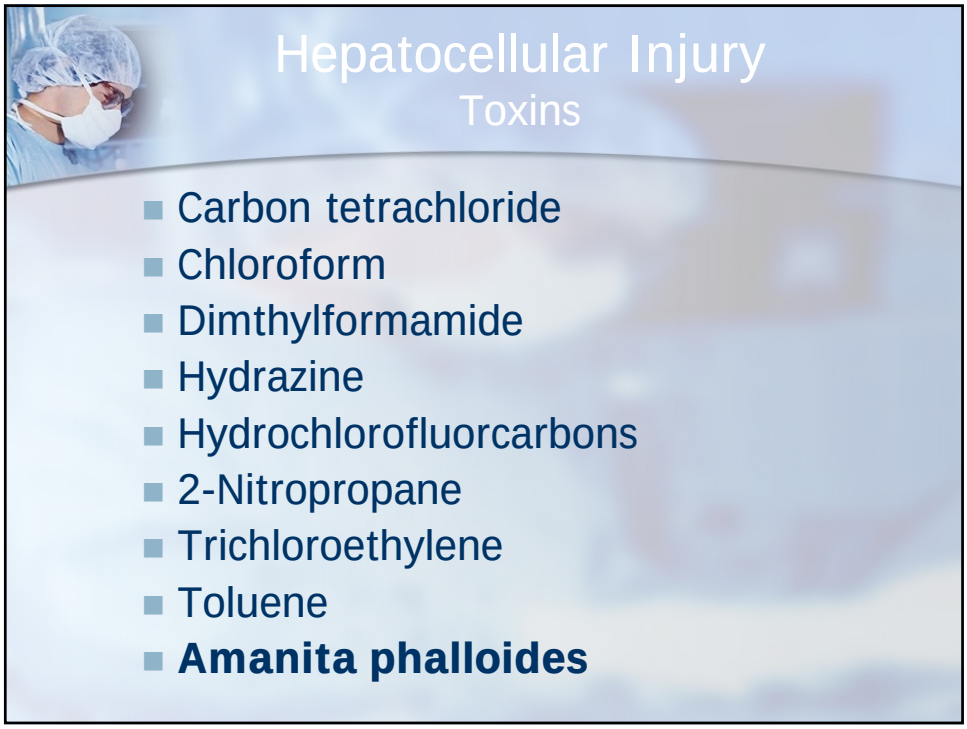

Hepatocellular Injury
ALT or AST <5x Normal
ALT Predominant
Chronic Hep C
Chronic Hep B
Acute Viral Hep (A-E, EBV, CMV)
Hemochromatosis
Medications/Toxins
Autoimmune hepatitis
Alpha 1 Antitrypsin Deficiency
Wilson's Dx
Celiac Dx

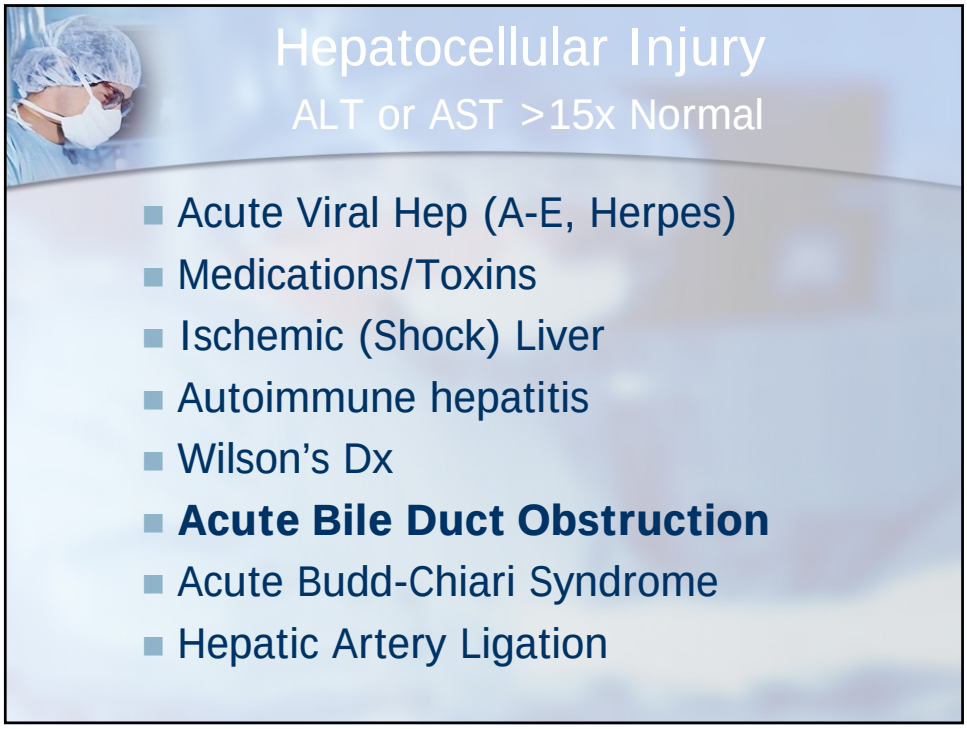

Hepatocellular Injury
ALT or AST <5x Normal
Non-Hepatic Causes
Hemolysis
Myopathy
Thyroid Dx
Strenuous Exercise

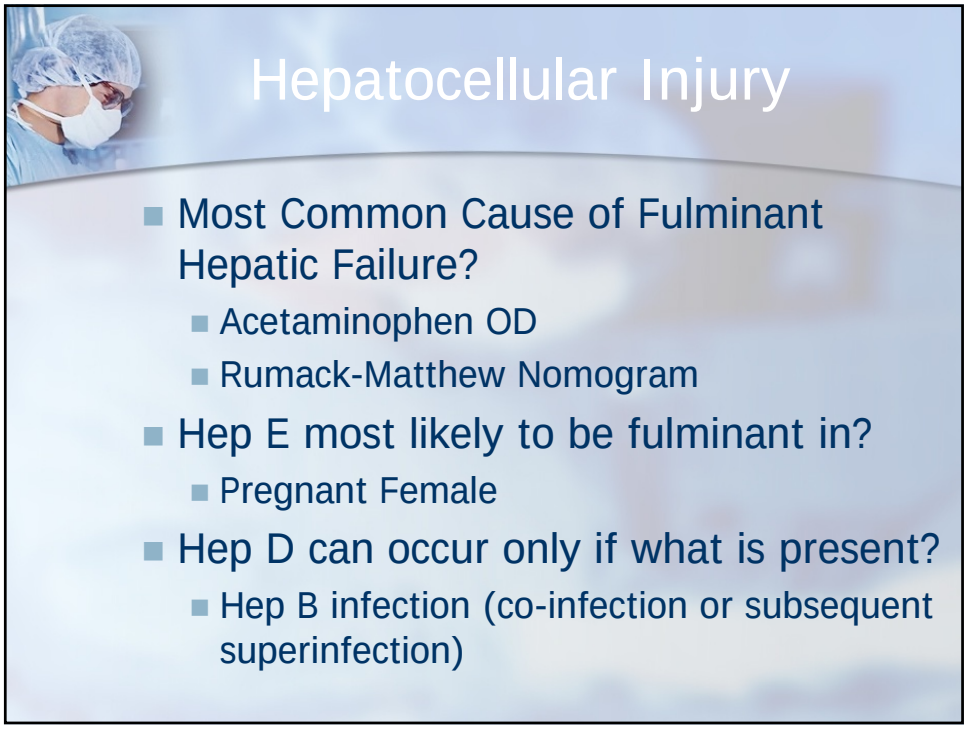

Hepatocellular Injury
Common Drugs
Acetaminophen
NSAIDs
Statins
Augmentin
Amiodarone
Fluconazole
INH
PTU
Protease Inhibitors
Trazadone
Labetolol
Methyldopa
Carbamazepine
Glyburide
Cipro
Halothane
Nitrofurantoin
Phenytoin
Zafirlukast
Dantrolene
Heparin
Valproic acid


Hepatocellular Injury
Herbs/CAM
Chaparral leaf
Ephedra
Gentian
Germander
Jin Bu Huan
Senna, Kavakava
Scutellaria
Shark Cartilage
Vit A

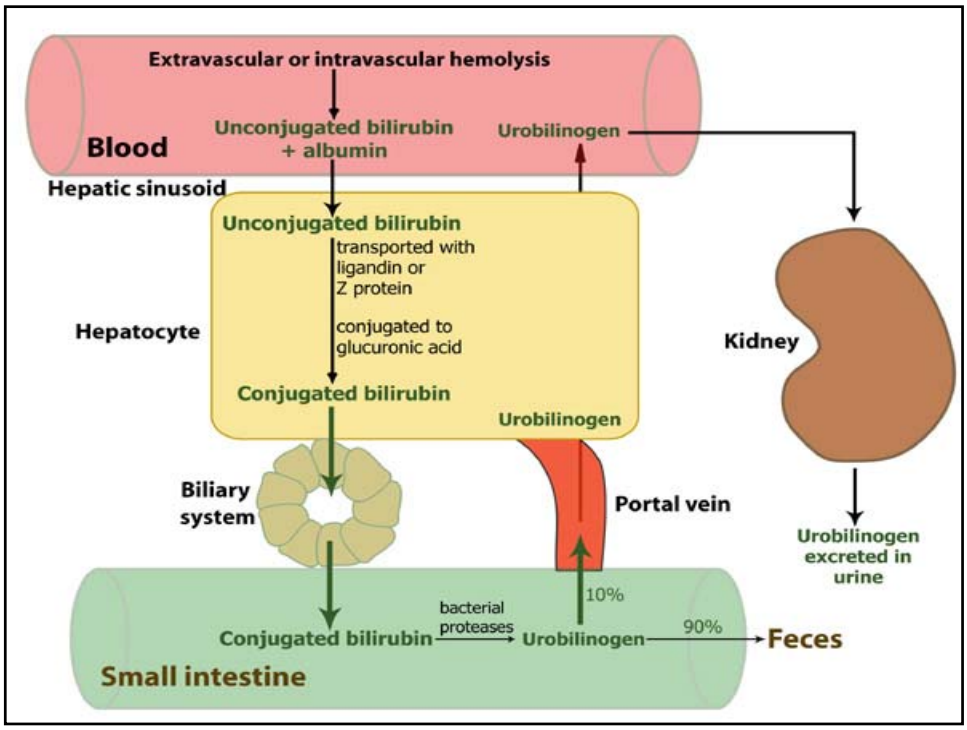

Hepatocellular Injury
Illicit Drugs
Anabolic Steroids
Cocaine
Ecstasy (MDMA)
Phencyclidine (PCP)

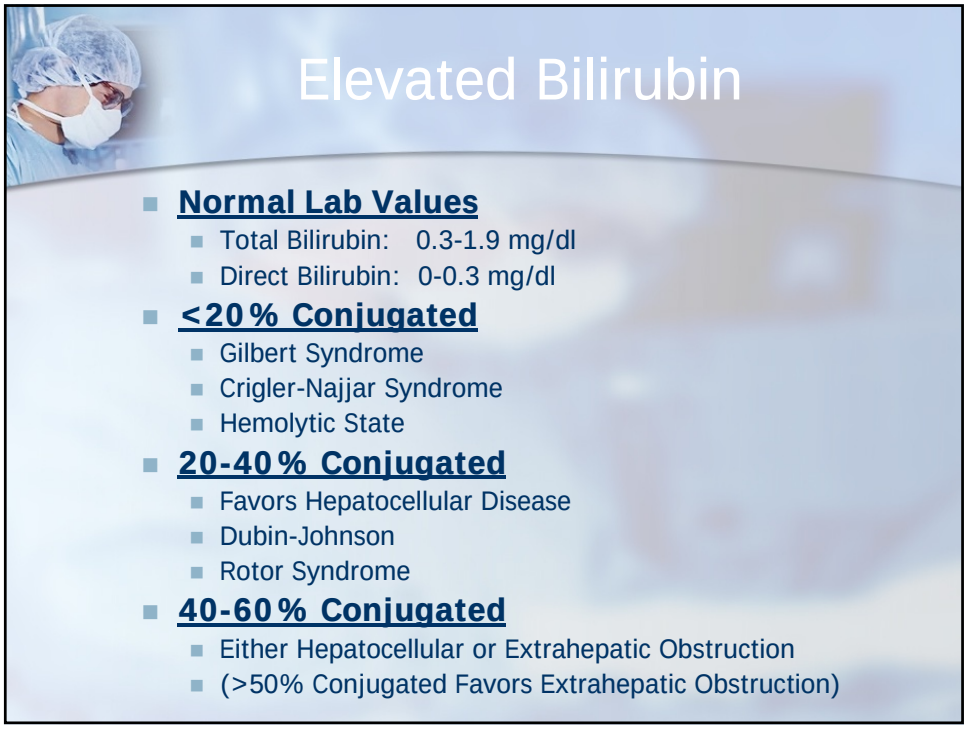

Hepatocellular Injury
Toxins
Carbon tetrachloride
Chloroform
Dimthylformamide
Hydrazine
Hydrochlorofluorcarbons
2-Nitropropane
Trichloroethylene
Toluene
Amanita phalloides

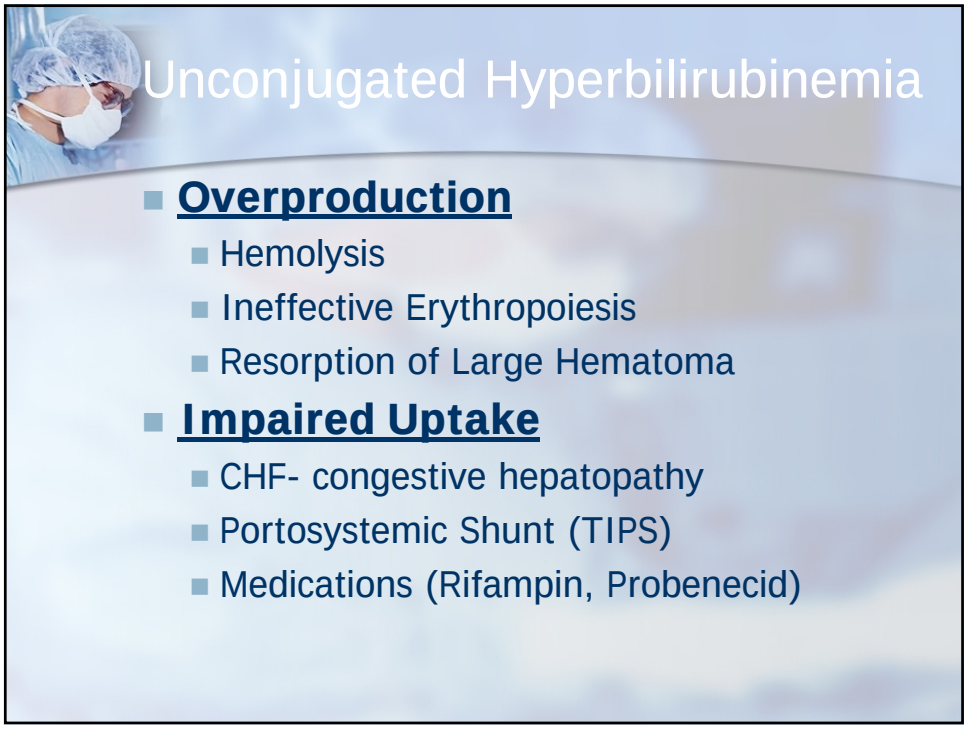

Hepatocellular Injury
ALT or AST >15x Normal
Acute Viral Hep (A-E, Herpes)
Medications/Toxins
Ischemic (Shock) Liver
Autoimmune hepatitis
Wilson's Dx
**Acute Bile Duct Obstruction**
Acute Budd-Chiari Syndrome
Hepatic Artery Ligation

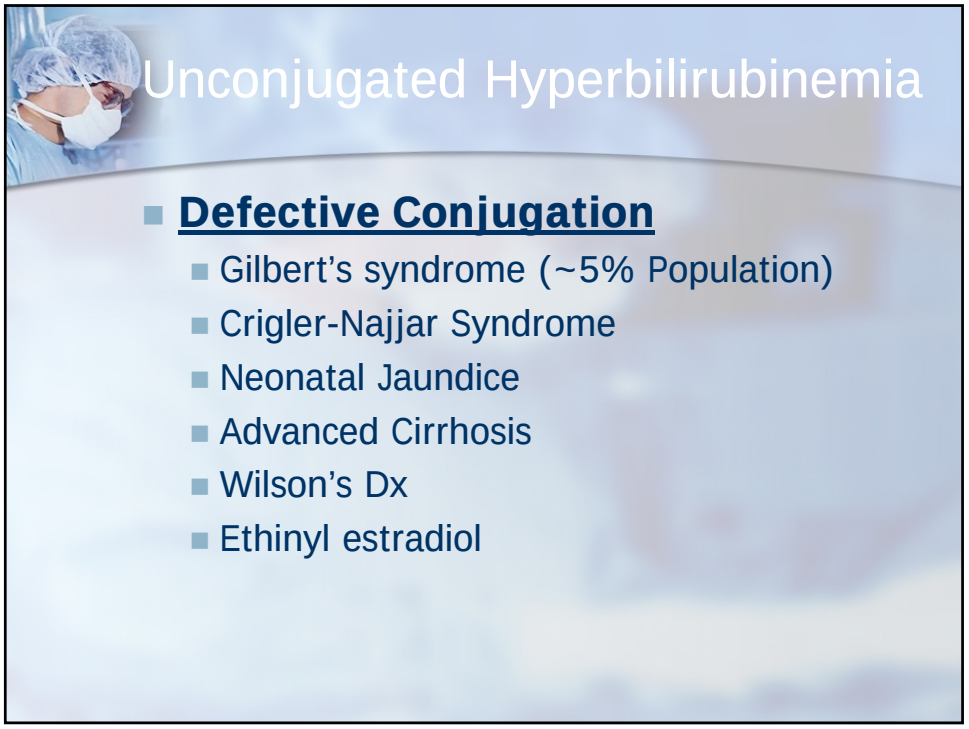

Hepatocellular Injury
Most Common Cause of Fulminant Hepatic Failure?
Acetaminophen OD
Rumack-Matthew Nomogram
Hep E most likely to be fulminant in?
Pregnant Female
Hep D can occur only if what is present?
Hep B infection (co-infection or subsequent superinfection)

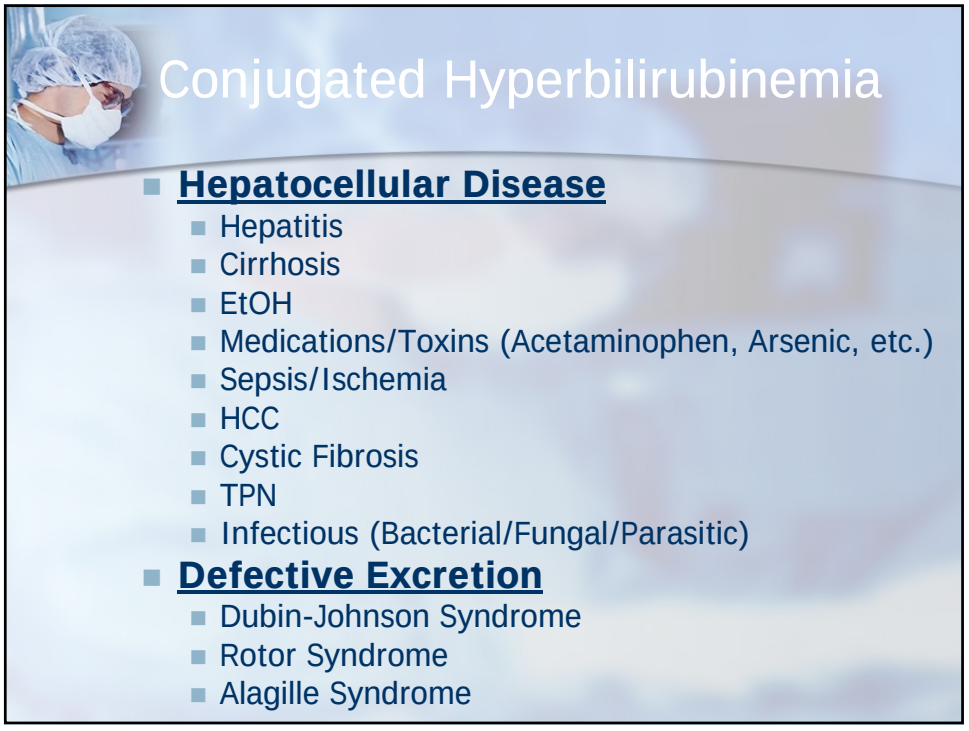

Bilirubin
Bilirubin
Heme degradation product
Unconjugated (Indirect) Insoluble
Conjugated (Direct) Water Soluble
Urine – Urobilinogen (Dark Amber Urine)
Stool – Stercobilinogen (Clay Stool)
What level will lead to Jaundice?
>2.5

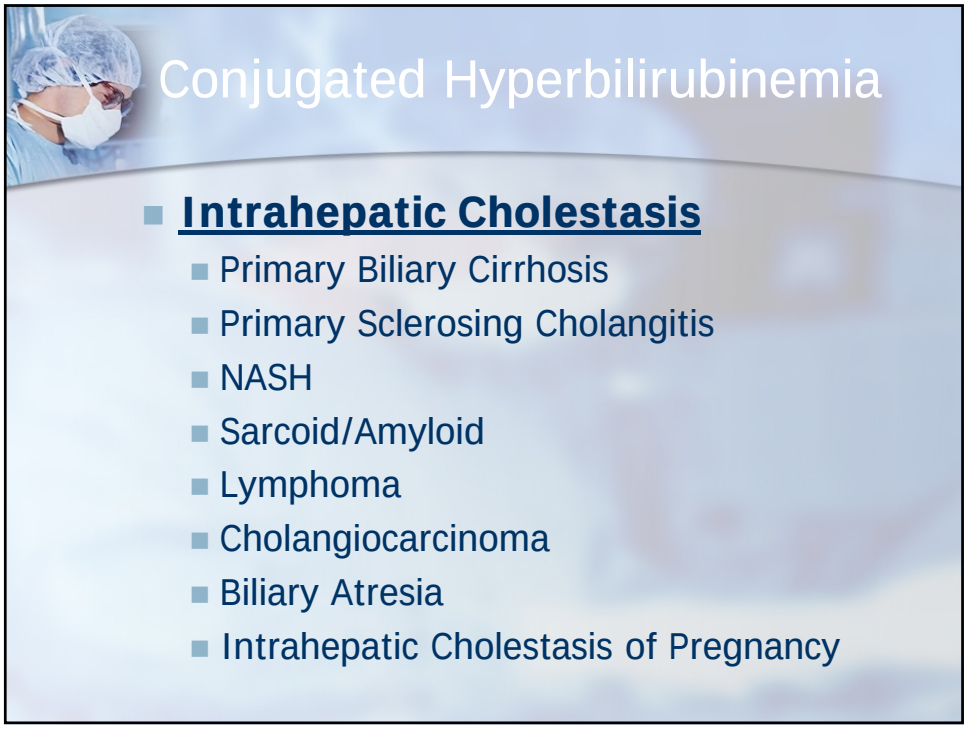

Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin + albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with ligandin or Z protein
conjugated to glucuronic acid
Hepatocyte
Conjugated bilirubin
Urobilinogen
Kidney
Biliary system
Portal vein
Urobilinogen excreted in urine
10%
bacterial proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

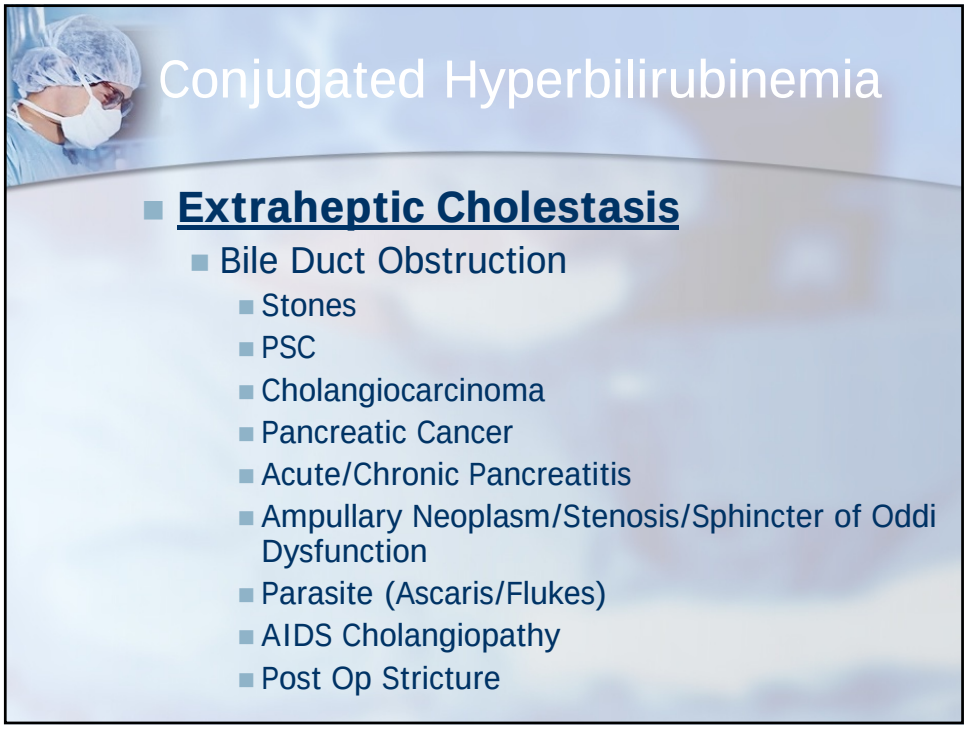

Elevated Bilirubin
Normal Lab Values
Total Bilirubin: 0.3-1.9 mg/dl
Direct Bilirubin: 0-0.3 mg/dl
<20% Conjugated
Gilbert Syndrome
Crigler-Najjar Syndrome
Hemolytic State
20-40% Conjugated
Favors Hepatocellular Disease
Dubin-Johnson
Rotor Syndrome
40-60% Conjugated
Either Hepatocellular or Extrahepatic Obstruction
(>50% Conjugated Favors Extrahepatic Obstruction)

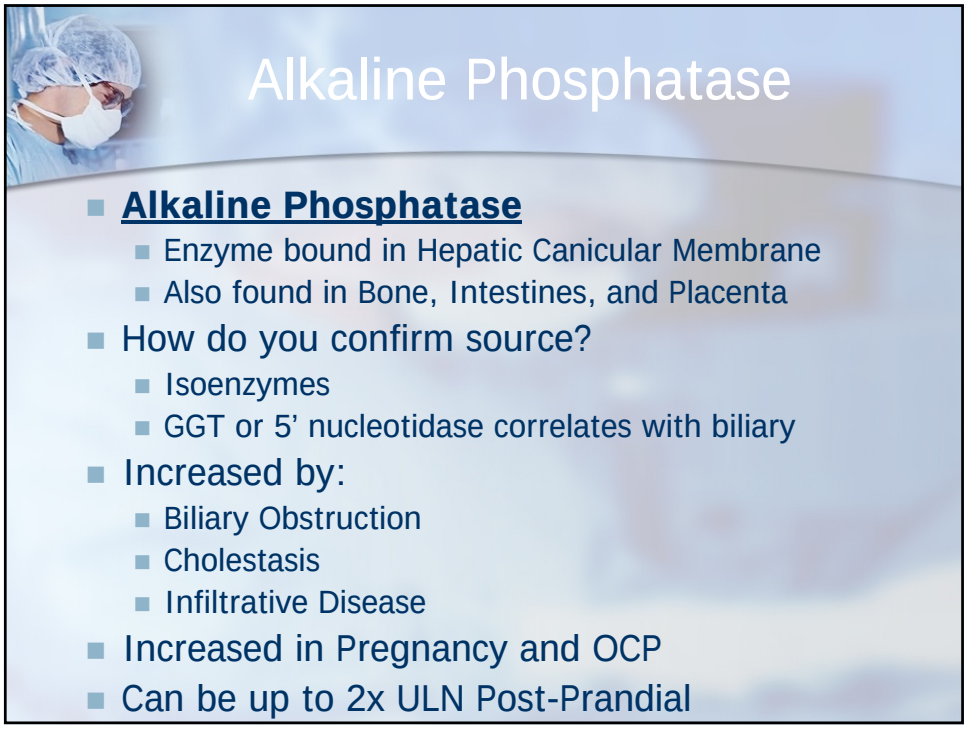

Unconjugated Hyperbilirubinemia
Overproduction
Hemolysis
Ineffective Erythropoiesis
Resorption of Large Hematoma
Impaired Uptake
CHF- congestive hepatopathy
Portosystemic Shunt (TIPS)
Medications (Rifampin, Probenecid)

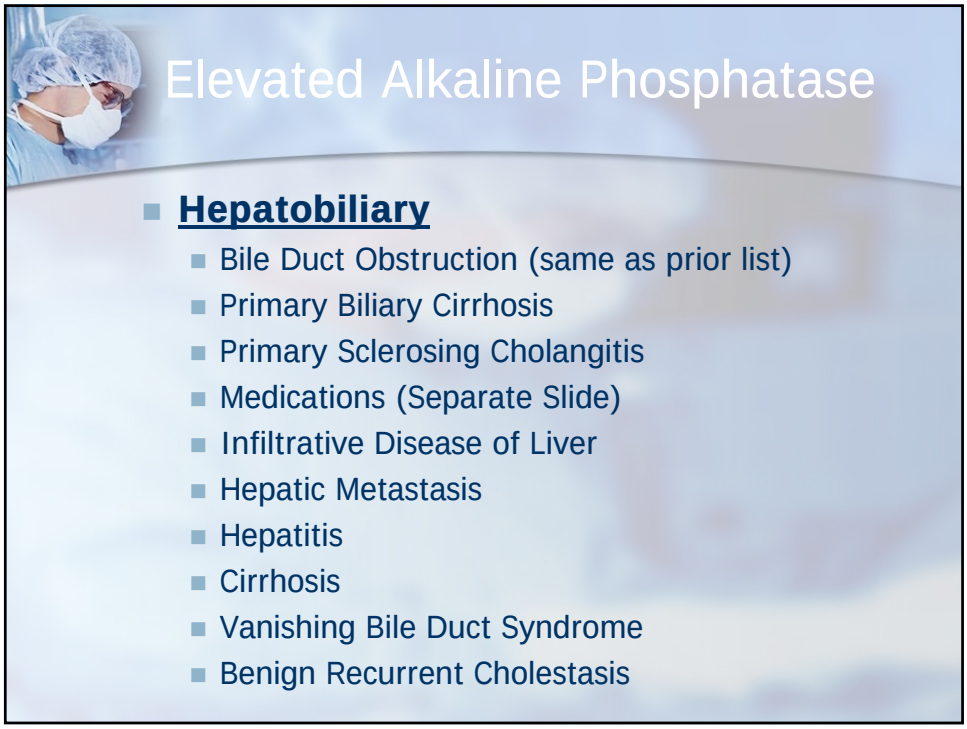

Unconjugated Hyperbilirubinemia
Defective Conjugation
Gilbert's syndrome (~5% Population)
Crigler-Najjar Syndrome
Neonatal Jaundice
Advanced Cirrhosis
Wilson's Dx
Ethinyl estradiol

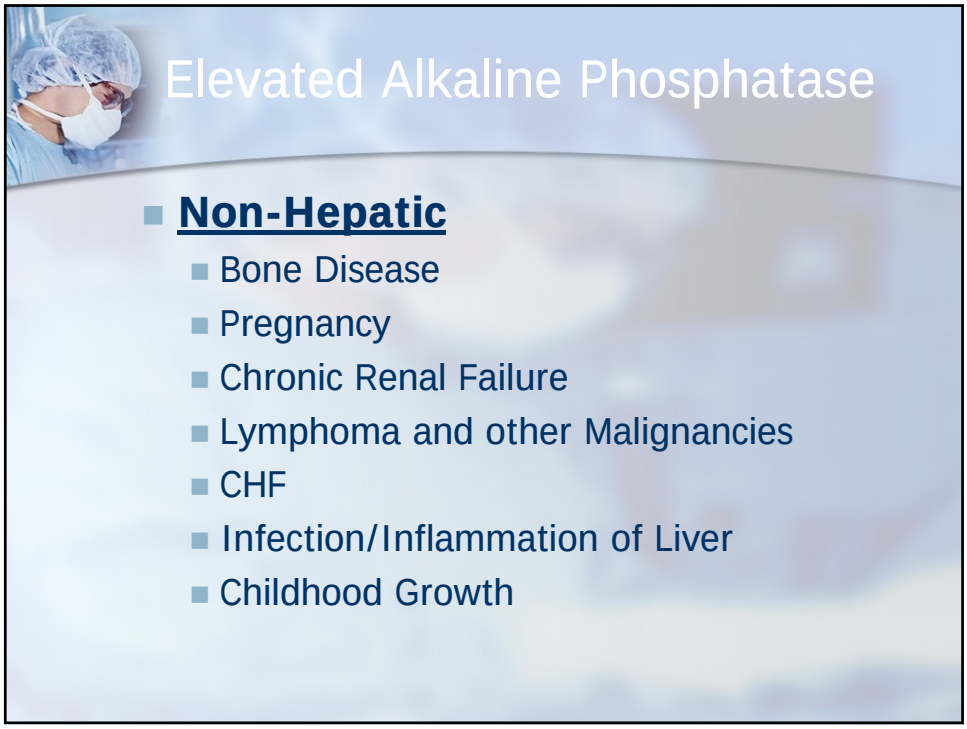

Conjugated Hyperbilirubinemia
Hepatocellular Disease
Hepatitis
Cirrhosis
EtOH
Medications/Toxins (Acetaminophen, Arsenic, etc.)
Sepsis/Ischemia
HCC
Cystic Fibrosis
TPN
Infectious (Bacterial/Fungal/Parasitic)
Defective Excretion
Dubin-Johnson Syndrome
Rotor Syndrome
Alagille Syndrome

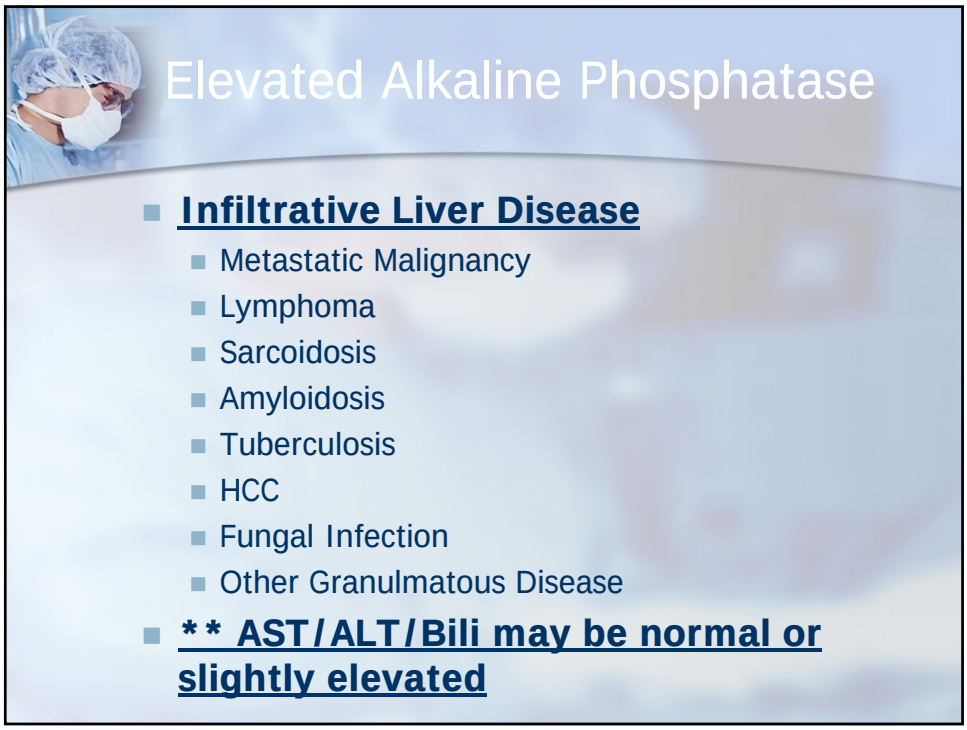

Conjugated Hyperbilirubinemia
Intrahepatic Cholestasis
Primary Biliary Cirrhosis
Primary Sclerosing Cholangitis
NASH
Sarcoid/Amyloid
Lymphoma
Cholangiocarcinoma
Biliary Atresia
Intrahepatic Cholestasis of Pregnancy

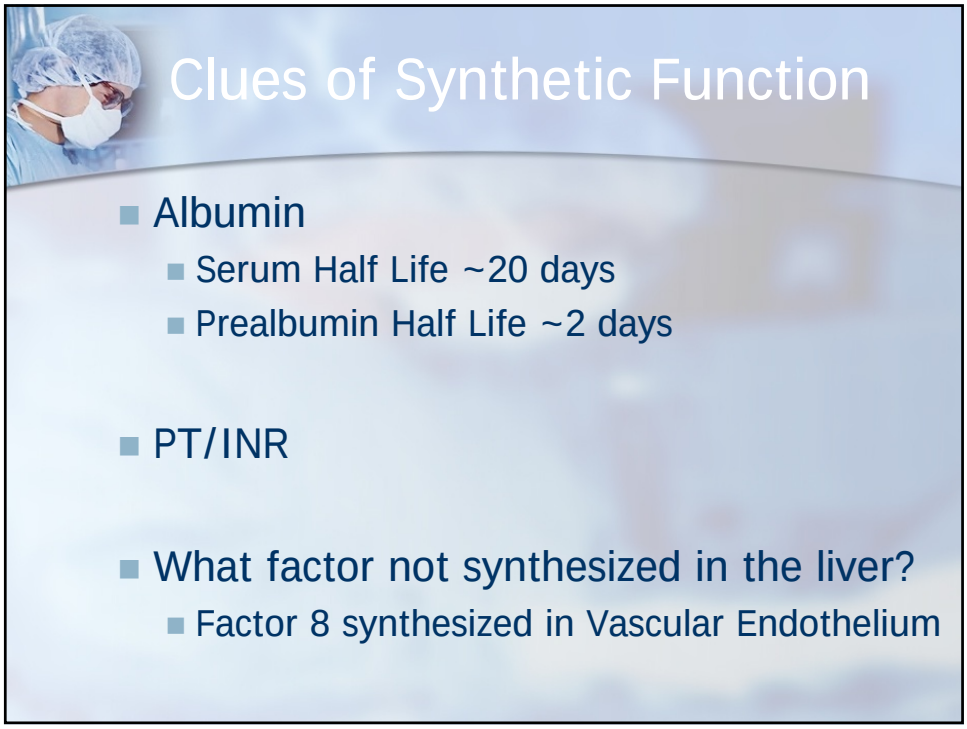

Conjugated Hyperbilirubinemia
Extraheptic Cholestasis
Bile Duct Obstruction
Stones
PSC
Cholangiocarcinoma
Pancreatic Cancer
Acute/Chronic Pancreatitis
Ampullary Neoplasm/Stenosis/Sphincter of Oddi Dysfunction
Parasite (Ascaris/Flukes)
AIDS Cholangiopathy
Post Op Stricture

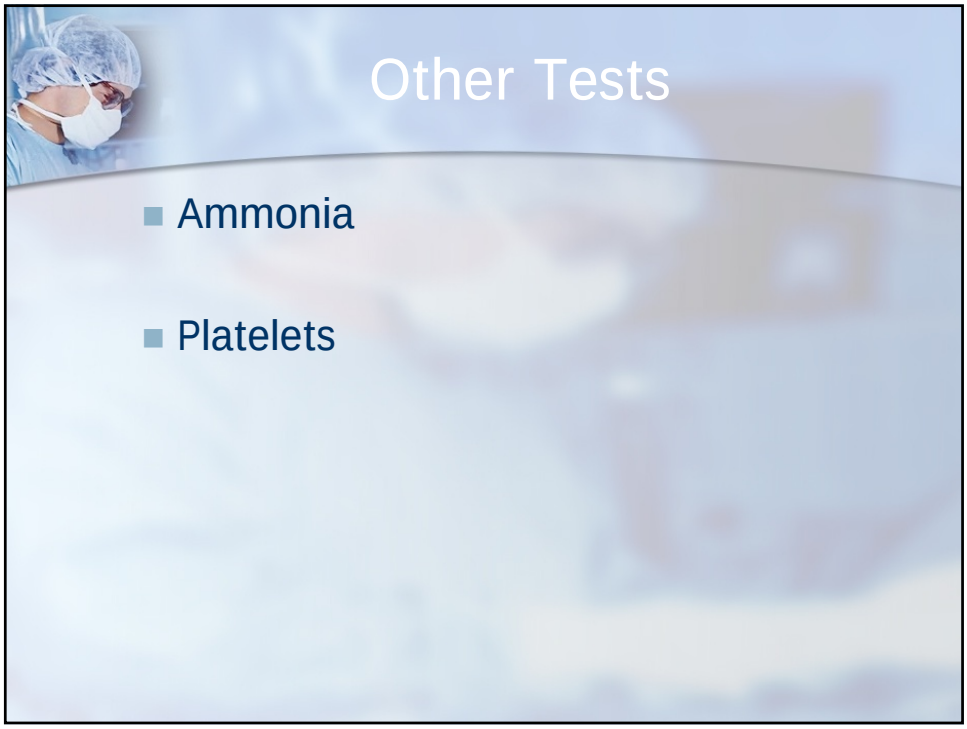

Alkaline Phosphatase
Alkaline Phosphatase
Enzyme bound in Hepatic Canicular Membrane
Also found in Bone, Intestines, and Placenta
How do you confirm source?
Isoenzymes
GGT or 5' nucleotidase correlates with biliary
Increased by:
Biliary Obstruction
Cholestasis
Infiltrative Disease
Increased in Pregnancy and OCP
Can be up to 2x ULN Post-Prandial

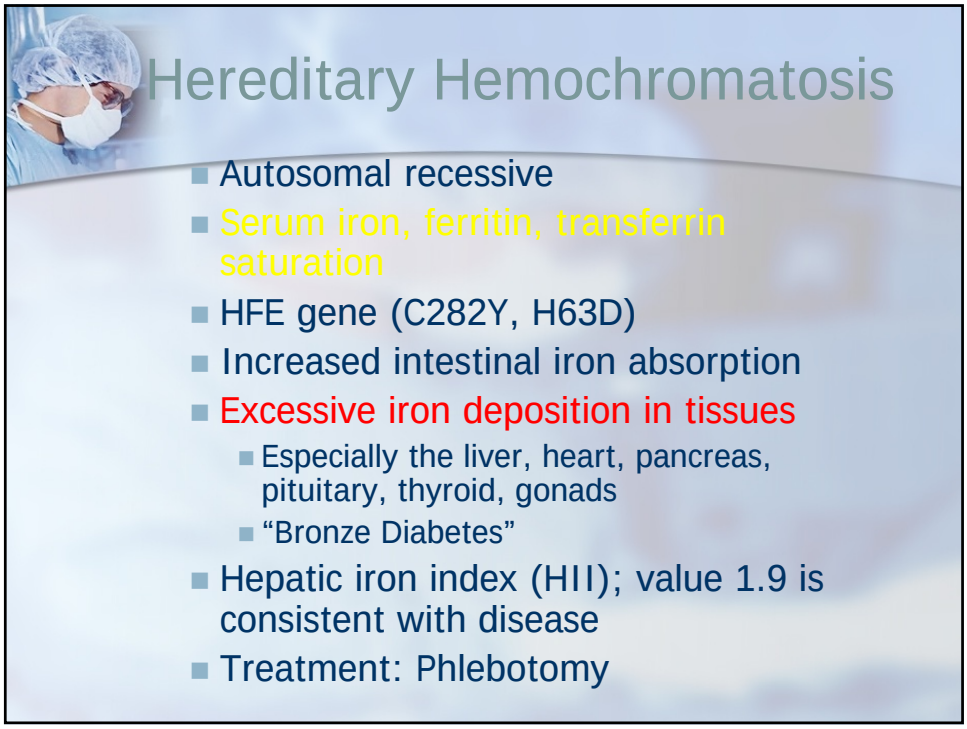

Elevated Alkaline Phosphatase
Hepatobiliary
Bile Duct Obstruction (same as prior list)
Primary Biliary Cirrhosis
Primary Sclerosing Cholangitis
Medications (Separate Slide)
Infiltrative Disease of Liver
Hepatic Metastasis
Hepatitis
Cirrhosis
Vanishing Bile Duct Syndrome
Benign Recurrent Cholestasis

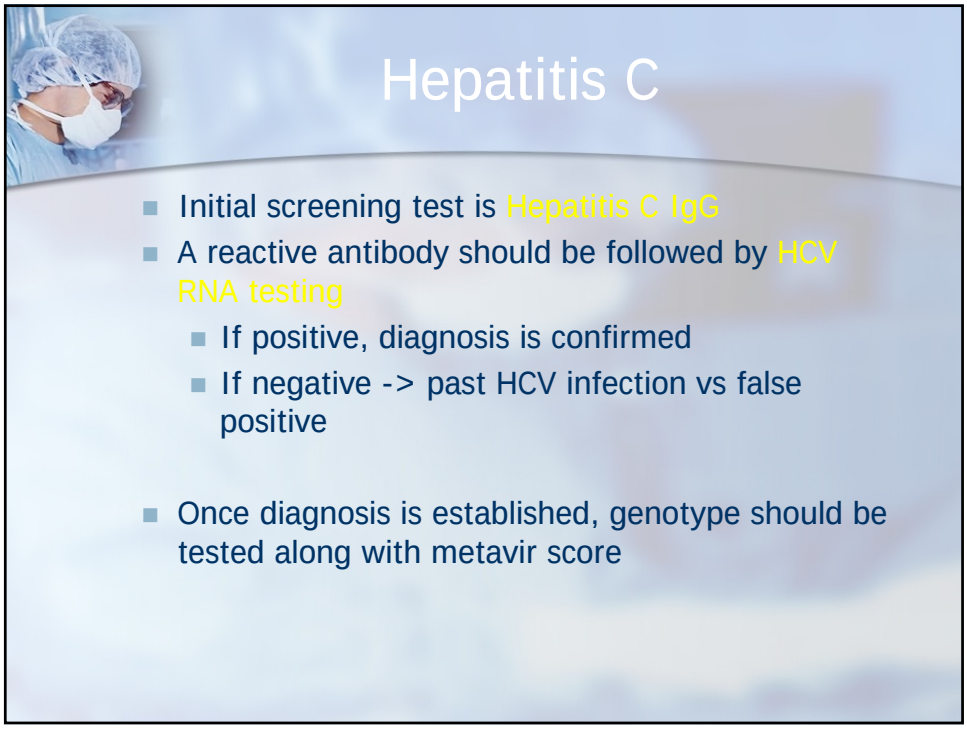

Elevated Alkaline Phosphatase
Non-Hepatic
Bone Disease
Pregnancy
Chronic Renal Failure
Lymphoma and other Malignancies
CHF
Infection/Inflammation of Liver
Childhood Growth

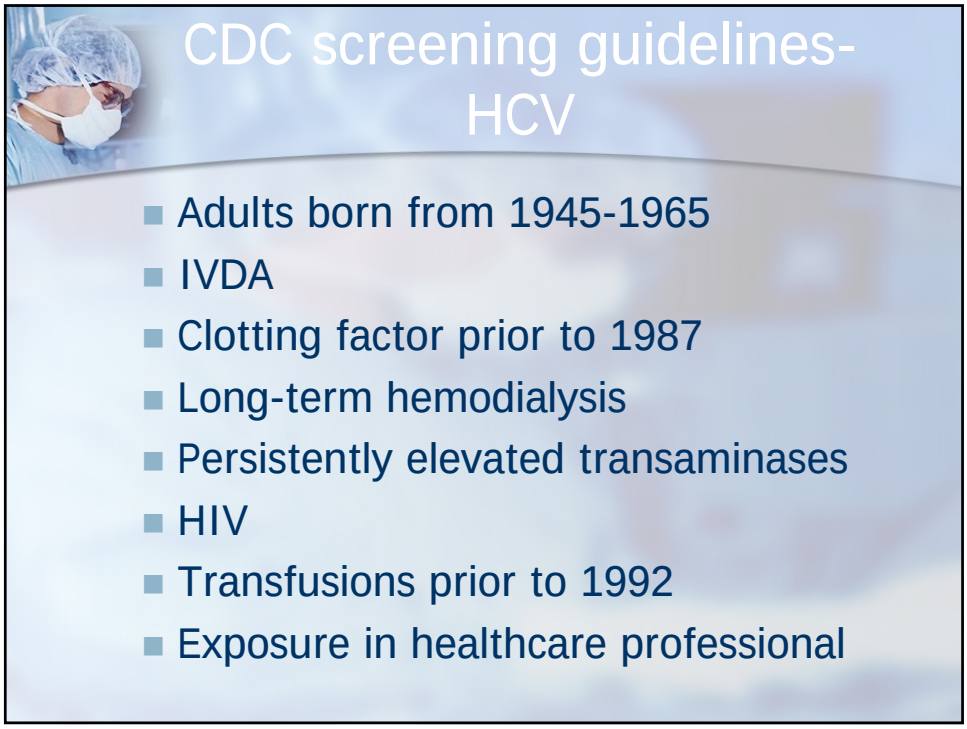

Elevated Alkaline Phosphatase
Infiltrative Liver Disease
Metastatic Malignancy
Lymphoma
Sarcoidosis
Amyloidosis
Tuberculosis
HCC
Fungal Infection
Other Granulmatous Disease
** AST/ALT/Bili may be normal or slightly elevated

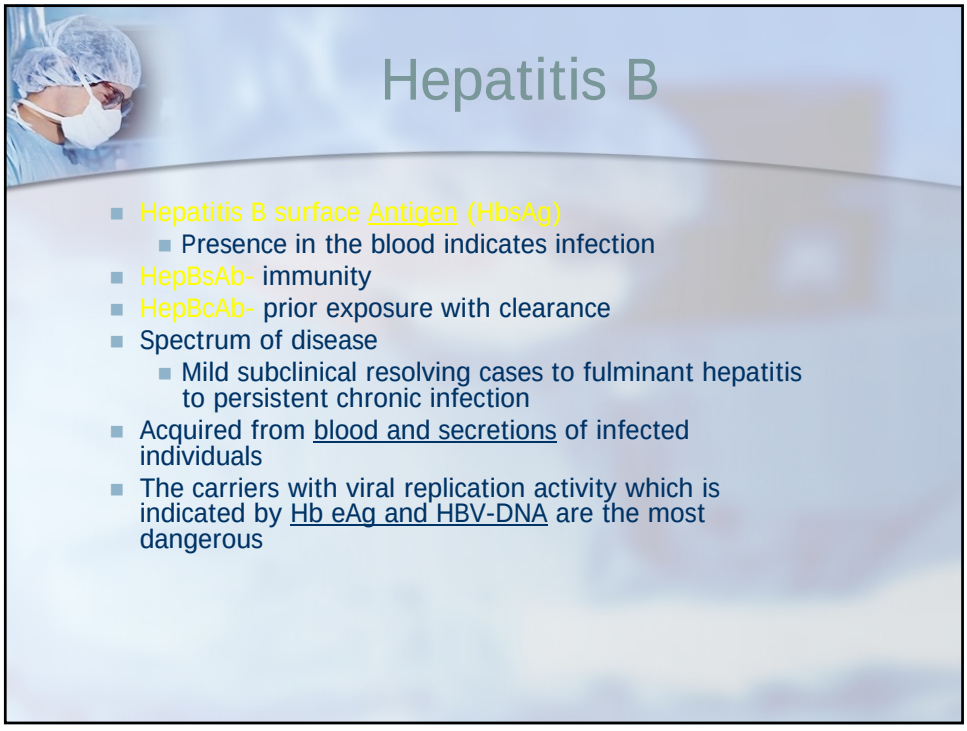

Clues of Synthetic Function
Albumin
Serum Half Life ~20 days
Prealbumin Half Life ~2 days
PT/INR
What factor not synthesized in the liver?
Factor 8 synthesized in Vascular Endothelium

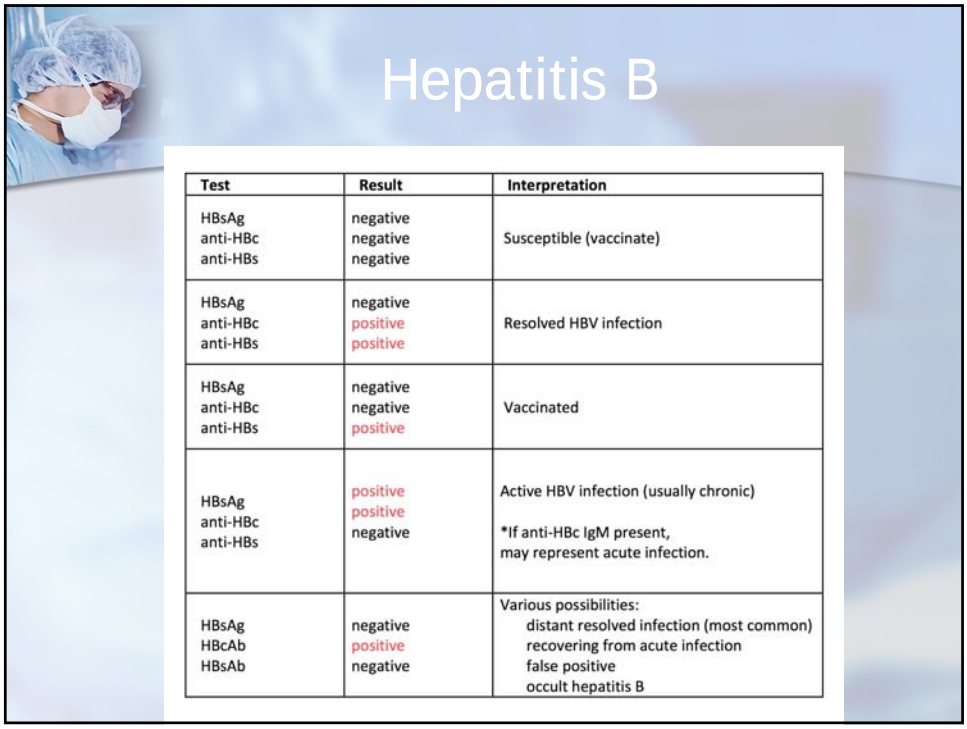

Other Tests
Ammonia
Platelets

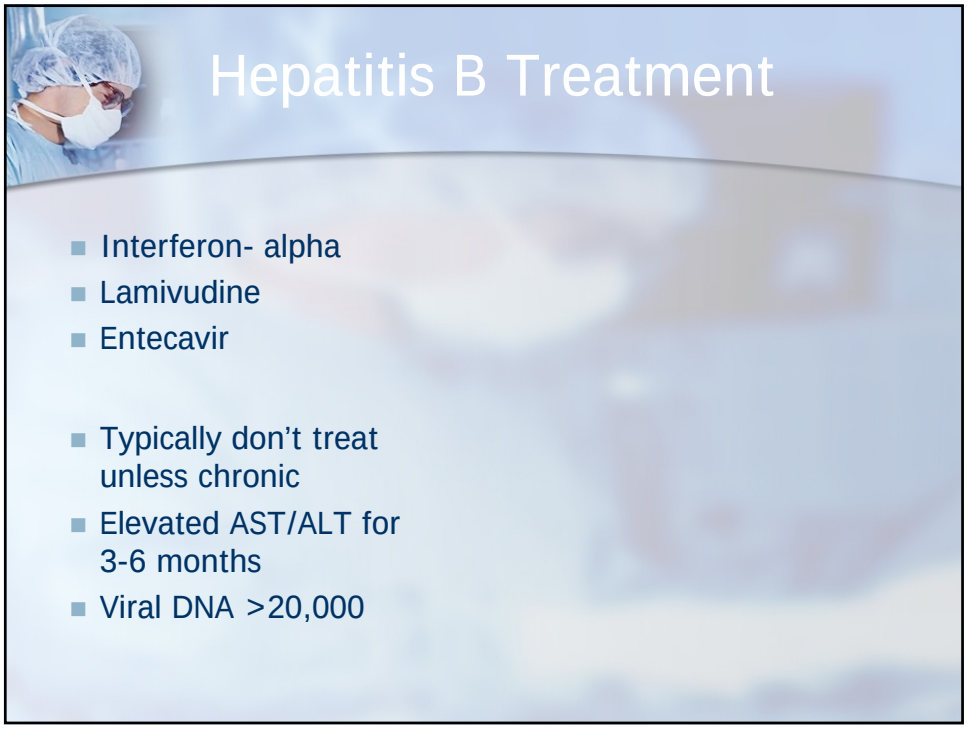

Hereditary Hemochromatosis
Autosomal recessive
Serum iron, ferritin, transferrin saturation
HFE gene (C282Y, H63D)
Increased intestinal iron absorption
Excessive iron deposition in tissues
Especially the liver, heart, pancreas, pituitary, thyroid, gonads
"Bronze Diabetes"
Hepatic iron index (HII); value 1.9 is consistent with disease
Treatment: Phlebotomy

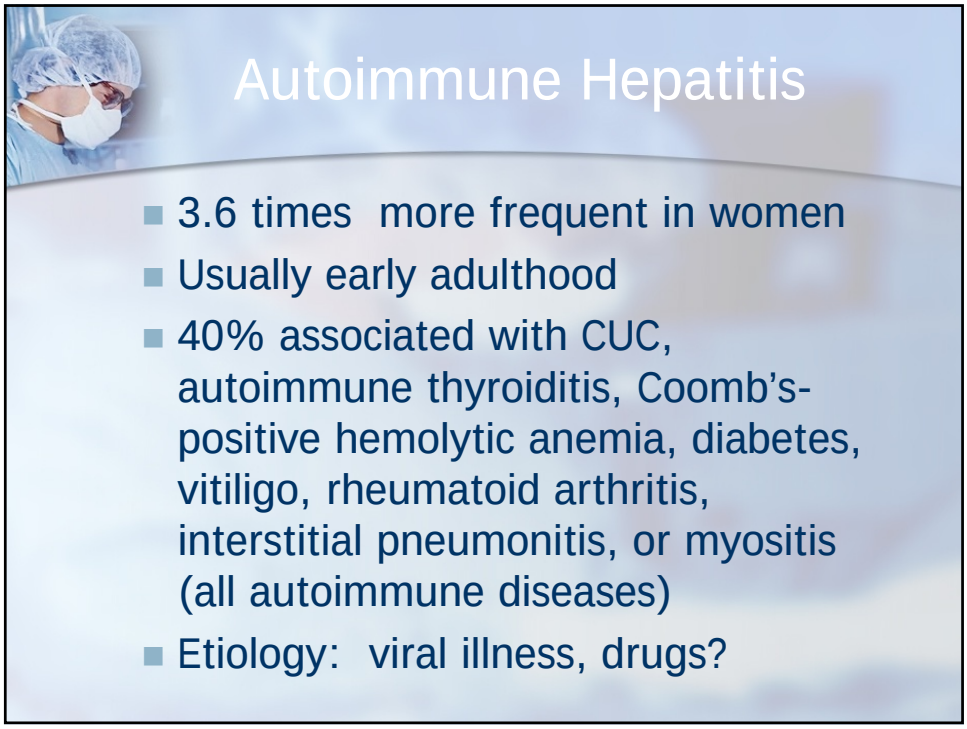

Hepatitis C
Initial screening test is Hepatitis C IgG
A reactive antibody should be followed by HCV RNA testing
If positive, diagnosis is confirmed
If negative -> past HCV infection vs false positive
Once diagnosis is established, genotype should be tested along with metavir score

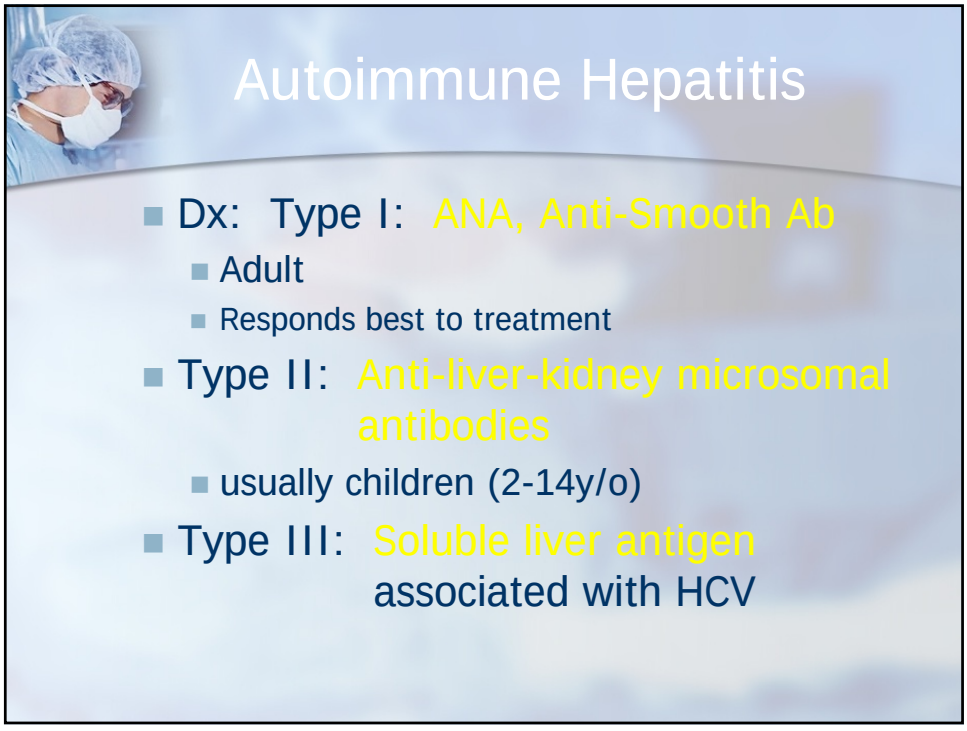

CDC screening guidelines-HCV
Adults born from 1945-1965
IVDA
Clotting factor prior to 1987
Long-term hemodialysis
Persistently elevated transaminases
HIV
Transfusions prior to 1992
Exposure in healthcare professional


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
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

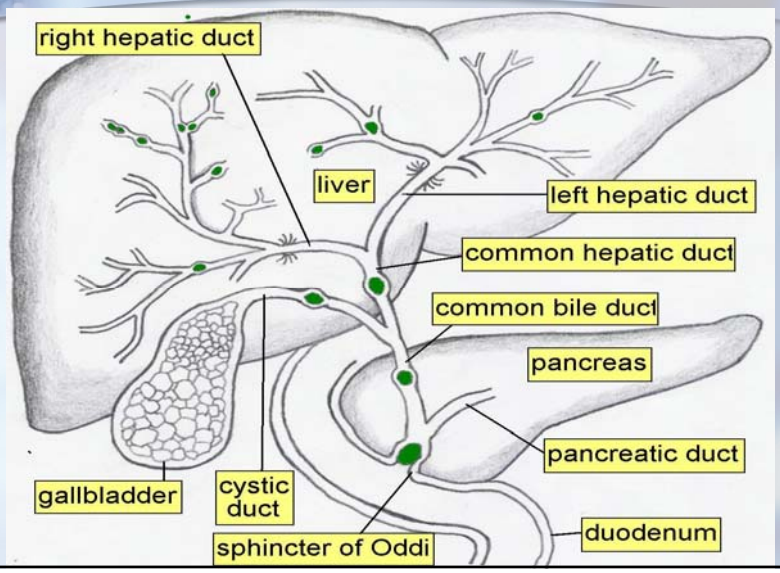

Autoimmune Hepatitis
3.6 times more frequent in women
Usually early adulthood
40% associated with CUC, autoimmune thyroiditis, Coomb's-positive hemolytic anemia, diabetes, vitiligo, rheumatoid arthritis, interstitial pneumonitis, or myositis (all autoimmune diseases)
Etiology: viral illness, drugs?


Autoimmune Hepatitis
Dx: Type I: ANA, Anti-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

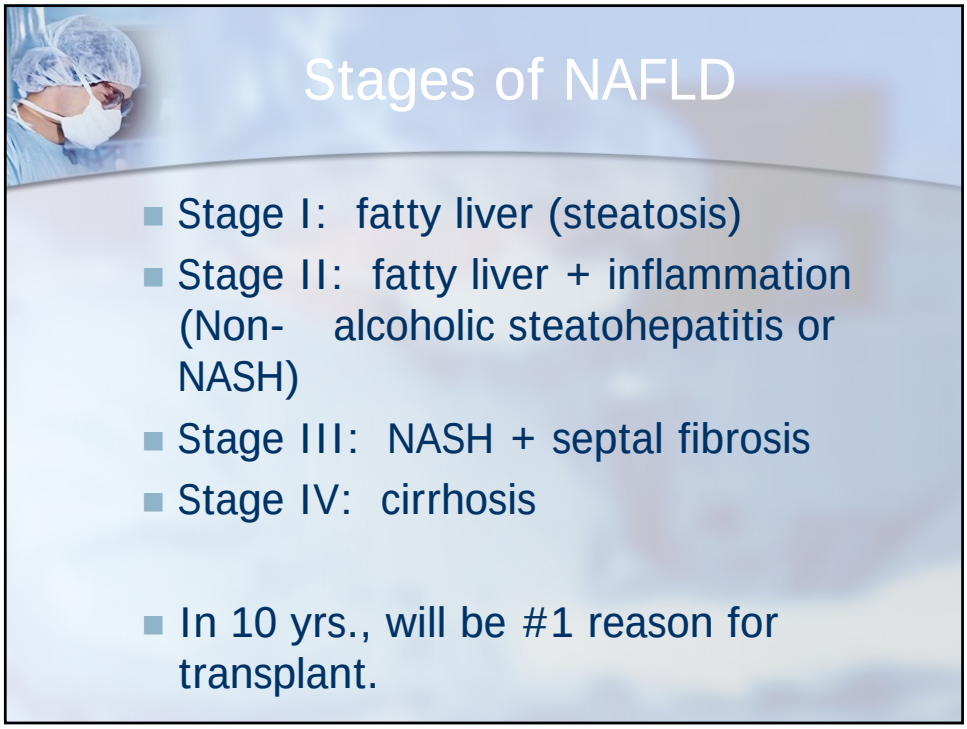
# PBC
## Introduction

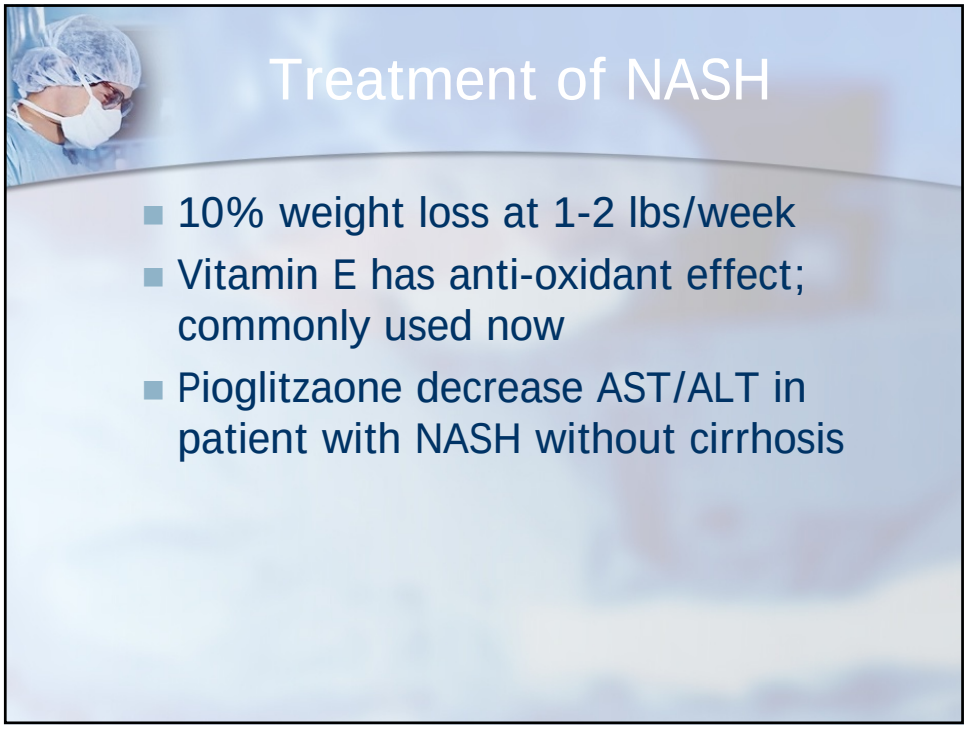
- Diagnosis
  - Cholestasis (elevated alkaline phosphatase and bili)
  - Antimitochondrial antibodies (AMA)
  - Histology
- UDCA for all patients
- Transplantation
  - Marginal liver reserve
  - Poor quality of life
  - Prognostic models

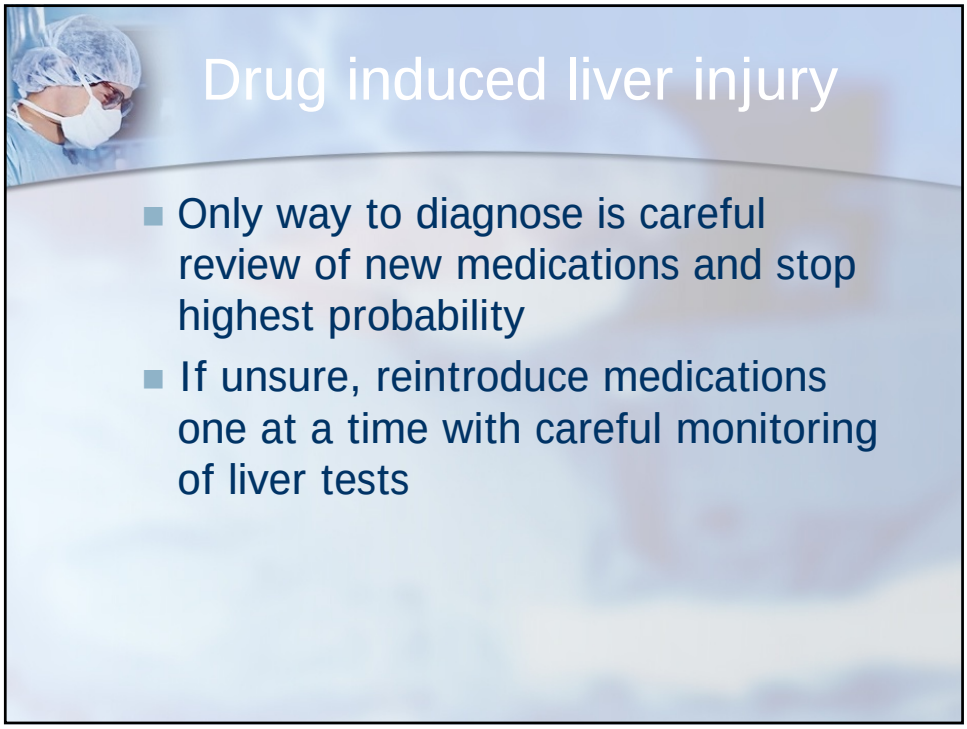
# Primary Sclerosing Cholangitis

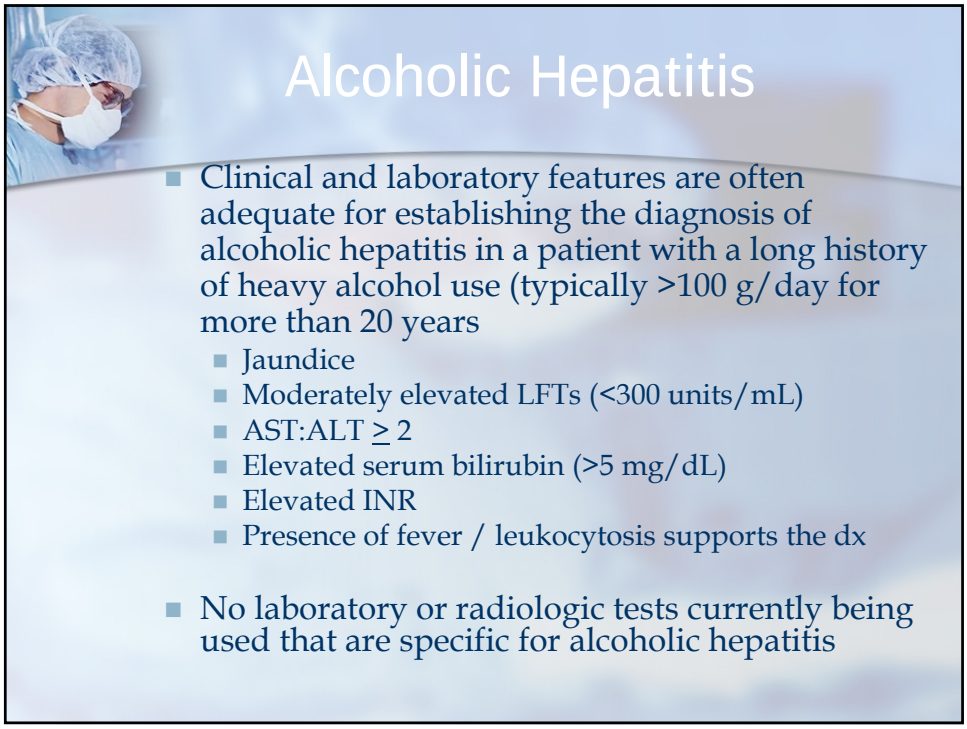


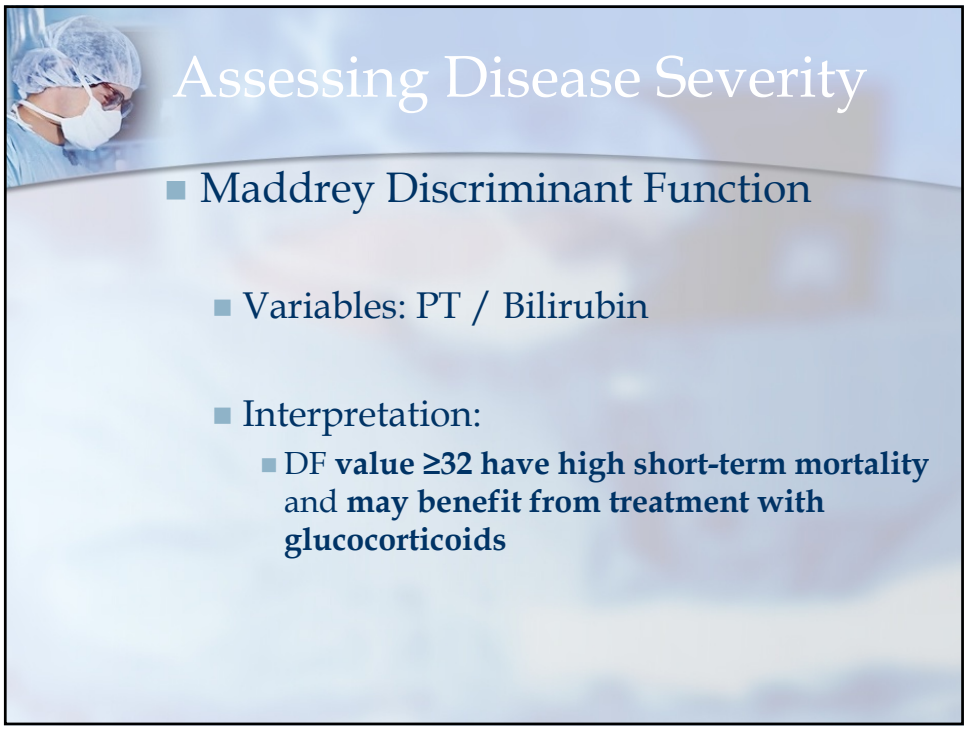

Non-alcoholic Fatty Liver Disease (NAFLD)
Most common liver disease in U.S.
Associated with insulin resistance, type II DM, obesity, hyperlipidemia, DM, hypothyroidism
No serological marker for this disease- clinical

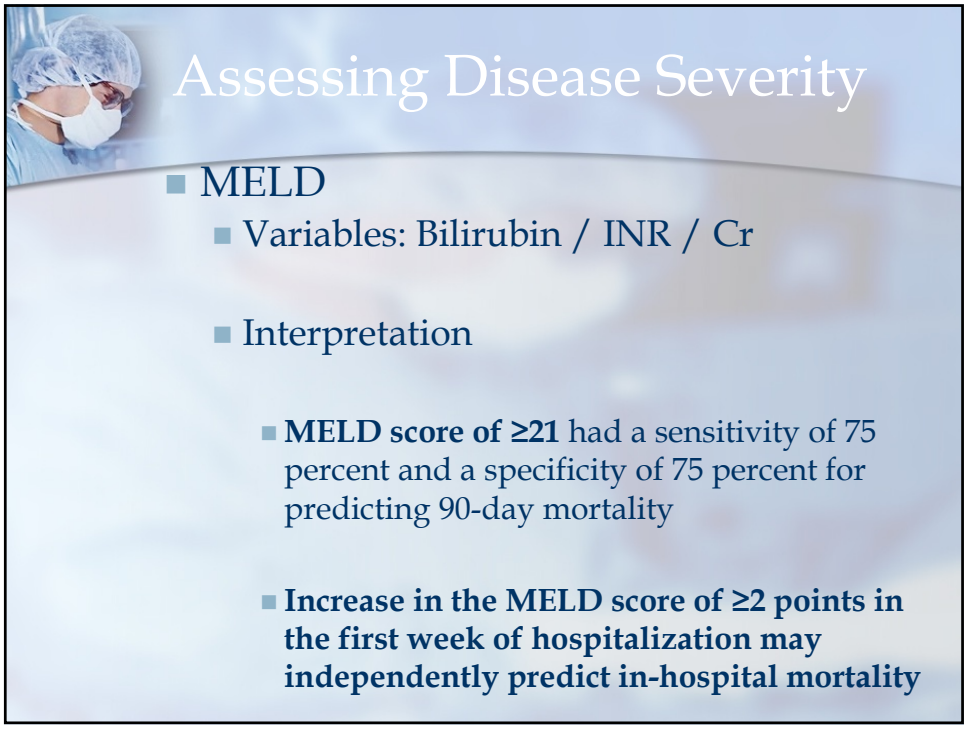

Stages of NAFLD
Stage I: fatty liver (steatosis)
Stage II: fatty liver + inflammation (Non- alcoholic steatohepatitis or NASH)
Stage III: NASH + septal fibrosis
Stage IV: cirrhosis
In 10 yrs., will be #1 reason for transplant.

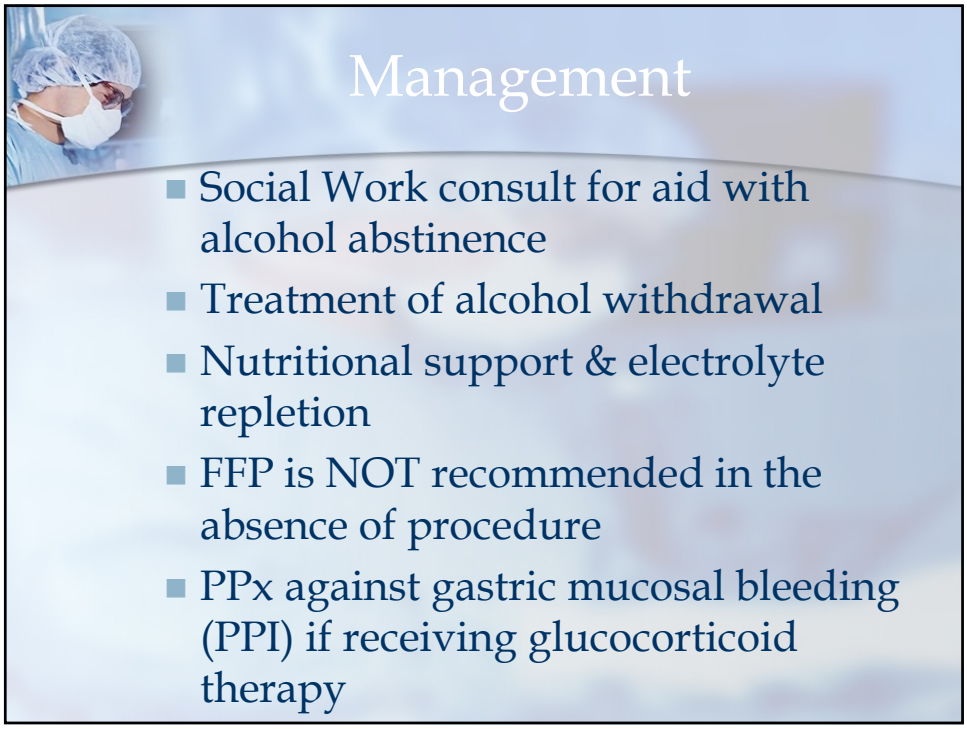

Treatment of NASH
10% weight loss at 1-2 lbs/week
Vitamin E has anti-oxidant effect; commonly used now
Pioglitzaone decrease AST/ALT in patient with NASH without cirrhosis

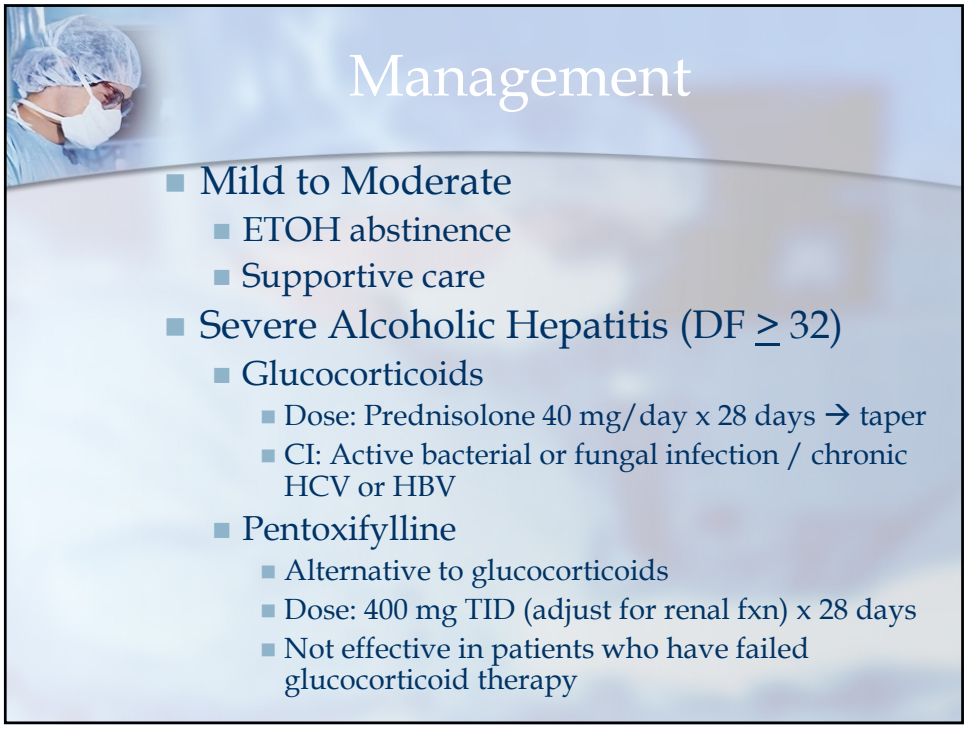

Drug induced liver injury
Only way to diagnose is careful review of new medications and stop highest probability
If unsure, reintroduce medications one at a time with careful monitoring of liver tests

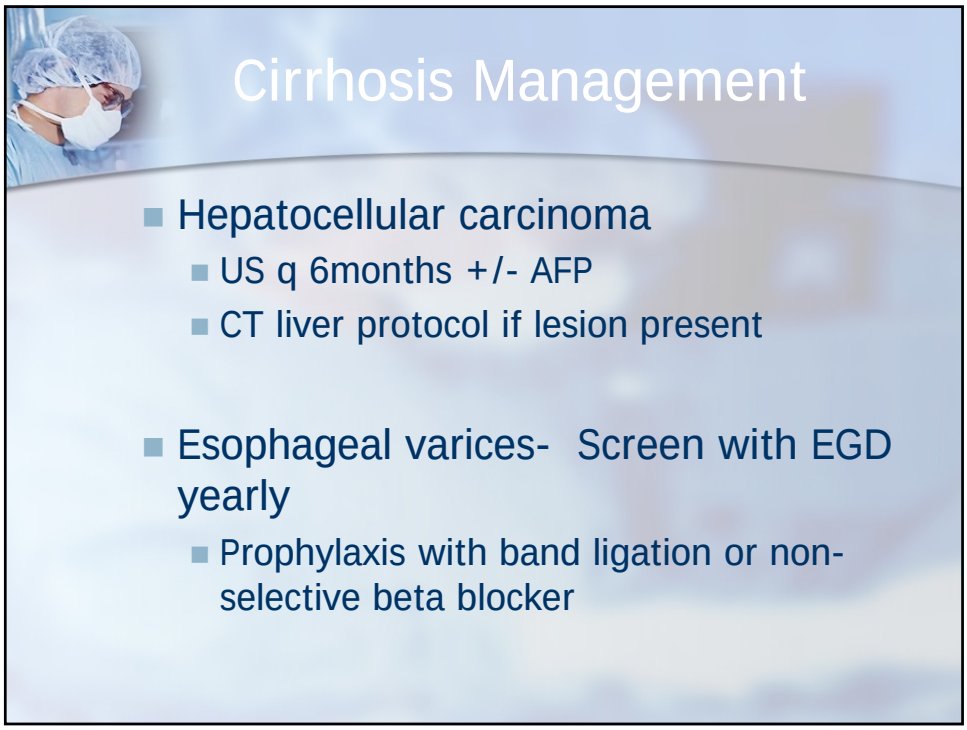

Alcoholic Hepatitis
Clinical and laboratory features are often adequate for establishing the diagnosis of alcoholic hepatitis in a patient with a long history of heavy alcohol use (typically >100 g/day for more than 20 years
Jaundice
Moderately elevated LFTs (<300 units/mL)
AST:ALT ≥ 2
Elevated serum 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

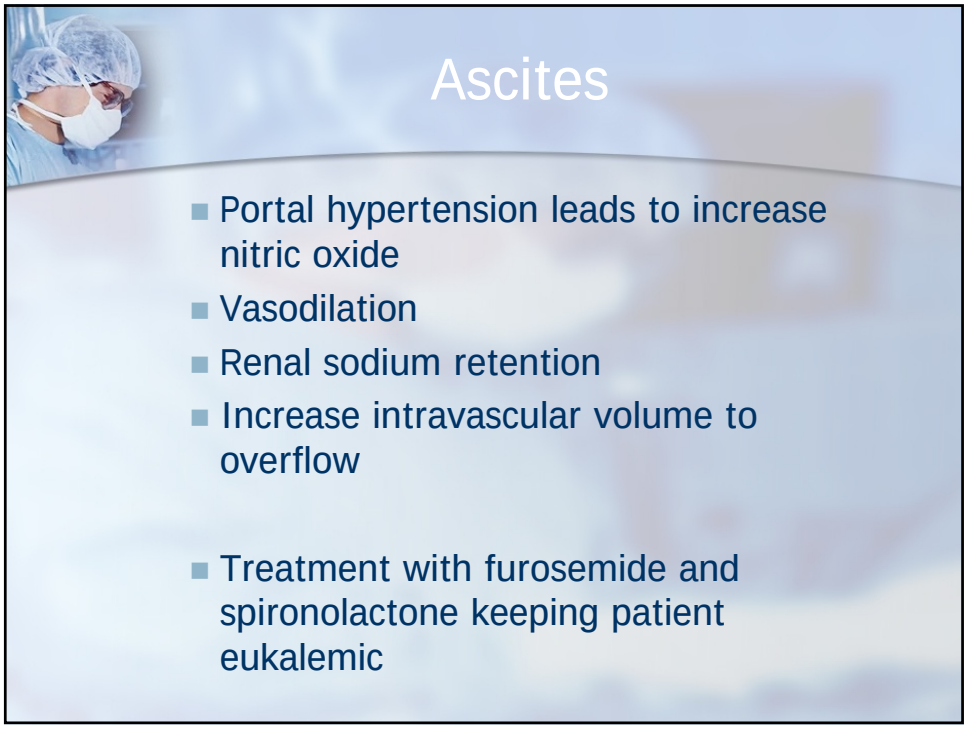

Assessing Disease Severity
Maddrey Discriminant Function
Variables: PT / Bilirubin
Interpretation:
DF **value ≥32 have high short-term mortality** and **may benefit from treatment with glucocorticoids**

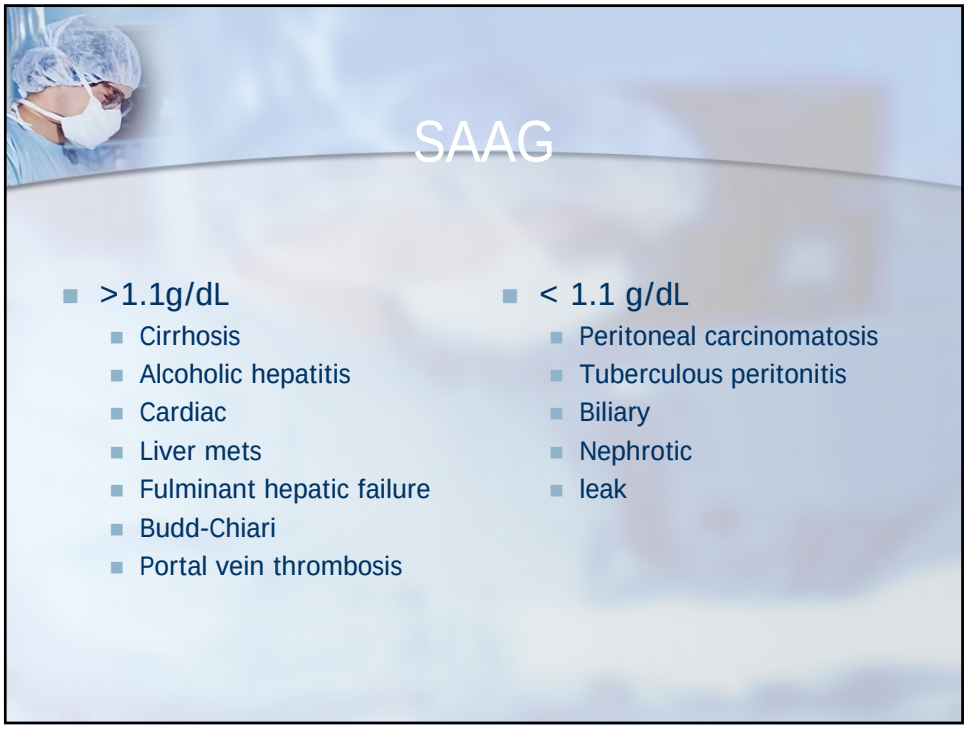

Assessing Disease Severity
MELD
Variables: Bilirubin / INR / Cr
Interpretation
MELD score of ≥21 had a sensitivity of 75 percent and a specificity of 75 percent for predicting 90-day mortality
Increase in the MELD score of ≥2 points in the first week of hospitalization may independently predict in-hospital mortality

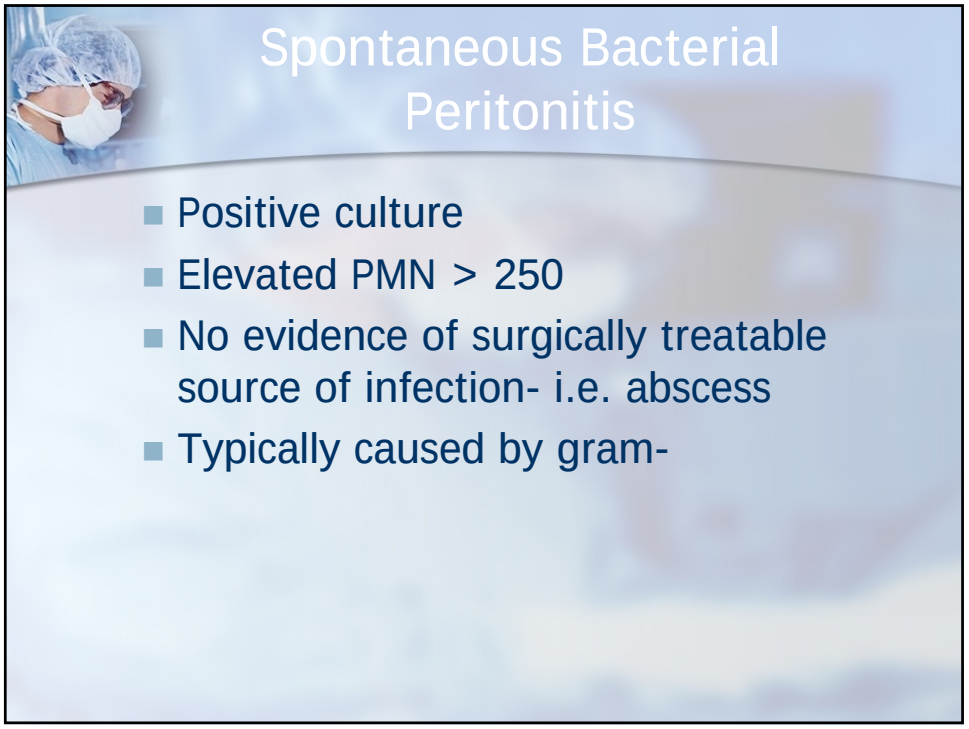

Management
Social Work consult for aid with alcohol abstinence
Treatment of alcohol withdrawal
Nutritional support & electrolyte repletion
FFP is NOT recommended in the absence of procedure
PPx against gastric mucosal bleeding (PPI) if receiving glucocorticoid therapy

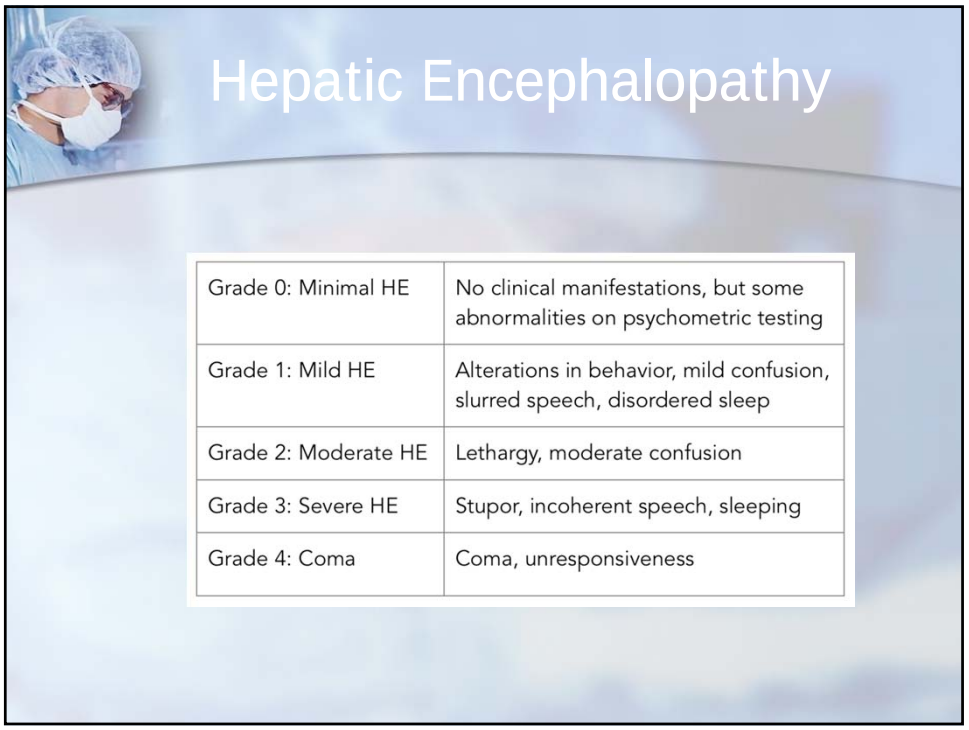

Management
Mild to Moderate
ETOH abstinence
Supportive care
Severe Alcoholic Hepatitis (DF ≥ 32)
Glucocorticoids
Dose: Prednisolone 40 mg/day x 28 days → taper
CI: Active bacterial or fungal infection / chronic HCV or HBV
Pentoxifylline
Alternative to glucocorticoids
Dose: 400 mg TID (adjust for renal fxn) x 28 days
Not effective in patients who have failed glucocorticoid therapy

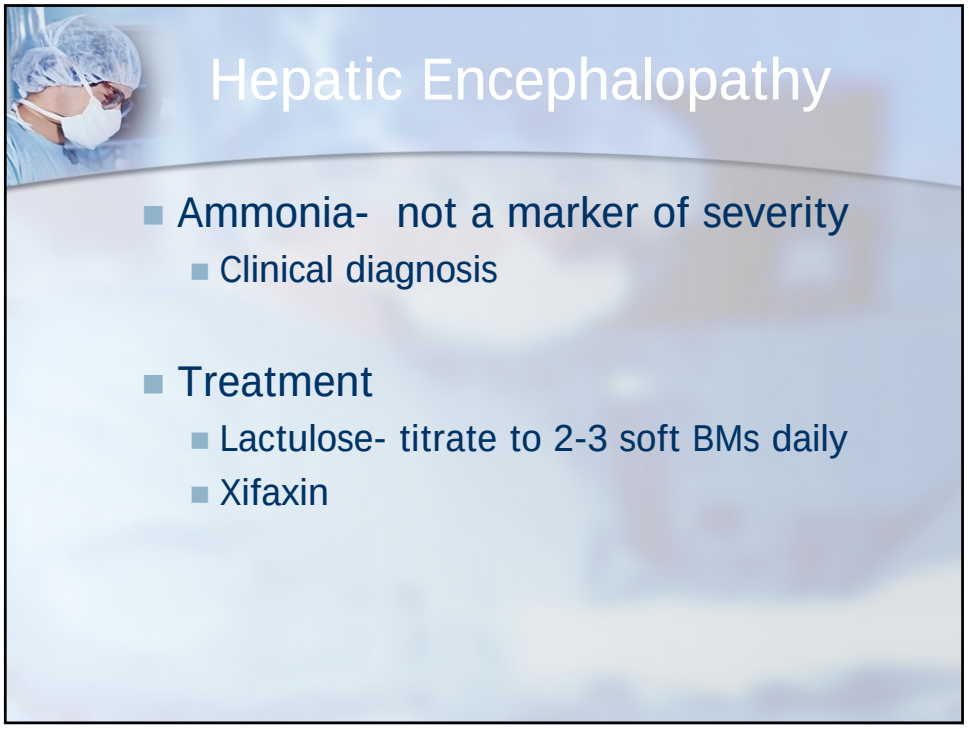

Cirrhosis Management
Hepatocellular carcinoma
US q 6months +/- AFP
CT liver protocol if lesion present
Esophageal varices- Screen with EGD yearly
Prophylaxis with band ligation or non-selective beta blocker

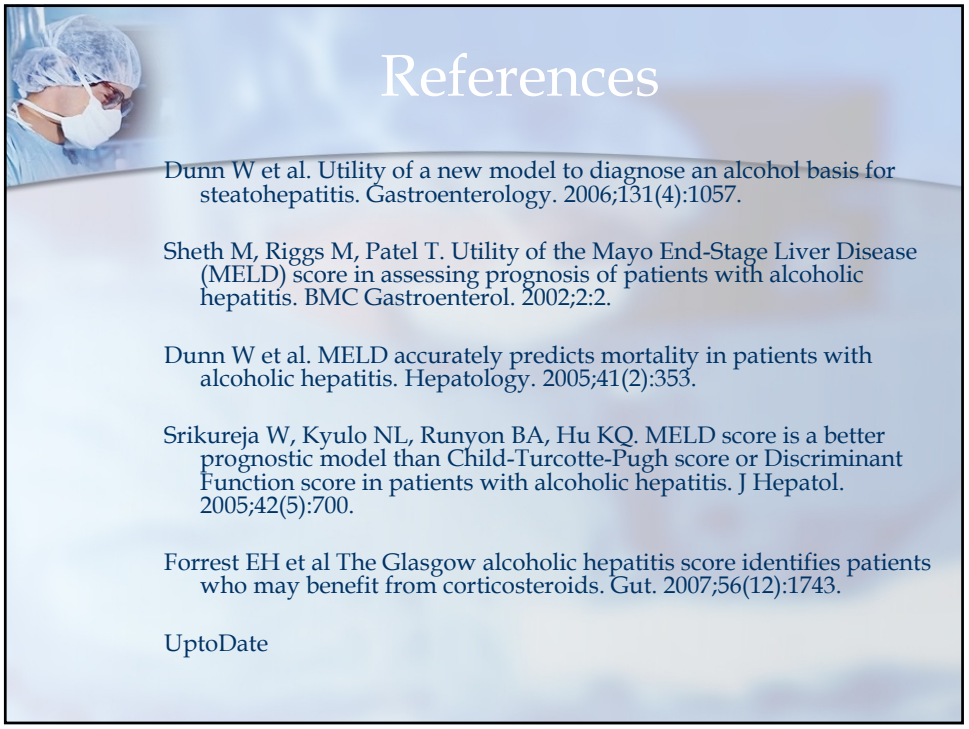

Ascites
Portal hypertension leads to increase nitric oxide
Vasodilation
Renal sodium retention
Increase intravascular volume to overflow
Treatment with furosemide and spironolactone keeping patient eukalemic


SAAG
>1.1g/dL
Cirrhosis
Alcoholic hepatitis
Cardiac
Liver mets
Fulminant hepatic failure
Budd-Chiari
Portal vein thrombosis
< 1.1 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-


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


Hepatic Encephalopathy
Ammonia- not a marker of severity
Clinical diagnosis
Treatment
Lactulose- titrate to 2-3 soft BMs daily
Xifaxin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UptoDate

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