Board Review 2019

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Liver Diseases

disclosure

- none

Alcoholic Liver disease

- Risk Factors for Alcoholic Liver Disease
  - Amount of alcohol consumed
  - Duration of alcohol consumption
  - Gender
  - Viral hepatitis
  - Nutrition
  - Iron overload
  - Genetics

Alcoholic Hepatitis

- Typically seen in malnourished patients
- Frequently precipitated by a period of binge drinking
- Prodrome: (2-3 weeks)
  - Anorexia
  - Nausea
  - Fatigue
  - Weight loss

Alcoholic Hepatitis

- Persistence of ETOH Hep. is associated with relentless progression to cirrhosis over months to years.
- Complications can be identical to those of cirrhosis.
- Poor prognostic signs:
  - Advanced age, jaundice, azotemia, and coagulopathy.

Alcoholic Hepatitis

- Clinical manifestations
  - Hepatomegaly, mild fever, jaundice
  - More severe cases: ascites, encephalopathy
- Lab
  - Increased AST&ALT→not more than 10x normal
  - Increased AST/ALT ratio (2-3:1)
  - Decreased albumin
  - Prolonged PT
  - Elevated Bilirubin

Alcoholic hepatitis–treatment

- Abstinence
- Bed rest
- Nutrition
- +/- steroids

Liver question

- What is most commonly used to assess the prognosis of patients with alcoholic hepatitis?

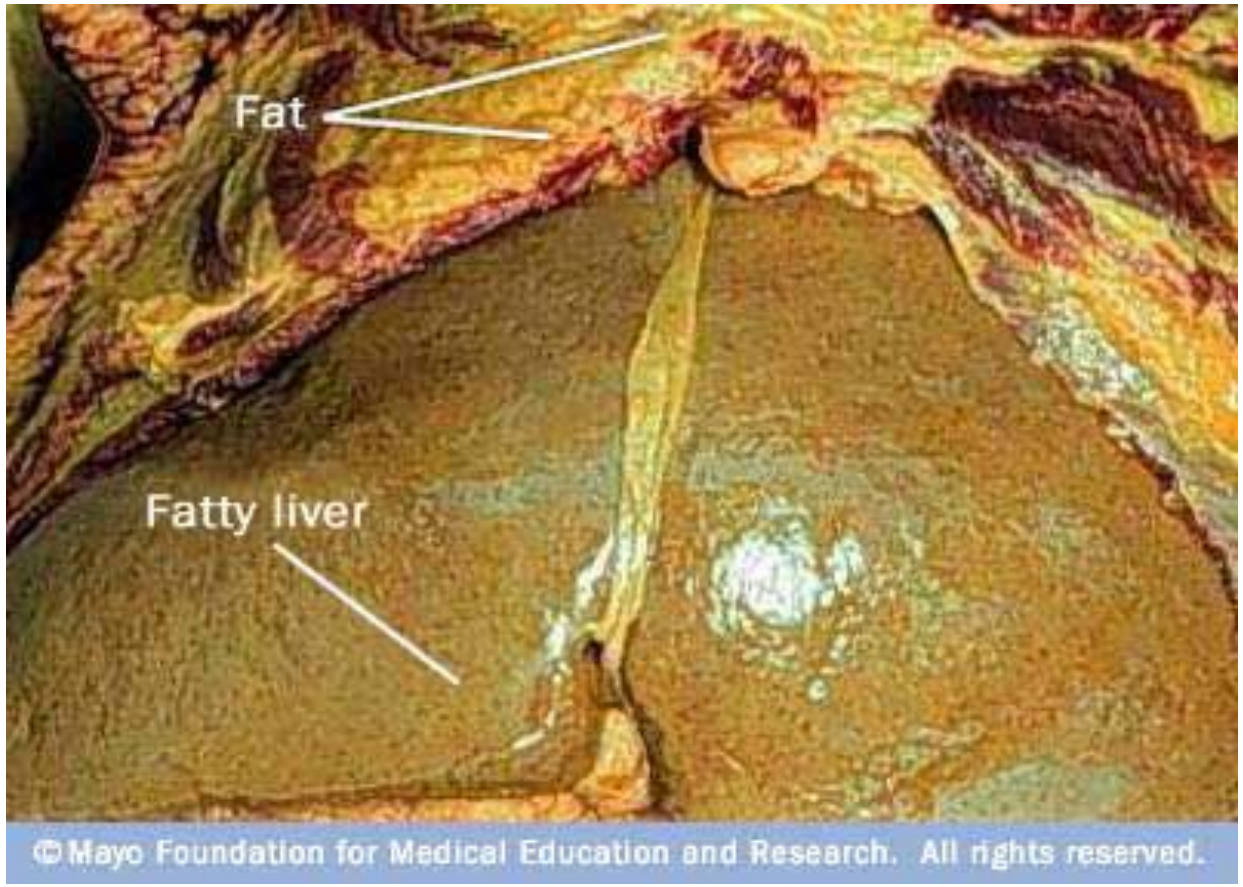
Answer: Maddrey Discriminant Function analysis (DF)

- Discriminant function= 4.6(prothrombin time-control) + serum bilirubin (mg/dL)
- Discriminant function >32 effectively identifies patients whose risk of death is higher than 50%
  - Consider steroids

Nonalcoholic Fatty Liver Disease

- Clinical
  - Nonalcoholic (<20g alcohol/day)
  - Exclusion of viral, autoimmune, genetic, and drug-induced liver disease.
- . Nonalcoholic Steatohepatitis (NASH)
  - Chronic inflammatory condition in people who don't have significant alcohol history.
    - *Characteristics: steatosis, hepatocellular necrosis, and inflammation.*

Fat liver—pale yellow coloring



Nonalcoholic Fatty Liver Disease

- Clinical manifestations
  - Central obesity (apple-shaped not pear-shaped)
    - Abd. Obesity (waist >40" in men and 34.5" for women)
  - NIDDM
  - +/- hyperlipidemia
  - Most patients are asymptomatic
  - Occasional RUQ discomfort, malaise, fatigue
  - Hepatomegaly→ 75% of patients

Nonalcoholic Fatty Liver Disease

- Lab
  - Elevated aminotransferase (<300UI/L)
  - AST/ALT ratio <1
  - Mild elevation alkaline phosphatase and GGTP

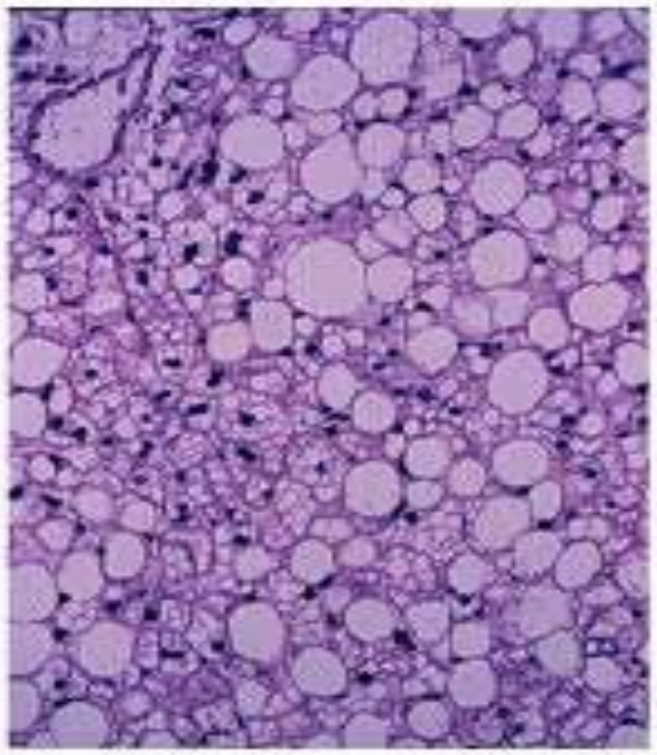
Nonalcoholic Fatty Liver Disease

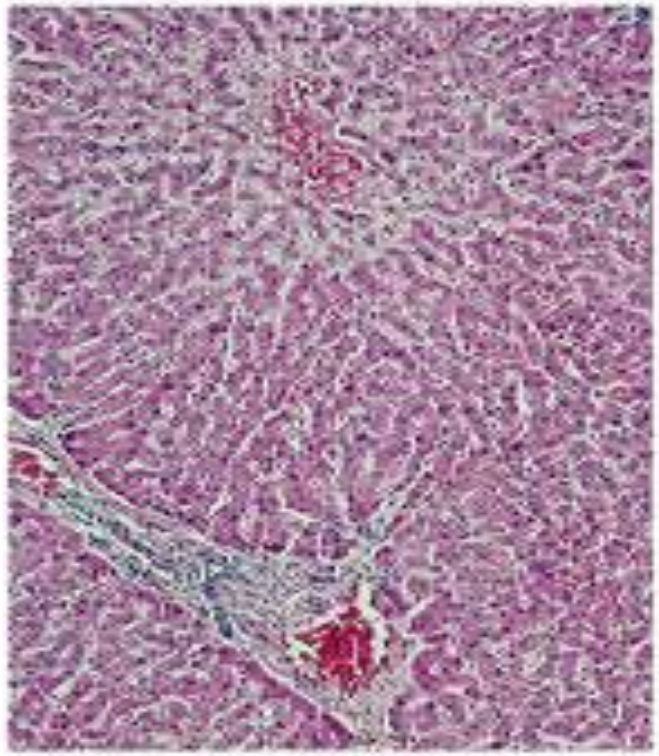
- Diagnosis
  - Findings of fatty infiltrate on imaging studies.
  - Exclusion of other liver diseases by history, physical, and serology.
  - Alcohol consumption should be <40g/week.
  - Liver biopsy is the definitive method of diagnosis. Not indicated in asymptomatic patients with normal AST, ALT.

Nonalcoholic Fatty Liver Disease

- Histologic finding
  - Steatosis-macrovasicular mild to severe
  - Inflammation
  - Hepatocyte injury- focal necrosis and ballooning
  - Hepatocyte degeneration- mallory hyaline
  - Fibrosis- varying degree

Liver





Fatty liver

Normal liver

Nonalcoholic Fatty Liver Disease

- Management
  - Directed at associated risk factors.
  - Gradual weight loss (>5% of body weight)
  - Control of hyperglycemia and hyperlipidemia.
  - Exercise (>6 METs) >5 times per week
  - Alcohol use <20g/day. Alcohol abstinence if significant fibrosis
  - HAV and HBV vaccination
  - Avoid drugs that may promote steatohepatitis (amiodarone,tamoxifen)
  - Premature to add newer medications

Viral Hepatitis

Hepatitis B

A DNA virus.

- Risks in US: sexual promiscuity and IVDA
  - Many immigrants likely contracted at birth or young childhood
- Prevention:
  - Hep B immune globulin should be given to household and sexual contacts of patients with acute hepatitis B.
  - Infants and previously unvaccinated should receive hep B vaccine.

Hep B Serologic Markers

1.HBsAG	1.Current infection
2. Anti-HBs	2.Immunity (immunization or resolved infection)
3. IgM anti-HBc	3. Recent infection, occasionally reactivation
4. IgG anti-HBc	4. Remote infection
5.HBeAg and/or HBV DNA>105 viral copies/mL	5. Active viral replication

Interpretation of Hep B serologic panel- examples

- HBsAg +
- Anti-HBc +
- IgM anti-HBc +
- Anti-HBs -

Acutely infected

- HBsAg +
- Anti-HBc +
- IgM anti-HBc -
- Anti-HBs -

Chronically infected

Hep B

- Treatment –when?
  - If pt at increased risk of progression:
    - LFTs >2x normal,
    - active viral replication HBeAg-(DNA > 2,000 IU/ml) or HBeAg+ (DNA > 20,000 IU/ml)
    - And active disease identified in liver biopsy specimens

Hep B treatment

- Interferon
  - Pegylated—once weekly and better efficacy
- Oral agents
  - Lamivudine, Tenofovir, Entecavir
  - Become popular for treatment of chronic HepB
  - Few side effects
    - Adefovir→ nephrotoxicity
  - Useful in pts with decompensated cirrhosis

Hepatitis question

- 21 y/o presents to the ER with abdominal pain, fatigue, and loss of appetite. He admits to IV heroin use and drinks 2-3 beers/d.
- PE: mild icterus, hepatomegaly-tender, +needle tracks antecubital
- Lab: T Bili: 5.6mg/dL; AST & /ALT 950 & 1280 AlkPhos 115; Albumin 3.4
  - HBsAg -
  - HBsAb +
  - HBcIgM -
  - HAV IgM -
  - HCV Ab -
- What lab is most likely to make a diagnosis?

Hepatitis question

- What lab is most likely to make a diagnosis?

a. Antimitochondrial and Anti-smooth muscle Ab
b. HCV RNA
c. HCV RIBA
d. HBc IgG
e. HAV total

Answer: b

- Pt with signs and symptoms of acute hepatitis
- Initial serology shows immunity to HepB otherwise negative
- With active IV drug use acute Hep C must be considered
  - HCV ab may take up to 6 weeks to develop
- RIBA confirms + HCV ab
  - No longer recommended by CDC
- HAV total and HBV signal prior exposure and not for acute disease concerns

Hepatitis C

Leading indication for liver transplantation

- Diagnostic tests
  - anti-HCV: indicates current infection or previous exposure with clearance.
  - “gold standard” presence of HCV RNA by PCR—now the preferred test, bypassing RIBA.
- Level of RNA does not correlate with severity of disease.
- Genotyping: genotype 1most common in US

HCV testing recommendations(CDC)

Adults born from 1945 through 1965 should be tested once (without prior ascertainment of HCV risk factors)

- Currently injecting drugs; Ever injected drugs
- Have certain medical conditions, including persons:
  - who received clotting factor concentrates produced before 1987
  - who were ever on long-term hemodialysis
  - with persistently abnormal alanine aminotransferase levels (ALT)
  - who have HIV infection

HCV

- Were 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
  - received a transfusion of blood, blood components, or an organ transplant before July 1992
- HCV testing based on a **recognized exposure** is recommended for:
  - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCVpositive blood
- Children born to HCV positive women

Hepatitis question

- 56 y/o male presents to his PCP for an annual physical. He is in good health, but is found to have ALT of 86 and a skin rash diagnosed by his dermatologist as porphyria cutanea tarda. The PCP should order which blood test to help explain the findings?

a. Hep A IgM
b. Hep B surface Ab
c. Hep C Ab
d. Hep E Ab

Answer: c

- Hep C associated with a variety of dermatologic findings
- HCV therapy may result in resolution of the skin findings.

Hepatitis C

Subgroup of pts likely to develop progressive liver disease

1. duration of infection
2. alcohol intake >50g/d
3. coinfection with HIV or HBV
4. male sex

Pts with cirrhosis due to HCV generally have disease >20 years.

Hepatitis question

- 19 y/o college student presents with 8 days of N/V/D and fatigue. She recently returned from a 2 week mission trip to Haiti.
- PE: low grade fever, tender hepatomegaly, mild scleral icterus
- Lab: T Bili 4.9; AST 1280 ALT 1980; Alk 99 INR 0.9
- Which of the following lab tests is most likely to reveal the diagnosis?

a. HAV IgM
b. HAV total
c. CMV stool PCR
d. HBsAb
e. HCV Ab

Answer: a

- Pt presents with acute hepatitis
- Recent travel to endemic area
- HAV total: only reveals prior infection and immunity
- *CMV* unlikely with no history of immunosuppression
- HBsAb describes immunity rather than acute
  - Given her age, likely vaccinated as baby
- No clear risk factors for HCV exposure

Hepatitis D

- A defective virus
  - Requires the presence of HBsAg to replicate

Hepatitis E

- Single stranded RNA
- The highest incidence of HEV infection is in Asia, Africa, Middle East, and Central America.
- HEV is the second most common cause of sporadic hepatitis in North Africa and the Middle East.

Hepatitis E

- HEV is spread by fecal-oral route via contaminated water in endemic areas
- Person-to-person transmission is uncommon
- HEV can be transmitted by blood transfusion, particularly in endemic areas

Cirrhosis--Complications

Portal hypertension

- An increase in hepatic venous pressure gradient.
- In cirrhosis it occurs through an increase in resistance to portal venous outflow
  - Due to distortion of liver
  - ~30% of the increase is through potentially reversible vascular factors---where pharmacotherapy targets

Esophageal varices

- Risk factors for hemorrhage from esophageal varices:
  - radius of varix,
  - thickness of varix wall
  - pressure gradient between the varix and the esophageal lumen.

Esophageal varices

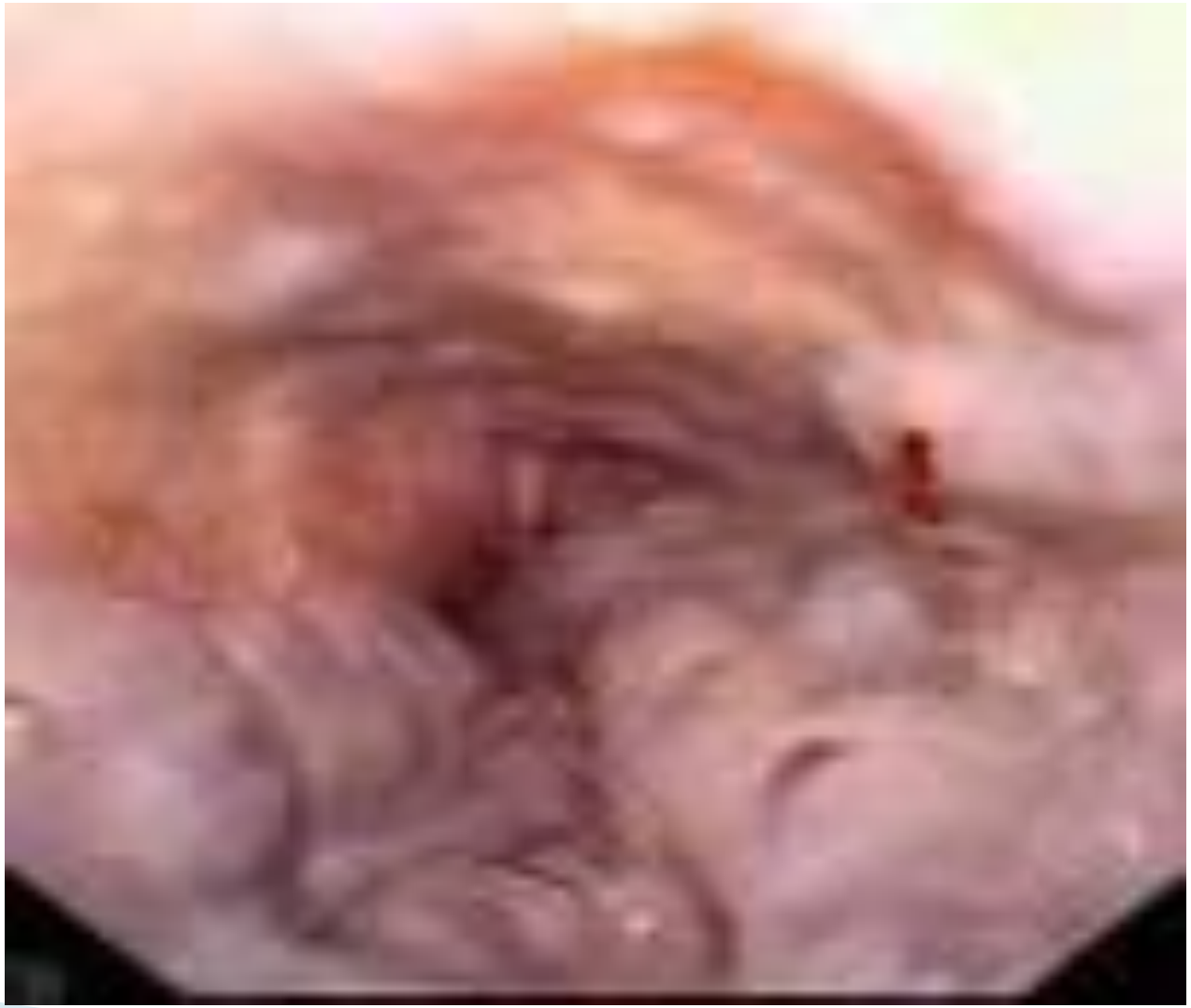
Recommendations for treatment of esophageal varices

- Primary prophylaxis: all patients with cirrhosis should have EGD for screening.
  - If no varices repeat endoscopy in 2-3 years.
  - -1st line therapy : nonselective beta blockers (propranolol or nadolol)
  - -2nd line therapy: endoscopic band ligation
- Control of bleeding: best managed by endoscopic means preferable band ligation.
  - - begin Octreotide, continue for up to 72 hours.
  - -2nd line therapy: TIPS

Esophageal varices

- Secondary prophylaxis: prevent rebleeding.
  Essential—80% of patients who bleed will have a rebleed within 2 years.
    1st line therapy: endoscopy and beta blockers.
    other: liver transplantation

EGD esophageal varices



Liver question

- A 47 y/o female presents with new onset ascites that has developed over ~ 4 months. She denies ETOH, +tobacco. She is obese but no other medical problems.
- +fatigue, decreased appetite, dyspnea
- Diagnostic paracentesis: ascites albumin 1.5g/dL, ascites protein 2.6g/dL, and ascites cell count 101 neutrophils/mm3. Her serum albumin is 2.9.
- US is limited due to body habitus, reveals patent portal and hepatic veins.

Liver question

- What is the next most appropriate diagnostic step?

a. Exploratory laparotomy
b. Echocardiogram
c. Cytologic analysis of the fluid
d. Triple phase CT scan of the liver

Answer: b

- Pts SAAG (serum-ascites albumin gradient) is elevated at 1.4g/dL
  - Differential: cirrhosis, CHF, pericardial disease, Budd Chiari, and veno-occlusive disease
  - Mildly elevated protein in her ascitic fluid necessitates cardiac evaluation

Ascites

- Pathogenesis: renal retention of sodium and movement of this extra fluid into the peritoneal space.
- Diagnostic paracentesis is essential for patients who present with ascites.
  - the difference between serum albumin and ascitic albumin help determine portal hypertension (1.1g/dL or greater). Could be liver or heart disease. **(SAAG)**
  - A protein of 2.5g/dL or more favors heart disease.
- Cell count of more than 250 neutrophils/mm3 is spontaneous bacterial peritonitis (SBP).

Management of Ascites

- Low sodium diet
- Fluid restriction: only necessary if serum sodium is <125mEq/L
- Diuretic therapy:
  - urinary sodium excretion is used to determine the efficacy of therapy.
    - If urinary sodium excretion is more than 30mEq/d,
      spironolactone alone may be used.
      If urinary sodium excretion is between 10-30mEq/L then a combination of spironolactone and furosemide is used.
      If urinary sodium excretion is < 10mEq/L then large volume paracentesis is usually required.

Spontaneous Bacterial peritonitis

- End-stage liver disease
- No secondary source
- Clinical manifestations
  - Fever
  - Abdominal pain/tenderness
  - Altered mental status
- Index of suspicion should be high

SBP- Diagnosis

- +bacterial culture
- And/or pmn >250 cells/mm3

Hepatic encephalopathy

- Pathogenesis:
  - Ammonia and manganese considered etiologic factors for encephalopathy.
- Clinical features:
  - range from 0—no overt encephalophy to IV patient in a coma.
- Precipitating factors:
  - GI bleed, infection, large protein meal, use of sedatives, electrolyte abnormalities or hypoxia, constipation, and hypoglycemia.

Hepatic encephalopathy- Management

- Dietary: limit protein based on level of encephalopathy (1.2-1.5 g/kg/day)
  - Long-term restriction of dietary protein of < 1g/kg daily should be avoided.
- Nonabsorbable disaccharides:
  - Lactulose, may help remove dietary and endogenous ammonia.
    - Pt should have 2-3 semi-formed stools/day.
- Antibiotics:
  - neomycin, metronidazole, and rifaximin have been used for treatment.

Liver diseases

Liver question

- 46 y/o asymptomatic male has a brother with hemochromatosis
- Exam is normal. He drinks 2 beers/day
- Lab: Fe 180ug/dL, Transferrin sat 88%, ferritin 1200ug/L. CBC nl, AST 52 US normal.
- HFE gene test + C282Y/C282Y mutation

Most appropriate next step would be:

a. Liver biopsy
b. Therapeutic phlebotomy
c. Stop ETOH and repeat iron studies in 1 year
d. MRI of the liver

Answer: a

- Ferritin <1000ug/L and normal AST→phlebotomy
- **Ferritin >1000ug/L and/or elevated AST→ liver biopsy and then phlebotomy**
- Normal ferritin→ repeat ferritin q 2-3 years

Hemochromatosis

- Autosomal recessive disorder with increased intestinal absorption of iron.
- Excess iron is deposited in the liver, pancreas, and other organs.
- About 1 in every 250 white persons in the US is homozygous for the mutation.

Hemochromatosis

- Suspect in pts with elevated iron sat, ferritin, or family hx.
- Most pts asymptomatic
- Cirrhosis, heart failure, hypogonadism, and arthritis
- HFE gene mutation
  - Autosomal recessive dz
    - 85% homozygous for C282Y mutation

Hemochromatosis–Treatment

- Reserved for patients with evidence of iron overload, indicated by an increase in the serum concentration of ferritin.
  - therapeutic phlebotomy: simple, relatively inexpensive and effective.
  - avoid supplements with iron
  - avoid raw fish due to risk of *Vibrio vulnificus* infection
  - avoid alcohol
- If diagnosed and treated before diabetes and cirrhosis develops survival rate is normal

Liver question

- 18 y/o male is seen for 6 month hx of abnormal liver tests. He is asymptomatic.
- Recent poor school performance and ADD
- PE: mild obesity, no stigmata of chronic liver dz.
- Lab: AST 65, ALT 87 bili 1.2 ALP 120. Hepatitis panel, ANA negative. Ceruloplasmin 19.2 (nl 22.9-43.1) Eye exam neg. 24h urine Copper >40. bx: mild steatosis, minimal inflammation copper >250mcg/g
- What is the most likely diagnosis?

What is the most likely diagnosis?

a. Primary biliary cholangitis
b. Wilson's disease
c. Drug induced liver disease
d. Autoimmune liver disease
e. Fatty liver

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Wilson's disease

- Inherited
- Excess copper
- Hepatic, neurologic, and psychiatric manifestations

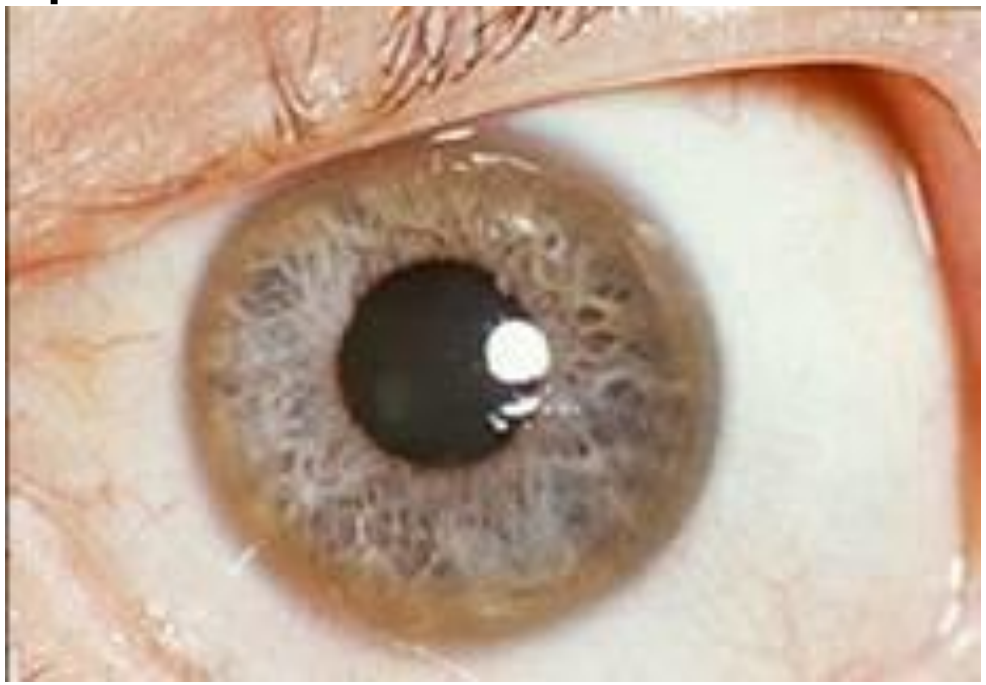
- Gene mutation
  - *ATP7B* genes
- All ethnic groups
- ~1 in 30,000

Wilson's disease

- Diagnosis
  - Reduced ceruloplasmin
  - Increased urinary excretion of copper
  - Presence of K-F rings
  - Elevated hepatic copper level
  - Coombs-negative intravascular hemolysis
  - Low level of Alk Phos
- Treatment
  - Copper-chelating medications (D-Penicillamine, Trientine, Zinc)

Wilson's

- Kayser-Fleischer rings (KF)
- Seen with slit-lamp



Liver question

- 16 y/o presents with AST and ALT elevation for 4 months. Originally felt to be Mono, due to fatigue and low grade fever. However, Monospot was negative.
- PE: no stigmata of chronic liver disease
- Lab: AST 356 ALT 435. T Bili 1.1 PT 13.2, hepatitis panel neg, ANA 1:640, Anti-smooth muscle Ab 1:320, AMA normal Liver bx: cirrhosis with increased lymphoplasmocytes

What is the likely diagnosis?

What is the likely diagnosis?

a. Autoimmune hepatitis
b. Primary biliary cholangitis
c. Wilsons disease
d. Acute viral hepatitis
e. Primary sclerosing cholangitis

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Autoimmune Hepatitis

- Occurs in children and adults
  - 3.6 to 1 female to male
- All ethnic groups

Clinical Manifestations

- Asymptomatic→ liver failure
  - Subclinical
- Present with cirrhosis

Diagnosis

- Aminotransferase elevation
- ANA
  - Anti-smooth muscle antibody
- Hypergammaglobulinemia
- Histology: nonspecific
  - Portal mononuclear cell infiltration
    - Lymphoplasmacytic
  - fibrosis

Treatment –Autoimmune Hepatitis

- Liver transplant
- Prednisone
- Azathioprine

Autoimmune Hepatitis: Typical lab

- Increased AST and Alt 100%
- Increased gamma globulin and IgG 90%
- Mild hyperbilirubinemia 83%
  - <3 mg/dL
- Alkaline phosphatase increase 67%
  - <2x normal
- ANA, SMA, or anti-LKM1 87%

Primary Biliary Cholangitis

- Cholestatic liver disease
- 90% women
- 95% will be AMA + (anti-mitochondrial Ab)
- Fatigue common
- Pruritis 30-50%
- Frequently being picked up in pts with asymptomatic lab abnormalities
- IgM high

Alpha 1-antitrypsin (AAT) deficiency

- Autosomal co-dominant disorder with lung and liver injury
- Can cause premature emphysema and liver disease
- Pt with cirrhosis due to AAT have a significant increased risk of HCC up to 30%
- Diagnosed by phenotyping. Liver damage does NOT correlate with serum AAT levels (unlike lung). Diagnosis confirmed with biopsy
- No effective medical treatment for the liver manifestations of AAT deficiency.

Thank You
Good Luck!