Abnormal Liver Tests: work-up and diagnosis

Robert G. Gish MD

Professor Consultant

Stanford University

Thank you to:

- Carrie Frenette for the great cases !

Differential Diagnosis

- Population based survey in US 1999-2002 estimated abnormal ALT in 8.9% of population

- Symptomatic vs Asymptomatic?
- Acute vs Chronic?
- Hepatitic vs Cholestatic?

Differential Diagnosis

Hepatitic:

- Viral Hepatitis: A, B, C, D, E
- Alcoholic and Nonalcoholic Steatohepatitis
- Autoimmune
- Hemachromatosis
- Wilson's disease
- Alpha-1 antitrypsin

Cholestatic:

- Obstruction
  - Gallstones, malignancy, parasites
- Primary Biliary Cirrhosis
- Primary Sclerosing Cholangitis
- Infiltrative diseases: metastatic cancer, sarcoidosis, amyloidosis

Either:

- Drugs
- Thyroid disorders
- Celiac disease
- Vascular disease: CHF, Budd Chiari syndrome, Sinusoidal obstructive syndrome

Liver Tests " Liver Panel "

- AST, ALT
- Alkaline Phosphatase
- GGT

- Bilirubin
- Albumin
- Protime/INR

True "liver function tests"

  - Also: Lactate, glucose, cholesterol, clotting factors
  - Ammonia very poor liver function test, poor correlation with HE status

AST, ALT

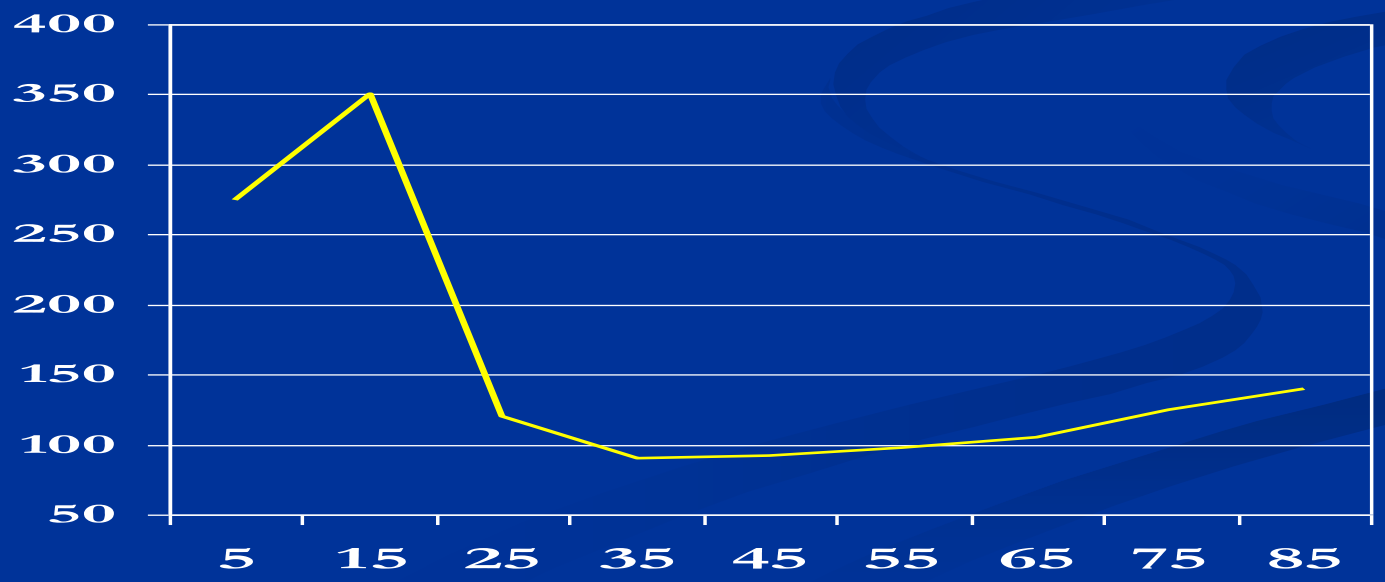
- Aspartate aminotransferase, alanine aminotransferase
  - Enzymes that are in the hepatocyte and function during gluconeogenesis
  - Leak out of the hepatocytes in times of injury and can be measured in the serum
- Normally present in serum at levels ~20-30 U/L
  - <30 for men
  - <20 for women

AST/ALT

- AST:
  - liver > cardiac muscle > skeletal muscle > kidney > brain > pancreas > lung > leukocytes > erythrocytes
  - Less specific for liver damage
    - Can increase with strenuous exercise, MI
  - Located in cytosol and mitochondria of hepatocytes
  - Cleared more rapidly than ALT
- ALT
  - Mainly from cytosol of hepatocytes
  - more specific for liver damage

Alkaline Phosphatase

- Exists in liver in membrane of hepatocyte where it lines the canaliculus
- Liver > bone > intestine
- Placenta
- Normally changes with age



Other cholestatic enzymes

- GGT: gamma-glutamyltransferase
  - Found in hepatocytes and biliary epithelial cells
- 5' nucleotidase

- Both these enzymes can be used to confirm alk phos elevation is coming from liver
- GGT is also sensitive to alcohol ingestion

Bilirubin

- Breakdown product of heme
  - 70-80% of normal production is from breakdown of hemoglobin in senescent RBC
- Conjugation of bilirubin occurs in ER of hepatocyte, and conjugated bilirubin is then transported into bile (rate limiting step)
- Almost 100% of bilirubin in healthy people is indirect

Bilirubin

- Increased bilirubin can occur from:
  - Overproduction of bilirubin
    - Uncomplicated hemolysis (rarely levels >5 mg/dL)
  - Impaired uptake, conjugation, or excretion
    - Gilbert Syndrome, others
  - Blockage of bile duct
  - Regurgitation from damaged hepatocytes of bile ducts
    - Hepatocellular damage
- Urinary bilirubin is only conjugated

Albumin

- Important plasma protein synthesized by the liver
- Half-life 20 days
- Levels <3.5 mg/dL should raise the suspicion of chronic liver disease or inflammatory disease
  - ***not specific for liver disease
- Also reduced in heavy alcohol consumption, chronic inflammation, protein malnutrition

Protime/INR

- Liver synthesizes all major coagulation proteins: I, II, V, VII, IX, X, XII, XII
  - vWF is synthesized in the vascular endothelium, including the liver
- Protime measured II, VII, IX, X: vitamin K dependent factors
- Can be elevated in liver disease or Vitamin K deficiency
- *** one of the most important abnormalities to signify development of fulminant hepatic failure in course of acute liver disease, with bilirubin and encephalopathy
- Degree of elevation is a prognostic factor in many liver diseases
- Best test for coagulation factors is TEG

Evaluation of Abnormal Liver Tests

- First step is to repeat the test!!
  - Many many things can cause a one-time elevation of liver tests
  - Mild elevations should be monitored for at least 6 months before a full serologic work-up is done
    - Exception is viral hepatitis serologies in high risk people

Evaluation of Abnormal Liver Tests

- Evaluate how high the test is
  - Normal values are calculated from "normal" people
  - Normal = 2 SD above and below the mean
    - B y definition, this makes 2.5% of normal people have abnormal test!
- Think of situations where a high test is normal
  - Alk phos in pregnancy
  - AST in marathon runners

Evaluation of Abnormal Liver Tests

- History
  - How long has elevation been present?
  - Any symptoms: pruritus, fatigue, RUQ pain, arthralgias, myalgias, rash, anorexia, fever, weight loss, changes in urine/stool
  - Symptoms of more severe liver disease: jaundice, ascites, LE edema, GI bleeding, confusion or slowed thinking
- Other Medical Problems?
- Family history of liver disease?
- Personal or family history of autoimmune disease or thyroid disease?

Medication History

- What medications do you take?
  - When did you start them?
  - Any change in doses?
- Over the counter medications?
- Herbals? – ask specifically!!

Social History
Essential in Eval of liver disease

- How much do you drink? – be specific!!!
- Any recent travel? Born abroad?
- Have you had any blood transfusions?
- Have you ever had hemodialysis?
- Do you work in healthcare? Any needlesticks?
- Any tattoos?
- Have you ever injected drugs, even once?
- Have you ever snorted drugs, even once?
- Any recent mushroom ingestion?
- Any unprotected sex? Multiple sex partners?
- Are you a Vietnam veteran?

Physical Examination

- Look for signs of chronic liver disease
  - Spider angiomata
  - Firm liver edge
  - Splenomegaly
  - Leukonychia
  - Ascites
  - LE edema
  - Abdominal wall collateral vessels
  - Proximal and temporal muscle wasting
- Look for signs of other diseases: acanthosis nigricans, signs of thyroid disease, xanthomas, LAD, etc
  - Check cardiac exam for JVD, hepatojugular reflex

Most of the time, with the history and physical you should have a good idea what's the likely culprit of the elevated liver tests!

Case #1

- 48 year old man is found to have abnormal liver tests on routine physical examination
- No significant PMH
- On no medications
- Tried IV drugs “once in college”
- PE normal
- Labs: CBC, BMP normal
- AST 62, ALT 88, Alk phos 75, Tbil 0.7, INR 1.0, Albumin 4.1

Case #1, continued

- Hepatitis C: Antibody positive
- What now?
  - Check HCV RNA, genotype, refer to hepatology
  - Check other viral serologies also

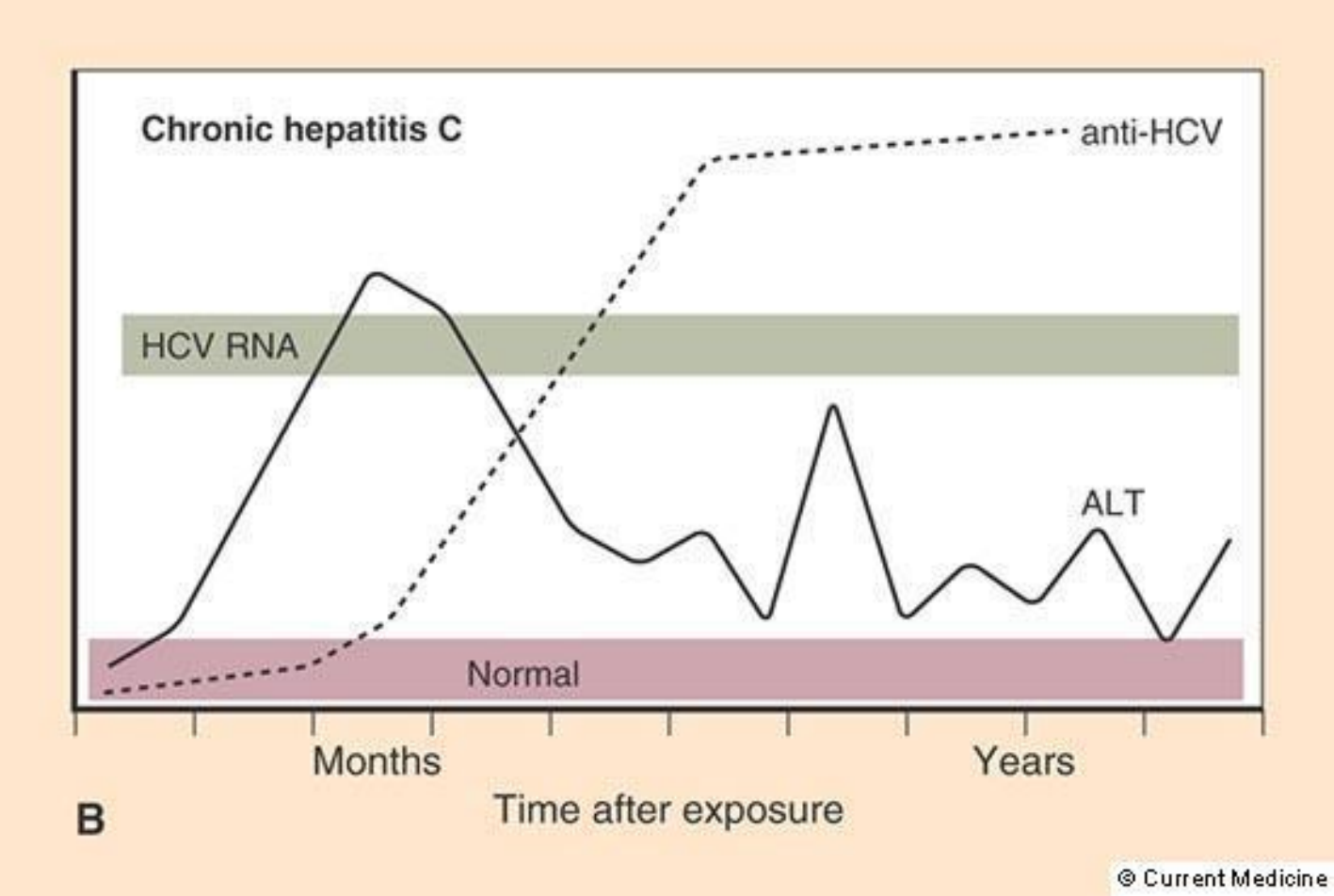
Hepatitis C

- HCV-Ab (hepatitis C antibody)
- (+) in chronic or previous infection
- Sensitive screening test with elevated ALT or age or history of blood exposure
- Detectable 8-16 weeks after exposure to virus
- False positives in autoimmune dz or hypergammaglobulinemia
- False negatives in immunosuppressed

Hepatitis C

- Hepatitis C viral level in IU/ml
- Quant and Qualitative by PCR to < 10-25 IU/ml
- HCV-RNA detectable 2-4 weeks after exposure
- Level of HCV RNA is a historical factor that could predict response to Rx but NOT severity of disease

Hepatitis C


Chronic hepatitis C
anti-HCV
HCV RNA
ALT
Normal
Months
Years
B
Time after exposure
© Current Medicine

Case #2
45 year old South African man

- Presents for routine physical and found to have elevated liver tests
- PMH: hyperlipidemia
- Soc: drinks 2 beers/week, no Hx drug use
- Born in South Africa, came to US in 1985
- Family history: none (but he mentions that they don't go to the doctor)
- PE: normal

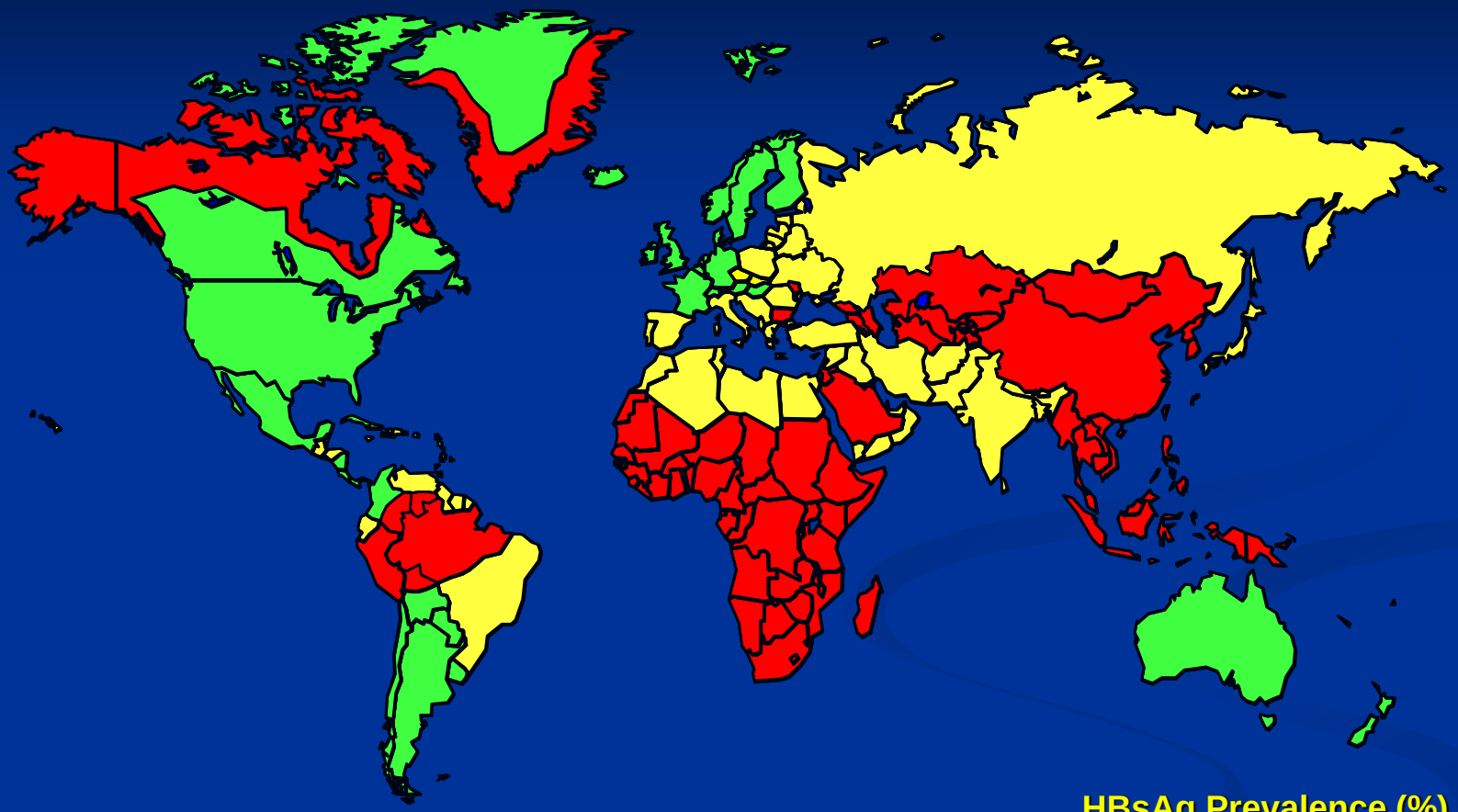
Case #2
45 year old South African man

- Labs: CBC, BMP normal
- AST 50, ALT 60, Alk phos 70, Tbili 0.5
- INR, Albumin normal
- US normal
- What now?

Case #2
45 year old South African man

- Hepatitis B s Ag: positive
- HBsAb: negative
- HBcAb: positive
- What now?
- HBV DNA 1.5 billion IU/mL, HBeAg pos, anti-HBe neg
- Diagnosis?
  - Chronic Hepatitis B
- What if HBV DNA was 2000 IU/mL?

Global Distribution of Chronic HBV Infection



- 350 million chronic carriers worldwide
- Ninth leading cause of death
- Nearly 75% of HBV chronic carriers are Asian

HBV Serologies

HBsAg	HBsAb	HBcAb	HBV DNA	Interpretation
+	-	+ IgM	+	Acute infection
+	+	+ IgG	+	Chronic infection
-	+	-	-	Immunized
-	+	+	-	Past Exposure
-	-	+	-	False pos or Past Exp

HBV Serologies

- HBe Ag: only applicable in patients who are chronically infected or carriers
- Positive: increased infectivity
- Negative: precore mutant of virus if DNA positive, still can be infective, still has advancing disease

- Levels of HBV DNA important to decide if patient active or inactive with ALT level and imaging

Case #3
19 year old female college student

- c/o severe fatigue of new onset, jaundice, mild pruritus of few days duration
- No EtOH
- Meds: minocycline, multivitamin
- No Hx of contacts with viral hepatitis, travel
- PE: heent: mild scleral icterus

  abd: nl bs, no organomegaly, no tenderness or palpable mass

Case #3, continued

- Labs: alb 4.2, t bili 4.2, alk phos 248,
- AST 180, ALT 252;
- CBC normal, BMP normal
- Acute viral hepatitis serologies neg.

What is the most likely diagnosis?

Case #3
19 year old female college student

Drug induced cholestasis secondary to minocycline.

Symptoms resolved within 2 weeks of drug d/c, liver profile normalized in 8 weeks.

Hepatocellular (Elevated ALT)	Mixed (Elevated ALP + Elevated ALT)	Cholestatic (Elevated ALP + TBL)
Acarbose	Amitriptyline	Amoxicillin–clavulanic acid
Acetaminophen	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Baclofen	Clindamycin	Oral contraceptives
Buproprion	Cyproheptadine	Erythromycins
Fluoxetine	Enalapril	Estrogens
HAART drugs	Flutamide	Irbesartan
Herbals: kava kava and germander	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Phenothiazines
Ketoconazole	Phenytoin	Terbinafine
Lisinopril	Sulfonamides	Tricyclics
Losartan	Trazodone	
Methotrexate	Trimethoprim–sulfamethoxazole	
NSAIDs	Verapamil	
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
Statins		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

TABLE 3. MEDICATIONS, HERBS, AND DRUGS OR SUBSTANCES OF ABUSE REPORTED TO CAUSE ELEVATIONS IN LIVER-ENZYME LEVELS.

- **Medications**
  - Antibiotics
    - Synthetic penicillins
    - Ciprofloxacin
    - Nitrofurantoin
    - Ketoconazole and fluconazole
    - Isoniazid
  - Antiepileptic drugs
    - Phenytoin
    - Carbamazepine
  - Inhibitors of hydroxymethylglutaryl–coenzyme A reductase
    - Simvastatin
    - Pravastatin
    - Lovastatin
    - Atorvastatin
  - Nonsteroidal antiinflammatory drugs
  - Sulfonylureas for hyperglycemia
    - Glipizide
- **Herbs and homeopathic treatments**
  - Chaparral
  - Chinese herbs
    - Ji bu huan
    - Ephedra (mahuang)
  - Gentian
  - Germander
  - Alchemilla (lady's mantle)
  - Senna
  - Shark cartilage
  - Scutellaria (skullcap)
- **Drugs and substances of abuse**
  - Anabolic steroids
  - Cocaine
  - 5-Methoxy-3,4-methylenedioxymethamphetamine (MDMA, "ecstasy")
  - Phencyclidine ("angel dust")
  - Glues and solvents
    - Glues containing toluene
    - Trichloroethylene, chloroform

Drug Induced Liver Injury

- Any drug can cause any injury!!!!
- Higher risks in women, older age
- Can be at start of medication, or in some cases at *any time* during therapy
- Should rule out other causes of liver injury

Drug Induced Liver Injury

- A note: acetaminophen is the most common cause of DILI, and also the most common cause of acute liver failure in US
- Normal dose for acetaminophen toxicity is 6 to12 grams/d, but toxicity can occur in much lower doses in certain circumstances, 2 gm/d
  - Alcohol use
  - Fasting state

Case #4
56 year old woman

- Presents with fatigue, myalgias
- PMH: hypothyroidism, HTN
- Meds: Synthroid, Atenolol, MVI, Ca
- Soc: no T/E/D
- FHx: father with vitiligo
- PE: appears fatigued, Abd with mild RUQ tenderness to deep palpation

Case #4
56 year old woman

- CBC, BMP normal
- AST 245, ALT 280, TBili 2.0, Alk phos 207
- Alb 3.8, INR 1.2
- US: mild hepatomegaly, otherwise normal
- Differential diagnosis?
- What further labs?

Case #4
56 year old woman

- ANA >1:640
- F-actin >1:380
- Quantitative Ig: Elevated IgG
- Viral Markers negative

- Diagnosis: Autoimmune Hepatitis

Autoimmune Hepatitis

- Middle-aged (or teenage) woman, non-drinker without viral hepatitis
- Fatigue, arthralgias/myalgias, oligomenorrhea, jaundice
- Increased AST/ALT, gamma globulins
- Positive ANA and SMA
- Interface hepatitis with lymphoplasmacytic infiltrate
- Responds to corticosteroids

Case #5:
60 year old man

- Presents with new onset diabetes, found to have elevated LTs
- PMH: DM II newly diagnosed, OA in hips
- Fhx: none
- Soc: drinks 3 beers/day, no drug use
- PE: normal

Case #5:
60 year old man

- CBC, BMP normal
- AST 80, ALT 65, Alk phos 125, TBili 0.6
- Alb 3.6, INR 1.0
- US: increased echogenicity of the liver

- Differential?
- Tests?

Case #5:
60 year old man

- Fe % sat 70%, Ferritin 800
- Viral studies negative

- Differential: ETOH (ASH) vs NAH vs Hemochromatosis
- or all three ?

- HFE gene test: C282Y homozygote

Hemochromatosis

- Inherited abnormality of iron absorption
- Affects 0.5% of Caucasian people
  - Rare in other races
- C282Y/H63D gene abnormalities
  - Iron overload seen in C282Y homozygotes and sometimes compound heterozygotes (C282Y/H63D)
- No role for gene testing without elevated iron tests?
  - Use for family members
- Iron tests esp ferritin can be falsely elevated in alcohol, acute inflammation, non fasting state

Alcoholic Liver Disease

- Seen in 25% of heavy drinkers
  - >5 drinks/day in men, much lower in women
- AST>ALT
  - AST in mitochondria, and alcohol is a mitochondrial toxin
  - Also seen when cirrhosis develops in other diseases
- Cirrhosis can develop without LT abnormalities!
- Alcohol hepatitis rarely has AST>300s

Case #6

A 47 year old Caucasian female presents with complaints of itching, dry mouth, and RUQ abdominal pain. She also notices some pigmentation changes on her eyelids. Her medical history includes frequent UTI's and osteopenia.

What labs are you most interested in seeing for this patient?

Case #6

You obtain the following labs:

AST=55, ALT=75, Alk Phos=350, GGT=110,

AntiNuclear Ab. (ANA) is positive

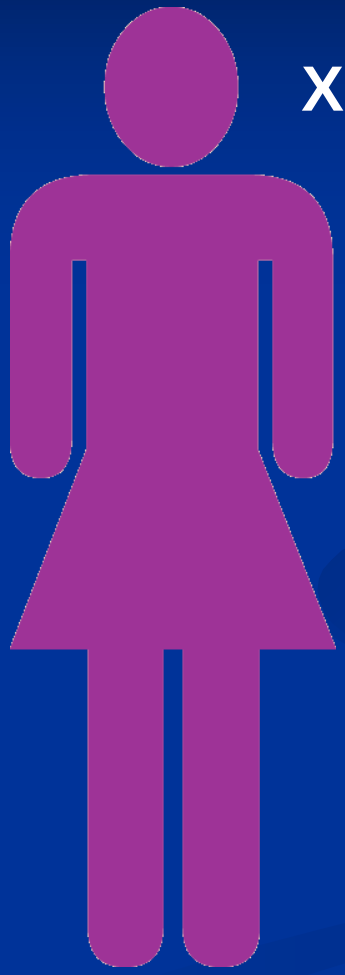
Anti-Mitochondrial Ab. is positive

What is the diagnosis?

Primary Biliary Cholangitis

- Destruction of bile ducts
- Predominantly women
- Ages 30-65
- AMA positive in 95% of cases
- ANA positive in 60% of cases
- Commonly present with fatigue, pruritus
- Treatment with Ursodiol can improve the course of disease

Extrahepatic Manifestations of PBC



Xanthomata

Fat Soluble Vitamin Deficiency

Osteopenia

Hyperlipidemia

Urinary Tract Infections

Gallstones

Steatorrhea

Renal Tubular Acidosis

Malignancy

Case #6

- A 55 y.o. male with a history of Ulcerative Colitis presents with recurrent low-grade fevers, RUQ abdominal pain, pruritus and jaundice.
- Alk Phos is high at 380
- TBili high at 4.5
- AST and ALT are both mildly elevated <100.
- What test would confirm the diagnosis?
- What cancer is this patient at risk for?

Diagnosis of PSC

- ERCP is most commonly used
- Percutaneous cholangiography is rarely used now because it is invasive
- MRCP is gaining popularity because it is non-invasive, and cost-effective

PSC

- Increased risk for cholangiocarcinoma
  - No role of screening currently
- 90+% associated with inflammatory bowel disease
  - More commonly UC than Crohn's
- p-ANCA positive in 80%

Case #7

- 68 year old Hispanic woman
- Elevated liver tests on routine screening
- PMH: DM, HTN, obesity
- Meds: metformin, lisinopril, ASA
- FHx: both parents died of CAD, brother with DM
- PE: acanthosis nigricans on neck, BMI 38

Case #7

- AST 85, ALT 120, Alk phos 68, Tbili 0.8
- Alb 4.1, INR 1.1
- US: increased echogenicity, multiple gallstones

- Diagnosis?

NASH

- Serologically, a diagnosis of exclusion
- Abnormal buildup of fat in hepatocytes, sometimes causing inflammation
- Increasing incidence due to increase in obesity
- Risk factors: obesity, hypertriglyceridemia, HTN, insulin resistance, family history
- Treatment: weight loss, treat risk factors
- Statins are ok to use!!!

Other liver diseases

- Alpha-1-antitrypsin
  - Abnormal excretion of alpha-1-antitrypsin protein out of hepatocytes: increased buildup in liver, low levels in lung causing emphysema
  - Check Phenotype: ZZ is abnormal
  - Results of a-1-antitrypsin level can change with various disease states, so less specific
- Wilson's disease
  - Abnormal copper excretion
  - Low ceruloplasmin (copper binding protein)
  - High 24 hour urine copper
  - Generally young people

So what does all this mean?

How to evaluate a patient with abnormal LTs

- Full H&P
- Have patient completely quit ETOH
- Stop ALL unnecessary medications
  - Emphasize to patient to avoid herbal supplements/teas

How to evaluate a patient with abnormal LTs

- If LT abnormalities are low (1-2x ULN)
  - Recheck
  - Rule out chronic viral hepatitis
    - HBsAg, HBsAb, HBcAb, HCV Ab
  - Monitor for 6 months
- If they remain elevated
  - Check ANA, AMA (if cholestatic), p-ANCA, quantitative immunoglobulins, Fe studies in Caucasian patients, alpha-1-antitrypsin phenotype, ceruloplasmin if patient <45, TSH, celiac panel (anti-endomysial Ab, anti-TTG)

How to evaluate a patient with abnormal LTs

- If LT abnormalities are ≥3x ULN
  - Check acute viral serologies: HAV IgM, HBsAg, HBsAb, HBcAb (IgM), HCV Ab
  - ANA, ASMA, pANCA
  - AMA if cholestatic
  - Fe studies
  - Alpha-1-antitrypsin phenotype
  - Ceruloplasmin if age <45
  - Quant Ig
  - TSH
  - Celiac Panel

How to evaluate a patient with abnormal LTs

- Every patient needs an imaging study
  - Ultrasound with doppler flow of portal vein, hepatic veins, hepatic artery
- If LTs significantly elevated or persistently elevated
  - Consider referral to hepatology

Questions?