Case Studies In Elevated Liver Enzymes

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Learning Objectives:

- To understand the difference between liver enzymes and liver function tests, and the importance of each
- To understand the difference between abnormalities in liver function tests, abnormalities in hepatocellular markers, abnormalities of biliary excretion and abnormalities in cholestatic markers
- To be able to list both common and uncommon causes of liver test abnormalities
- To be able to list the important follow up tests necessary to diagnose different diseases of the liver

Reference ranges for tests in a “Hepatic Function Panel”

- AST 12-37 U/L
- ALT 15-65 U/L
- GGT 0-50 U/L
- Albumin 3.4 – 5.0 mg/dl
- Total Protein 6.4-8.2 mg/dl
- Total Bilirubin 0.2 – 1.0 mg/dl
- Alk. Phosphatase 50 -136 U/L

4 Catagories of Liver Tests

- Tests for hepatocellular damage (AST, ALT)
- Tests for Cholestasis (Alk Phos, GGT)
- Tests for Biliary excretion (TBili, DBili)
- Tests for Liver synthetic Function (Albumin, PT/INR)
Serum Aminotransferases
ALT = alanine aminotransferase
Mainly from cytosol of hepatocytes, as well as other organs.
ALT is more specific than AST for acute and chronic liver injury.
AST = aspartate aminotransferase
From both cytosol and mitochondria of hepatocytes, as well as other organs such as skeletal muscle, heart, kidney, brain and pancreas.

Why are transaminases (liver enzymes) elevated in liver diseases?
Elevation of the aminotransferases indicates inflammation and/or injury to hepatocytes.
Damaged hepatocytes leak their contents into the interstitial spaces and plasma, and this fluid is reabsorbed into the circulation.

How are normal levels of transaminases determined?
• They are arbitrarily defined by samples from “healthy” population (e.g. blood donors), or from the average of patients who have their drawn at a certain lab. That is why the “normal range” differs in different clinics and hospitals. The cutoff for the normal range is determined by calculation of a standard deviation from the median value. Some experts suggest the true normal values for ALT are up to 20 for women, and up to 30 for men.
• Therefore, even transaminases at the ULN in a young healthy patient are potentially higher than they should be, and you may want to repeat the transaminases in 3-6 months to see if they are increasing.

Tissue/Serum Ratios
Lowest ratio of AST: ALT occurs in liver
ALT in order of concentration
Liver>Kidney>Myocardium>Muscle
AST in order of concentration
Heart>Liver>Muscle>Kidney>Pancreas>Spleen
Serum AST>ALT in 2 important situations:
1) Alcohol use
2) Cirrhosis
Liver Function Tests (LFTs)

- Indicate hepatic synthetic function NOT inflammation or injury

The true Liver Function Tests are:
- Albumin (liver makes proteins)
- Total Bilirubin (liver conjugates Bilirubin)
- Protime/INR (liver makes clotting factors including prothrombin)

Questions to ask when evaluating abnormal liver enzymes:

- Does this look like an acute problem (aminotransferases >5XULN) or a chronic problem (aminotransferases <5X ULN)?
- Is there anything in the social history, past medical history, med list, or physical exam that points me in a particular direction?
- Does think look like a cholestatic problem or more like a hepatocellular problem?

Typical Transaminase Elevations in Hepatocellular Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic Hepatitis</td>
<td>160</td>
<td>80</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>120</td>
<td>180</td>
</tr>
<tr>
<td>Chronic Hepatitis C</td>
<td>46</td>
<td>78</td>
</tr>
<tr>
<td>Acute Viral Hepatitis C</td>
<td>400</td>
<td>800</td>
</tr>
<tr>
<td>EtOH + Tylenol toxicity</td>
<td>19,000</td>
<td>16,000</td>
</tr>
<tr>
<td>Acute Hepatitis A</td>
<td>2,000</td>
<td>2,000</td>
</tr>
</tbody>
</table>

Chronic Liver Disease:
Prevalence in United States

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonalcoholic Fatty Liver Disease</td>
<td>17.33%</td>
</tr>
<tr>
<td>Nonalcoholic Steatohepatitis</td>
<td>5.7%-17%</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>1.3%</td>
</tr>
<tr>
<td>Alcoholic liver disease C</td>
<td>0.8-1.3%</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>0.5%</td>
</tr>
<tr>
<td>Chronic Hepatitis B</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hepatocellular Cancer</td>
<td>19,429</td>
</tr>
</tbody>
</table>

Who Should be Tested for Viral Hepatitis?

- Patients typically enter this diagnostic group with a history of
  - Elevated liver tests
  - or
  - Risk events, immigrant status, blood exposure
  - or
  - For HCV: Birth cohort 1945 -1965
- Also, few symptoms are specific for liver disease, thus an evaluation should take place if there are
  - signs of liver failure

Key Tests for Chronically Increased Liver Enzymes

- Alcohol history
  - CAGE, MAST
- HCV antibody
- HBsAg
- Iron Saturation
- Medication and herbal, OTC history
- Metabolic syndrome tests
  - BMI
  - HTN
  - Lipids
  - Glc fasting
  - Waist circumference

Key Tests for Acutely Increased Liver Enzymes

- Tox screen
- Acetaminophen level
- HAV IgM
- HBV anti-HBc IgM
- Alcohol blood level
- Alcohol history
- Heart disease, shock
- Medication history

Clinical Question:

What causes are in your differential diagnosis of Chronic Hepatitis (aminotransferases <5X ULN)?
Differential Diagnosis of Chronic Hepatitis (aminotransferases <5X ULN)

- Chronic Hepatitis B or C
- Non-Alcoholic Steatohepatitis (NASH)
- Chronic Alcoholic Hepatitis
- Drug-Induced Liver Injury (DILI)
- AutoImmune Hepatitis (AIH)
- Primary Biliary Cirrhosis (PBC)
- Primary Sclerosing Cholangitis (PSC)
- Hereditary Hemochromatosis (HH)
- Wilson's Disease
- Alpha-1-antitrypsin deficiency
- Celiac Disease
- Primary Liver Cancer (Hepatocellular Carcinoma)
- Metastatic Cancer

Liver Tests for Cholestasis

1. Alkaline phosphatase
   - isoenzymes, bone, liver, small intestine
   - differentiate liver from bone by gamma GT or 5’ nucleotidase
   M > F in age 15 to 50
   Age > 60, M=F
   Children have ↑ levels as their bones are still growing.

2. GGT: very sensitive for biliary tract disease, eg obstruction, cholestasis, and EtOH toxicity
   Leaks from hepatocytes in response to some chemicals/drugs
   Clinical value: confirmation of source of elevated ALP
   Hyperbilirubinemia may interfere with assay rxn
   GGT lacks sensitivity. It is elevated in pancreatitis, obesity, DM, MI, CA, EtOH.

3. Total Bilirubin: may be elevated in severe cholestasis or obstruction

Causes of Cholestasis

- Gallstones
- Intra or Extrahepatic compression of bile ducts (pancreatic cancer, polycystic liver disease)
- Bile Duct CA (Cholangiocarcinoma, order serum CA 19-9 if clinically suspected)
- AutoImmune Bile Duct Diseases (PBC, PSC)

Case #1

19 y/o female college student

- c/o severe fatigue of new onset, jaundice, mild pruritis of few days duration
- No EtOH
- Meds: minocycline, multivit
- No Hx. of contacts with viral hepatitis
- PE: heent: mild scleral icterus
  abd: nl bs, no organomegaly, no tenderness or palpable mass
Case #1, Continued

• Labs: alb 4.2, t bili 4.2, alk phos 248,
• AST 180, ALT 252;
• hgb/hct 13.1/36, wbc 5.2k, plts 210k
• Acute viral hepatitis serologies neg.

What is the most likely diagnosis?

Clinical Question:

What is the most common cause of Drug-Induced Liver Injury (DILI)?
Is this cause more often intentional or unintentional?

Case #1 Answer
19 y/o wf college student

Drug induced cholestasis secondary to minocycline.
Symptoms resolved within 2 weeks of drug d/c, liver profile normalized in 8 weeks.

Answer:

Acetaminophen (Tylenol) is the most common cause of DILI.

The majority of cases are unintentional, as patients exceed 4 grams of Tylenol due to poor understanding that Tylenol is contained in many different medications such as multi-symptom cold relievers, and pain meds like Darvocet, Fioricet, Lortab, Norco, Percocet, T3 (Tylenol with codeine), Ultracet, and Vicodin.
What drugs commonly cause elevations in aminotransferases?

• Tylenol
• Statins
• Glucophage
• Minocycline
• Fat Soluble Vitamins in high doses

Make sure to ask about meds and herbal supplements when evaluating these patients!

Case #2

• 26 y/o Asian Female grad. student, notified by blood bank she was HBsAg (+).
• Liver profile: alb 4.1, t bili 0.6, alk p 82, ast/alt 18/22.
• HBsAg (+), HBcAb (+), HBeAg (-), HBV-DNA 400 IU/ml

What is your diagnosis?

• ANSWER: Hepatitis B Chronic Carrier State

Chronic HBV

• Globally
  – 350 million chronic carriers\(^1\); 75% in Asia
  – 520,000 deaths per year

• United States
  – 1.25 million carriers\(^2\); 0.3% of adult population
  – 100,000 new cases per year
  – 5000 deaths per year\(^3\)

• Premature mortality from cirrhosis or hepatocellular carcinoma: 15%-25%

\(^1\)Lee W. N Engl J Med. 1997;337:1735-1745
\(^2\)McQuillan GM et al. Am J Public Health 1999;89:14-18
\(^3\)Paterusch J et al. Ann Intern Med 1997;126:885-887
Global Distribution of Chronic HBV Infection

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

Hepatitis B Disease Progression

- >90% of infected children progress to chronic disease
- <5% of infected immunocompetent adults progress to chronic disease

Hepatitis B Serologies

- HBsAg (+) chronic carrier or active dz
- HBsAb (+) immunity or previous exposure
- HBeAb(IgM) acute exposure
- HBeAb(IgG) previous exposure
- HBeAg (+) active viral replication
- HBeAb (+) strong viral suppression or pre-core mutant if DNA (+)
- HBV-DNA < 10^5 chronic carrier or well suppressed
- HBV-DNA > 10^5 active chronic infection

HBV DNA (Viral Load)

- Quantitative marker of viral replication
- Used to assess and monitor the treatment of patients with chronic HBV infection
- High HBV DNA increases risk for liver CA (HCC)
- Persistent viremia indicates ongoing viral replication and potential liver damage
- Reduction of HBV DNA is associated with
  - Normalization of ALT
  - Improvement in liver histology
  - HBeAg loss and seroconversion

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Laboratory Guidelines for Screening, Diagnosis and Monitoring of Hepatic Injury. Dufour RD (ed), 2000; National Academy of Clinical Biochemistry; Washington, DC.
### Chronic Hepatitis B

- **Wild type**
  - HBsAg (+) > 6 mos
  - HBeAg (+)
  - HBeAb (-)
  - HBV-DNA > 10⁵ copies/ml
  - ALT persistent or intermittent elevations

- **Pre-core mutation**
  - HBsAg (+) > 6 mos
  - HBeAg (-)
  - HBeAb (+)
  - HBV-DNA > 10⁵ copies/ml
  - ALT persistent or intermittent elevations

### Chronic Hepatitis B Carrier State

- HBsAg (+) > 6 mos
- HBeAg (-)
- HBeAb (+)
- HBV-DNA < 10⁵ copies/ml
- Persistently normal AST/ALT
- Liver biopsy without inflammation [optional]

*Keefe et al. Clinical Gastroenterology & Hepatology, 2004; 2:87-106*

### Resolved Hepatitis B Infection

- Previous known hx acute or chronic HBV
- HBsAg (-)
- HBsAb (+) and/or HBcAb (+)
- HBV-DNA undetectable
- Normal ALT

### Hepatitis B vaccination

- HBsAg (-)
- HBsAb (+), becomes (+) with vaccination
- HBcAb (-), becomes (+) with infection only
- HBeAg (-)
- HBeAb (-)
- HBV-DNA (-)
- Normal ALT
Case #3
- 42 y/o male university professor with hyperlipidemia. Liver profile obtained before adding a ‘statin’.
- Liver profile: alb 4.2, t bili 0.5, alk p 105, ast/alt 82/164
- HepA-Ab (IgM) (-); HCV-Ab (-)
- HBsAg (+), HBcAb (+), HBeAg (-), HBeAb (+)
- HBV-DNA 1000 IU/ml
What is your diagnosis and treatment?

Case #3
- Liver profile: alb 4.2, t bili 0.5, alk p 105, ast/alt 82/164
- HepA-Ab (IgM) (-); HCV-Ab (-)
- HBsAg (+), HBcAb (+), HBeAg (-), HBeAb (+)
- HBV-DNA 1000 IU/ml
- ANSWER: Chronic Hepatitis B, pre-core mutant

Case #4
- 58 y/o wf with a Hx of IVDU 30 years ago.
- Liver profile: alb 3.0, t bili 1.1, alk p 88, ast/alt 85/68.
- CBC: wbc 4.1K, hgb/hct 11.2/32.8, MCV 101, platelets 105K
What is your suspected diagnosis?
What test do you want now?

Case #4
- Liver profile: alb 3.4, t bili 1.1, alk p 88, ast/alt 85/68.
- CBC: wbc 4.1K, hgb/hct 11.2/32.8, MCV 101, platelets 105K
- HepA-Ab (-), HBsAg (-), HCV-Ab (+),
- HCV-RNA 3.2 x 10^6 IU/ml
- ANSWER: Chronic hepatitis C with likely cirrhosis and possible portal hypertension
Social History Questions

**Essential** in eval of liver disease

- How much do you drink?
- Any recent travel?
- 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?

Chronic Hepatitis C

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

Hepatitis C

**HCV-RNA**

- Hepatitis C viral level in copies/ml or IU/ml
- Qualitative by PCR or TMA (transcription-mediated amplification) to < 10 IU/ml
- HCV-RNA detectable 2-4 weeks after exposure
- Level is factor in response to Rx but **NOT** severity of disease

Hepatitis C Genotypes

- 6 major genotypes (1-6)
- Genotype 1 is most common in US, > 70%
- Genotype Affects Response and Duration to Therapy but **NOT** severity of disease
Occupational Exposure to HCV

- HCV-Ab for previous exposure
- HCV-RNA 2-4 weeks after exposure
- ALT at exposure and when testing HCV-RNA
- Re-check HCV-RNA at 6-8 weeks
- Consider Treatment if still (+) at 12 weeks
- Spontaneous clearance in ~25% by 12 wks
- HCV-Ab usually remains despite clearance

Case # 5

- A 21 y.o. student from Quinnipiac University presents to your clinic, with complaints of nausea, vomiting, diarrhea and anorexia. On PE he has a low grade fever, he is jaundiced, and he has some tenderness to palpation in the RUQ.
- He has recently returned from spring break in Mexico, where he drank 8-10 beers per day, and ate food from the street vendors carts.
- AST and ALT were both >2000, and TBili is 3.5
- Alk phos is 250?
- What tests to you want to confirm your suspected Dx?
- What treatment will you prescribe?
Clinical Question:
What causes are in your Differential Diagnosis of Acute Hepatitis (aminotransferases >5X ULN)?

<table>
<thead>
<tr>
<th>Differential Diagnosis of Acute Hepatitis (aminotransferases &gt;5X ULN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute Hepatitis A, B, C, D, E or G</td>
</tr>
<tr>
<td>• Epstein-Barr Virus (EBV)</td>
</tr>
<tr>
<td>• Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>• Alcoholic Hepatitis</td>
</tr>
<tr>
<td>• Drug-Induced Liver Injury (DILI)</td>
</tr>
<tr>
<td>• Mushroom Ingestion</td>
</tr>
<tr>
<td>• Acute hepatitis of pregnancy</td>
</tr>
<tr>
<td>• “Shock Liver” which is low cardiac output, leading to hepatic ischemia</td>
</tr>
</tbody>
</table>

Clinical Question:
Now that you have your differential diagnosis, what lab tests would you like to order to evaluate a patient with acute hepatitis?

<table>
<thead>
<tr>
<th>Tests to further evaluate acute hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Repeat transaminases to see which way the trend is going, along with Alk Phos, Albumin, Total Bili, Direct Bili, and PT/INR.</td>
</tr>
<tr>
<td>• Hepatitis A Ab.</td>
</tr>
<tr>
<td>• HBsAg, HBcAb (IgM)</td>
</tr>
<tr>
<td>• Hep C Ab.</td>
</tr>
<tr>
<td>• EBV DNA</td>
</tr>
<tr>
<td>• CMV DNA</td>
</tr>
<tr>
<td>• EtOH level if there is a history of abuse or clinical suspicion</td>
</tr>
</tbody>
</table>
Acute Hepatitis A Tests

• Anti-HAV IgM:
  – acute infection
  – (+) at onset of symptoms
  – (+) for ~4 months

Anti-HAV IgG:
  - (+) at onset also
  - usually (+) for life and confers immunity
  - total HAV antibodies, test for previous infection or vaccination

Treatment for Acute Hepatitis A

• No meds necessary, except in rare cases of prolonged cholestasis.
• Patients with dehydration from nausea, vomiting, and diarrhea may require hospitalization for fluids. Most patients can drink increased fluids at home.
• Rest, avoid alcohol!!
• Hepatitis A never becomes chronic like Hep B and C do.

Hepatitis A Vaccination

• May vaccinate up to 3-4 wks before travel to endemic areas, eg S. America, Asia, Africa
• Follow with a booster in 6-12 months
• (+) Hep A-Ab (total) confers immunity
Case # 6

• A 40 y.o patient with a history of obesity, Diabetes Mellitus, and hyperlipidemia comes to see you. Their last labs showed mildly elevated transaminases:
  • AST=45, ALT=70
  • Alk Phos, TBili, Albumin, GGT and quantitative Immunoglobulins are all normal. Tests for HAV, HBV, HCV, ANA, Ceruloplasmin, and alpha-1 antitrypsin level are all normal. Abd. Ultrasound shows “increased echogenicity” of the liver.
  • What is the diagnosis? Any Rx for this?

Non-Alcoholic SteatoHepatitis (NASH)

This diagnosis is made by excluding other causes of liver disease, along with the presence of fatty liver seen on Abdominal Ultrasound or liver biopsy.

Risk factors for NASH include obesity, Diabetes, and Hyperlipidemia. Treating these underlying disorders helps the NASH. Weight loss helps. Many patients with “Cryptogenic Cirrhosis” are now known to have NASH.

Case # 7

• A 60 year-old male patient with a longstanding history of alcoholism presents to your clinic. He has not had labs drawn in the past 2 years. What would you expect the labs to show in this patient?

Chronic Alcoholic Hepatitis

• Causes fatty liver, like NASH.
• Quantitative Immunoglobulins shows an elevated IgA
• AST is often 2X > ALT, because EtOH causes inflammation of the mitochondria in the hepatocytes, where AST resides.
• GGT often elevated
• Refer patient to AA or treatment center
Acute Alcoholic Hepatitis

- Presents with jaundice, scleral icterus, muscle wasting, ascites, edema, spider angiomata and asterixis.
- Hospital admission for aggressive nutritional therapy, either enterally or parenterally.
- Start Prednisone 40 mg po qd and pentoxyfylidine (Trental) 400 mg po TID.
- Consider U/S to R/O biliary obstruction
- Consider OLTx eval if pt quits EtOH X6 months

Hepatic Synthetic Dysfunction

- Decreased serum albumin
- Increased Total bilirubin
- Increased INR (not responsive to vit K, poor prognosis)
- Often associated with episode of decompensation
- Synthetic function may improve after treatment
- Gradual decline indicates failing liver, consider liver transplant evaluation

Tests for Biliary Excretion

<table>
<thead>
<tr>
<th>Unconjugated Bilirubin</th>
<th>Conjugated Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconjugated = Indirect Bili</td>
<td>Conjugated = Direct Bili</td>
</tr>
<tr>
<td>By product of normal RBC breakdown in the spleen</td>
<td>Water soluble and is now excreted in urine</td>
</tr>
<tr>
<td>Not water soluble, so cannot be excreted in the urine</td>
<td>Elevated in liver cholestasis</td>
</tr>
<tr>
<td>Bound to albumin, and dissociated from albumin by the liver</td>
<td></td>
</tr>
<tr>
<td>Elevated in hemolysis or in Gilbert’s Syndrome</td>
<td></td>
</tr>
</tbody>
</table>

What are the 3 main causes of Jaundice (deposition of bile pigments in the skin)?

1) Increased rate of bilirubin formation
2) A defect in hepatic uptake or conjugation
3) Impairment of bile flow at the canalicular or bile duct level (AKA cholestasis)
Other causes of liver synthetic function abnormalities to rule out

- PT/INR is elevated in a patient taking anticoagulants such as warfarin (Coumadin)
- Albumin is low in patients with nephrotic syndrome, intestinal malabsorption and poor nutrition (alcoholism, cancer, some recent immigrants).

Case #8

- A 27 year old female presents with elevated transaminases. She feels well except for general malaise. She drinks alcohol only “socially.”
- Her medical history is significant for acne and hirsutism.
- AST = 60, ALT = 85, GGT and TBili are both normal.
- What other tests do you want on this patient?

Case #8, continued:

- ANA is positive
- Anti-Smooth Muscle Ab. is positive
- Quantitative Immunoglobulins shows a normal IgA and IgM, but high IgG
- Liver biopsy shows plasma cells

What is the diagnosis?

AutoImmune Hepatitis

- ANA is positive, often >1:160
- Confirmation antibodies are Smooth Muscle Ab. (SMA) and Liver Kidney Microsomal Ab. (Anti-LKM)
- IgG is high in quantitative immunoglobulins
- Plasma cells seen on liver biopsy
AutoImmune Liver Diseases
• AutoImmune Hepatitis (AIH)  
  Target of immune response is hepatocytes
• Primary Biliary Cirrhosis (PBC)  
  Target is small intrahepatic bile ducts
• Primary Sclerosing Cholangitis (PSC)  
  Target is large extrahepatic bile ducts

Lab Features of AutoImmune Liver Diseases
• Low titer antibodies are commonly found in the non-diseased population. Therefore, many hepatologists use titers > 1:160 as indicative of a possible disease process
• Alk Phos is nearly always elevated in PBC and PSC
• AST and ALT are usually <5X ULN in these diseases
• TBili becomes elevated, PT becomes elevated, and Albumin decreases only as disease becomes severe. These can all be normal in early disease.

Case Study # 9
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 # 9, continued:
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?
Diagnosing PBC

**Lab Results**

<table>
<thead>
<tr>
<th>Universal Hallmarks</th>
<th>Other Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase</td>
<td>± AST &amp; ALT</td>
</tr>
<tr>
<td>GGT</td>
<td>± Bilirubin</td>
</tr>
<tr>
<td></td>
<td>↑ Cholesterol</td>
</tr>
<tr>
<td></td>
<td>↑ IgM</td>
</tr>
<tr>
<td></td>
<td>+ AMA (&gt;1:40)</td>
</tr>
</tbody>
</table>


PBC Diagnosis Question:

What is the “Gold-Standard” best test to diagnose Primary Biliary Cirrhosis?

Primary Biliary Cirrhosis

Liver biopsy confirms the diagnosis, showing inflammation and fibrosis in the small intrahepatic bile ducts, and a loss of the total number of bile ducts.

Diagnosing PBC

**Further Tests**

- ↑ Alk Phos & GGT
- Ultrasound/CT
  - Dilated Bile Ducts
    - MCRP/ERCP
  - Normal Bile Ducts
    - AMA neg
    - AMA pos
- ANA Liver Biopsy
  - ERCP
- Liver Biopsy
PBC Epidemiology

- 20-250/million with PBC
  - 4-15/million diagnosed yearly
- 90-95% women
  - Predominantly caucasian
- Age of diagnosis
  - 30-65 years old


PBC Symptoms

**Symptomatic**
- More common
  - Fatigue (70%)
  - Pruritus (55%)
  - Jaundice (16%)
- Less common
  - Esophageal bleeding (3%)
  - RUQ Abdominal pain
  - Weight loss
  - Recurrent UTIs
  - Metabolic bone disease
  - Symptoms of associated autoimmune disorders (joint pains, dry eyes)
  - Fat soluble vitamin malabsorption


**Asymptomatic**

(48-60%)

PBC Imaging Study Findings

- Hepatomegaly – common
- ↑ Echogenicity – common
- Periportal adenopathy – 15%
- Increased risk for gallstones
- No sign of biliary obstruction


Physical Exam in a PBC Patient

- Hepatosplenomegaly
- Dark skin
- Finger clubbing
- Xanthelasmas
- Xanthomas
- Excoriations
PBC Histology

Stage 1
- Portal inflammation
- Granulomatous destruction of bile ducts

Stage 2
- U nod proliferation
- Periportal hepatitis

Stage 3
- Cholestasis
- Bridging fibrosis

Stage 4
- Cirrhosis

PBC Treatment

Extrahepatic Complications
- Osteopenia
- Pruritus
- Sicca Syndrome

Medical Treatment

Investigational
- Corticosteroids
- Chlorambucil
- Cyclosporine
- Azathioprine
- Penicillamine
- Colchicine

Proven Benefit
- UDCA

Extrahepatic Manifestations of PBC

- Fat Soluble Vitamin Deficiency
- Hyperlipidemia
- Gallstones
- Renal Tubular Acidosis
- U rinary Tract Infections
- Steatorrhea
- Malignancy

Extrahepatic Complications
- Hyperlipidemia
- Renal Tubular Acidosis
- Gallstones
- Steatorrhea
- Malignancy

Osteopenia
- HRT (estrogen)
- Vitamin D
- Calcium
- Calcitonin
- Bisphosphonates
- Other

Pruritus
- UDCA
- Bile acid sequestrates
- Rifampin
- Opiate antagonists
- Antihistamines
- Phenobarbital
- Other

Sicca Syndrome
- Artificial tears
- Vaginal lubricant
- Pilocarpine hydrochloride
Case # 10

- A 55 y.o. male with a history of Ulcerative Colitis presents with recurrent low-grade fevers, RUQ abdominal pain, pruritis 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?

Primary Sclerosing Cholangitis

- Alk Phos often elevated
- P-ANCA (Perinuclear Antineutrophil Cytoplasmic Antibodies) is positive in 80% of patients with PSC
- ANA (Anti-Nuclear Antibody) is present in 60% of patients with PSC
- SMA (Smooth Muscle Ab. is present in 35% of patients with PSC

Bile Duct Diseases

<table>
<thead>
<tr>
<th>Gender</th>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile Ducts</td>
<td>Intrahepatic</td>
<td>Intra- &amp; Extrahepatic</td>
</tr>
<tr>
<td>ERCP</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>AMA</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>UC Association</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cholangio CA Risk</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Age Range at Dx</td>
<td>30-65</td>
<td>4-65</td>
</tr>
</tbody>
</table>

Poor specificity of P-ANCA for PSC

Prevalence of P-ANCA in various Diseases:

- Primary Sclerosing Cholangitis (PSC) 80%
- Autoimmune Hepatitis (AIH) 80%
- Ulcerative Colitis (UC) 75%
- Primary Biliary Cirrhosis (PBC) 30%
Diagnosis of PSC is based on cholangiography
- 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

Case #11
- A 17 year-old male is dropped off at the emergency room by his friends. They say he “had a bad trip” on an unknown hallucinogen, and is now becoming confused and unresponsive.
- His AST and ALT are both >1500
- What is the most likely drug he ingested?

Common causes and treatments of Acute Liver Failure (ALF)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol Overdose</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Mushroom Poisoning</td>
<td>PCN, silibinin antidote</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Emergency C-section</td>
</tr>
<tr>
<td>Wilson's Disease</td>
<td>Liver Transplantation</td>
</tr>
</tbody>
</table>

Signs of Acute Liver Failure (AKA Fulminent Hepatitis)
- Hepatic Encephalopathy
- Cerebral edema
- Coagulopathy (prolonged PT/INR)
- Shock, with poor liver oxygenation
- Ascites and GI bleeding may or may not be present
Metabolic Disorders

**Hemachromatosis**
- Ferritin <300 ugm/L for ♂ < 200 ugm/L for ♀
- Fe sat = \( \frac{\text{Fe}}{\text{TIBC}} \times 100 \)
- (Normal < 33%)
- Investigate when saturation > 50-55%
- Fasting Fe > 175 ugm/dl suggests true abnormality
- C282Y and H63D gene defects
- One or both gene mutations is present in 85 to 95% of NA caucasians with genetic hemachromatosis and 5% of those without disease
- Heterozygotes - may have some degree of iron overload

**Wilson's Disease**
- Ceruloplasmin
  - Low levels suggest diagnosis (< 20mg/dl)
- Inflammation may elevate levels
- Urinary Copper > 100 ug/day (get 24 hour urine collection for copper)
- Low ALP: Bilirubin ratio

**α -1 Antitrypsin Deficiency**
- Serum α-1 antitrypsin level
- SPEP (serum protein electrophoresis)
- 85% of α-1 band consists of α-1 antitrypsin. If ↓ suggests A1-AT deficiency

**Celiac Disease**
- Can frequently cause elevated liver tests
- Diagnosed with Tissue transglutaminase Antibody (TTA), antigliadin antibody, and small bowel biopsy.

**Further Reading:**
- Approach to the Patient With Abnormal Liver Function Tests; Up To Date, by Marshall Kaplan, MD.
- Evaluating Abnormal Liver Tests; Clinical Reviews, September 2005, by Joann Deasy, PA-C.
- Abnormal liver studies: What happens next? The Clinical Advisor, April 2006, by Bruce Askey, MSN, CRNP.
- Increased Liver Chemistry in an asymptomatic Patient; Clinical Gastroenterology and Hepatology 2005;3:852-858. By Wolfram Goessling and Lawrence Friedman, MD.
Clinical question:

What if you are uncertain whether aminotransferase elevations are high due to liver vs. skeletal or cardiac muscle injury?

What test should you order?

Answer:

Order serum creatine kinase (CK), which is high in skeletal and cardiac muscle injury, but normal in liver injury.