Chronic Liver Diseases
Ryan M. Ford, MD
Assistant Professor of Medicine
Transplant Hepatology
Director of Viral Hepatitis
Emory Transplant Center
Internal Medicine Board Review
July 23, 2016

Chronic Hepatitis

**Definition:** Sustained (>3 months) elevation of liver tests on 2 or more occasions

<table>
<thead>
<tr>
<th>Hepatocellular (ALT/AST)</th>
<th>Cholestatic (Bilirubin/Alk phos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Viral hepatitis</td>
<td>1. Primary biliary cirrhosis (PBC)</td>
</tr>
<tr>
<td>2. Alcoholic liver disease</td>
<td>2. Primary sclerosing cholangitis (PSC)</td>
</tr>
<tr>
<td>3. Non-alcoholic fatty liver disease (NAFLD)</td>
<td>3. Infiltrative diseases (Lymphoma, Sarcoid, Amyloidosis)</td>
</tr>
<tr>
<td>4. Hereditary Hemochromatosis</td>
<td></td>
</tr>
<tr>
<td>5. Wilson disease</td>
<td></td>
</tr>
<tr>
<td>6. Alpha-1 antitrypsin deficiency</td>
<td></td>
</tr>
<tr>
<td>7. Autoimmune hepatitis (AIH)</td>
<td></td>
</tr>
</tbody>
</table>

Alcoholic liver disease

**Genetics/epidemiology:**
- Variations in metabolism (e.g., alcohol dehydrogenase)
- Addiction is genetic
- 20% of heavy drinkers may develop cirrhosis
  - Male: 40-80 gm/day, Female 20-40 gm/day (shorter duration)

**Pathophysiology:** Toxic metabolites → oxidative stress and free radical formation → immune activation and cytokine release → stellate cell activation → fibrosis

**Clinical manifestations:**
1. Steatosis (reversible)
2. Acute alcoholic hepatitis
3. Cirrhosis

Alcoholic liver disease

**Diagnosis:**
- a.) History and physical exam
- b.) Lab testing (AST: ALT ratio > 2:1, elevated MCV, elevated GGT)
- c.) Imaging studies (U/S, CT, or MRI of liver)
- d.) Liver biopsy in some cases
- e.) Exclude other causes of liver disease

**Treatment:**
- a.) Abstinence and relapse prevention
- b.) Improved nutrition and supplementation
- c.) Steroids or pentoxifylline for acute alcoholic hepatitis?
- d.) Liver Transplant in some cases

NAFLD

**Genetics/Epidemiology:**
- a.) 90% of patients with BMI > 35
- 20% of patients will develop NASH
- 20% of patients with NASH will develop cirrhosis
- b.) Risk factors: Metabolic Syndrome
  - Diabetes/insulin resistance, hypertension, obesity, elevated triglycerides, low HDL
  - Obstructive sleep apnea
  - PCOS
  - Pituitary disease

**Clinical Manifestations:**
- a.) Most patients are asymptomatic (hepatomegaly with pain may be encountered)
- b.) Elevated liver enzymes
- c.) "Cryptogenic" cirrhosis

**Diagnosis:**
- a.) History and physical (Calculate BMI)
- b.) Lab testing (ALT>AST, elevated ferritin, triglycerides >150, HDL < 40, insulin resistance)
- c.) Imaging (U/S, CT, MRI): Hepatomegaly, Steatosis +/- cirrhosis
- d.) Liver biopsy in some cases (to assess fibrosis or rule out other causes of liver disease)
NAFLD

Treatment:

a) Lifestyle Change with a goal of at least 10% body weight reduction
b) Control of metabolic syndrome risk factors (HTN, DM, dyslipidemia)
   - Statins
   - Metformin
   - Pioglitazone
   - Fenofibrates
c) Surgery: Gastric bypass surgery, gastric banding, gastric sleeve
d) Anti-inflammatories (Vitamin E, coffee, other antioxidants?)
e) Liver transplant: NASH cirrhosis is becoming a very common indication for liver transplant in the U.S.

Hereditary Hemochromatosis

Genetics/Epidemiology:
- Autosomal recessive (~1/250 Caucasians)
- Low penetrance of clinical disease
- HFE gene is most common mutation
  - C282Y homozygote is most commonly seen with clinical disease
- Pathophysiology: Unregulated, increased uptake of dietary iron without negative feedback loop
  - Results in iron overload with organ deposition and hepatic fibrosis

Clinical Manifestations:
- Presents later in life for females (due to menses)
- Fatigue is most common
- Erectile dysfunction
- Hepatomegaly
- Elevated LFTs
- Cirrhosis
- HCC
- CHF
- Conduction Disease
- Bronze pigmentation
- Diabetes
- Arthralgias
- Hook-like osteophytes
- Chondrocalcinosis
- Kayser-Fleischer rings
- Sunflower cataracts

Diagnosis:
1. Elevated liver tests
2. Clinical suspicion
3. Check transferrin saturation ➔ if elevated (>45%), order genetic testing

Treatment:
- a.) Phlebotomy
- b.) Diet – avoid iron and vitamin C supplementation
- c) If cirrhosis, need to screen for liver cancer

Wilson disease

Genetics/Epidemiology:
- a.) 1/30,000 prevalence
- b.) Autosomal recessive
- c.) ATP7B gene (multiple different mutations)

Pathophysiology:
- Mutated ATP7B gene → Unable to excrete copper in bile
- Copper accumulation → Organ deposition
- Tremor
- Dysarthria
- Ataxia
- Dystonia
- Psychiatric disease
- Elevated Liver Enzymes
- Steatosis
- Acute Liver Failure
- Cirrhosis
- Kayser-Fleischer rings
- Sunflower cataracts
Wilson disease

**Diagnosis:**
- a.) Clinical suspicion
- b.) Lab Testing: Low ceruloplasmin (<20), low alkaline phosphatase, elevated 24-hour urine copper (> 100 mcg)
- c.) Slit lamp: Kayser-Fleischer rings are diagnostic (50% sensitivity)
- d.) Liver biopsy in some cases

**Treatment:**
- a.) Pharmacotherapy: Trientine, Zinc
- b.) Avoid foods high in copper: liver, chocolate, nuts, shellfish, mushrooms

---

Alpha-1 Antitrypsin Deficiency

3. **Clinical manifestations:**
- a.) Liver: cirrhosis
- b.) Lung: emphysema

4. **Diagnosis:**
- a.) Alpha-1 antitrypsin phenotype: ZZ is most concerning
- b.) Liver biopsy: PAS +, diastase resistant globules
- c.) Alpha-1 antitrypsin level may be low (more important for lung disease)

5. **Treatment:**
- a.) Liver: No therapy other than liver transplant in advanced cases
- b.) Lung: Smoking cessation, enzyme replacement

---

Alpha-1 Antitrypsin Deficiency

**Pathophysiology:**
- Mutated gene
- Abnormal protein folding
- Polymers retained in endoplasmic reticulum
- Hepatotoxic

---

Autoimmune Hepatitis

**Genetics:**
- a.) Females > Males
- b.) Co-existing autoimmune diseases

**Pathophysiology:**
- a.) Unclear trigger (genetics + environmental)
- b.) May be precipitated by medications (e.g. nitrofurantoin, minocycline)

**Clinical Manifestations:** (variable presentation)
- a.) Acute liver failure
- b.) Acute or chronic hepatitis
- c.) Cirrhosis and portal hypertension

**Treatment:**
- a.) Induction with systemic steroids (Prednisone 30-40 mg daily initially)
- b.) Maintenance therapy: Azathioprine

---

Primary Biliary Cirrhosis

**Genetics/Epidemiology:**
- a.) Unknown Cause
- b.) Females >> Males
- c.) Associated with other autoimmune diseases (e.g. Sjogren’s)

**Pathophysiology:** Lymphocytic infiltrate and destruction of intrahepatic bile ducts

**Clinical Manifestations:**
- a.) Fatigue
- b.) Pruritus
- c.) Jaundice
- d.) Xanthomas/Xanthelasmas
- e.) Fat-soluble vitamin deficiency
- f.) Osteoporosis
- g.) Cirrhosis/portal hypertension
**Primary Biliary Cirrhosis**

**Diagnosis:**
- a.) Elevated liver tests (cholestatic pattern)
- b.) Positive anti-mitochondrial antibody (AMA)
- c.) Elevated HDL and LDL
- d.) Elevated IgM
- e.) Liver biopsy: Florid duct lesion is pathognomonic

**Treatment:**
- a.) Ursodiol
- b.) Obeticholic acid
- c.) Liver transplant

---

**Primary Sclerosing Cholangitis**

**Clinical Manifestations:**
- a.) Elevated liver tests (cholestatic pattern), jaundice
- b.) Cholangitis
- c.) Pruritus
- d.) Fat soluble vitamin deficiency; osteoporosis
- e.) Cirrhosis (portal hypertension)
- f.) Cholangiocarcinoma

**Diagnosis:** MRI/MRCP, ERCP

*Check IgG-4 levels to rule out a steroid responsive subtype*

**Treatment:**
- a.) No effective treatment (unless IgG-4 type)
- b.) Screen for cholangiocarcinoma
- c.) Liver transplant in some patients

---

**Ascites**

**Ascitic Fluid Analysis:**
High SAAG (serum-ascites albumin gradient >1.1)

**Treatment:**
1. Sodium Restriction (<2 grams/day)
2. Avoid NSAIDs
3. Diuretics (Furosemide and Spironolactone)

**Treatment of Refractory Ascites (10% of cases):**
1. Large volume paracentesis
2. TIPS (Transjugular Intrahepatic Porto-Systemic Shunt)
3. Liver Transplant

---

**Hepatic encephalopathy**

**Identify triggers:** infection, GI bleed, medications, dehydration, electrolyte abnormalities (hypokalemia), constipation, post-TIPS, non-adherence with medications, shunting

**Treatment:**
- a.) Treat and avoid triggers
- b.) Lactulose with a goal of 2-3 bowel movements daily
- c.) Rifaximin 550 mg BID
- d.) Daily zinc sulfate therapy (50-220 mg)

---

**CIRRHOSIS**

**Complications:**
- a.) Ascites/Spontaneous bacterial peritonitis (SBP)
- b.) Hepatic encephalopathy
- c.) Variceal bleeding
- d.) Coagulopathy
- e.) Hepatorenal syndrome
- f.) Hepatopulmonary syndrome
- g.) Porto-pulmonary syndrome
- h.) Hepatocellular carcinoma
- i.) Acute on chronic liver failure
- j.) Multi-organ failure and death

**Prognostic Scoring systems:**
- a.) Child-Pugh score (bilirubin, albumin, INR, ascites, encephalopathy)
- b.) MELD score (bilirubin, INR, creatinine)
Risks for bleeding
- Higher portal pressure
- Varix size
- High MELD score
- Child’s class B/C
- Prior variceal bleed

Screening recommendations:
EGD at time of diagnosis of cirrhosis
EGD every 1-3 years based on history and risk

Treatment/prophylaxis:
1. Non-selective beta blockers (Nadolol, Propranolol) with goal heart rate near 55-60 as long as blood pressure will tolerate
2. Variceal band ligation

*HCC is fastest-growing cause of cancer-death in USA
- Often asymptomatic until late stage

Screening:
- Ultrasound, CT, MRI q 6 months
- serum AFP

Who to screen?
- Any patient with cirrhosis
- Patients with chronic hepatitis B virus

Treatment?
- Resection, loco-regional therapy, liver transplant

Hepatocellular Carcinoma

Hepatitis B--Global
- 400 million carriers in the world
- #1 cause of cirrhosis in the world
- #1 cause of HCC in the world
- Highly endemic in Southeast Asia and Africa: 60-80% lifetime risk of infection
- Perinatal or horizontal spread as children

Hepatitis B in U.S.
- 1.25 million carriers in U.S.
- Most carriers are immigrants or first generation Americans

Prevalence of HBsAg Carrier State

- >8%
- 2-8%
- <2%
Who should be tested for Hepatitis B?
- Patients born in endemic regions
- MSM or patients with multiple sexual partners
- Patients with history of IV drug abuse
- Inmates
- Dialysis patients
- HIV positive patients
- Pregnant women
- Family members/close contacts of known cases
- Patients with abnormal liver enzymes

Diagnostic Testing for Hep B
- Blood tests:
  1. Hep B surface antigen (sAg)
  2. Hep B core antibody (total or IgG)
  3. Hep B surface antibody
  4. Hepatitis B DNA viral load (PCR)

Who to treat with medication?
- Patients with chronic, active hepatitis
- Patients with advanced fibrosis
- Patients with HCC
- Patients with acute liver failure
- Liver transplant patients
- Prophylactic in the setting of immunosuppression (chemotherapy, anti-TNF therapy)
- High risk pregnant females near delivery
- Patients with hepatitis D infection

HCC screening with Hep B—High Risk
- Asian men over age 40
- Asian women over age 50
- Africans over age 20
- Family history of HCC
- Cirrhosis
- Any carrier over age 40 with elevated ALT levels

Hep B Prevention
- Very effective vaccine
- Give vaccine and Hep B immune globulin to babies born to viremic mothers (95% effective)
Case #1

A 65 year old Chinese male is found to have a positive hepatitis B surface antigen. He immigrated to the United States many years ago. There is no evidence of cirrhosis on exam and his liver enzymes are normal. He has a normal CBC, serum albumin, and bilirubin. His hepatitis B viral load is low at 150 IU/mL. What is the best next step in management?

A) Return on an annual basis for repeat blood tests
B) Start on antiviral therapy
C) Order an ultrasound and serum AFP
D) No further testing or follow-up is necessary

Case #2

A 66 year old Caucasian gentleman comes in for a routine annual physical exam. He has no somatic complaints and takes a baby aspirin daily. He likes to play golf and travel internationally. His physical exam and lab testing are normal. What should be included in your work-up?

A) Cardiac catheterization
B) PET scan
C) Screen for hemochromatosis
D) EGD since he takes daily aspirin
E) Hepatitis C antibody test