Approach to Elevated Liver Tests

JOSHUA EVANS, MD, MPH, MRO, FACP
ASSOCIATE PROFESSOR
GENERAL INTERNAL MEDICINE
LOYOLA UNIVERSITY MEDICAL CENTER

CREDIT: ERIC R KALLWITZ, MD
Lecture Objectives

At the conclusion the audience should have a better understanding of

- What constitutes an abnormal aminotransferase
- How to make an initial evaluation of an abnormal test
- Understand disease specific serologic tests
- Understand laboratories which are prognostic in chronic liver disease
Lab Value Ranges

- **Alanine aminotransferase (ALT):**
  - Male: 29 to 33 units/L
  - Female: 19 to 25 units/L

- **Aspartate aminotransferase (AST):**
  - Male: 10 to 40 units/L
  - Female: 9 to 32 units/L

- **Alkaline phosphatase:**
  - Male: 45 to 115 units/L
  - Female: 30 to 100 units/L

- **Bilirubin, total:** 0.0 to 1.0 mg/dL (0 to 17 micromol/L)

- **Bilirubin, direct:** 0.0 to 0.4 mg/dL (0 to 7 micromol/L)

- **Gamma-glutamyl transpeptidase (GGT):**
  - Male: 8 to 61 units/L
  - Female: 5 to 36 units/L

- **Prothrombin time (PT):** 11.0 to 13.7 seconds

- **Albumin:** 3.3 to 5.0 g/dL (33 to 50 g/L)
Normal versus Abnormal

- Most laboratories use $> 2$ SD to define abnormal
  - The differences in clinical laboratories abnormal is based on the health of the reference population

- Understand the difference between statistical significance and clinical significance
  - ALT = 35 ($> 2$ SD but is it relevant? . . )
  - Blood glucose 101 ($> 2$ SD but is it relevant? . . )

A “normal” ALT lab value does not exclude liver disease or histologic damage
Who to test? Do we screen?

No recommendation to routinely test healthy, asymptomatic persons

- **When Do We Screen for a Disease?**
  - Medically important
    - Yes
  - Relatively high prevalence
    - Yes
  - Natural history of disease should be known
    - Is it serious?
      - Limited data (Lack of population based data)
  - Effective intervention should exist
    - Limited interventions for some diseases (NAFLD)
  - Cost Effective
# LFTS: Worrisome?

<table>
<thead>
<tr>
<th>20 yo male</th>
<th>29 yo female</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB 1.8</td>
<td>TB 22.0</td>
</tr>
<tr>
<td>AP 180</td>
<td>AP 99</td>
</tr>
<tr>
<td>AST 2789</td>
<td>AST 560</td>
</tr>
<tr>
<td>ALT 6239</td>
<td>ALT 901</td>
</tr>
<tr>
<td>Alb 3.0</td>
<td>Alb 2.1</td>
</tr>
<tr>
<td>PT 20</td>
<td>PT 66</td>
</tr>
</tbody>
</table>
# LFTS: Worrisome?

<table>
<thead>
<tr>
<th>20 yo male</th>
<th>29 yo female</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB 1.8</td>
<td>TB 22.0</td>
</tr>
<tr>
<td>AP 180</td>
<td>AP 99</td>
</tr>
<tr>
<td>AST 2789</td>
<td>AST 560</td>
</tr>
<tr>
<td>ALT 3239</td>
<td>ALT 901</td>
</tr>
<tr>
<td>Alb 3.0</td>
<td>Alb 2.1</td>
</tr>
<tr>
<td>PT 20</td>
<td>PT 66</td>
</tr>
</tbody>
</table>
Interpretation of Liver Tests

True “liver function tests”
- What does the liver do?

Hepatocellular damage

Cholestasis

Are the abnormalities noted acute or chronic?
True Liver Function Tests

- **Prothrombin time**
  - High PT/INR: increased risk of bleeding
  - Vitamin K deficiency, consumptive coagulopathy

- **Albumin**
  - Low albumin: edema, anasarca
  - Nephrotic syndrome, malnutrition, protein losing enteropathy

- **Bilirubin**
  - Jaundice (total bilirubin > 2-3 mg/dL)

- **Cholesterol**
Markers of Hepatocyte Damage

- ALT (alanine aminotransferase--SGPT)
  - Cytosol of hepatocytes
  - More hepatocyte specific

- AST (aspartate aminotransferase--SGOT)
  - Cytosol and mitochondria
  - Muscle, intestine, brain, kidney, pancreas, red blood cells
  - Mitochondrial induction/damage by alcohol explains higher AST levels in persons consuming excessive ETOH, vitamin deficiency leads to lower ALT

- Lactate dehydrogenase (LDH)
  - Can be markedly elevated in shock liver
Markedly Elevated Aminotransferase Levels (> 1,000 U/L)

- Drug/toxin induced injury
  - Acetaminophen
  - NOT alcohol alone
- Acute viral hepatitis
- Shock liver / Ischemic Injury
- Veno-occlusive disease/Budd-Chiari syndrome
- Autoimmune hepatitis
- Common bile duct stone

**Acute liver failure**

1: alt/ast >10 times the upper limit of normal

2: hepatic encephalopathy

3: prolonged prothrombin time
ALT/AST ratios

- In most liver diseases ALT > AST

- Exceptions:
  - Alcoholic liver disease
  - >2:1 ratio Wilson’s disease
  - Accompanying hemolytic anemia
  - Advanced fibrosis
Markers of Cholestasis

- **Alkaline phosphatase**
  - Localized in microvilli of bile canaliculus
  - Hepatic synthesis ↑ in cholestasis
  - Fractionation can help
  - Bone, intestine, placenta

- **Gamma glutamyl transferase (GGT)**
  - Induced by alcohol, medications

- **5’-Nucleotidase**
  - Specific to liver

- **Bilirubin**
  - Mild cholestasis or partial biliary obstruction do not necessarily increase bilirubin.
  - Bilirubin level represents balance between production, conjugation, and excretion into bile.
## Cholestasis

<table>
<thead>
<tr>
<th>Unconjugated hyperbilirubinemia</th>
<th>Conjugated hyperbilirubinemia</th>
<th>Elevated Alkaline phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert’s syndrome</td>
<td>Bile duct obstruction</td>
<td>Hepatobiliary</td>
</tr>
<tr>
<td>Crigler-Najjer syndrome</td>
<td>Severe hepatitis</td>
<td>Bile duct obstruction</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Cirrhosis</td>
<td>PBC</td>
</tr>
<tr>
<td>Hematoma resorption</td>
<td>Medication/Toxin</td>
<td>PSC</td>
</tr>
<tr>
<td></td>
<td>PBC</td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td>PSC</td>
<td>Hepatic metastasis</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>Severe hepatitis</td>
</tr>
<tr>
<td></td>
<td>TPN</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Benign recurrent cholestasis</td>
<td>Vanishing bile duct syndrome</td>
</tr>
<tr>
<td></td>
<td>Vanishing bile duct syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dubin-Johnson syndrome</td>
<td>Infiltrating diseases</td>
</tr>
<tr>
<td></td>
<td>Rotor syndrome</td>
<td>Sarcoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fungal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heme malignancy</td>
</tr>
</tbody>
</table>
Bilirubin Metabolism

- Bilirubin is a normal heme degradation product
  - Predominant excretion is in bile
  - Unconjugated (indirect) is taken up by hepatocytes
  - Conjugated (direct) by the endoplasmic reticulum using enzyme bilirubin UDP-glucuronyltransferase
  - Water soluble bilirubin glucuronides secreted across canicular membrane into bile

- Clinical correlate: **Gilbert’s syndrome**
  - Diminished expression of bilirubin UDP-glucuronyltransferase
  - Up to 4-9% of population
  - Benign, unconjugated hyperbilirubinemia
  - Can be worsened by stress, fasting
First Approach

- Repeat abnormal tests (?????)
  - Many will normalize without intervention, **ONLY** consider if no risk factors are present
  - Discontinue alcohol, potential hepatotoxins
  - Would not wait however if there are signs of synthetic dysfunction
    - Elevated bilirubin, PT prolongation

- Continued Elevation
  - Work up is based on pattern of abnormalities
    - Hepatocellular injury versus cholestatic
    - Acute versus Chronic
Clinical scenario

A 55 year old man is admitted overnight, he is new to LUMC and presents with melena

On US he has a nodular appearing liver with possible fatty infiltration

Relevant labs ALT 55, AST 77, TB 0.9, AP 88, PLT 55, HGB 8.9

He undergoes endoscopy finding recently bleeding varices which were banded
Continued

Which of the following labs sent over night are unnecessary?

Acute hepatitis panel (hep A IgM, HB S AG, Anti-HBV core AB total, Anti-HCV)

ANA, ASMA, AMA

Ceruloplasmin

Alpha-1 antitrypsin

Ferritin, iron, TIBC

Tylenol level

Serum alcohol
The “shotgun” approach

Liver consult

- HAV IgM
- HBV s Ag, core IgM
- Anti-HCV
- AMA
- ANA, ASMA
- Ceruloplasmin
- Alpha-1 antitrypsin
- Iron, TIBC, ferritin
- Tox screen
- RUQ US
- Consider Biopsy

Chronic hepatitis?

Is there cholestasis?

Patient age?

Acute ingestion?
General Approach to Abnormal LFTs

Elevated ALT/AST

Persistently elevated
Symptomatic
Impaired synthetic function

Acute hepatitis
US, IgM anti-HAV, HBsAg, IgM anti-HBc, HCV RNA, ANA, ASMA
Ceruloplasmin if < 40 yo, consider biopsy

Chronic hepatitis
US, HBVsAg, ANA, ASMA, anti-HCV, iron studies, A1AT phenotype, ceruloplasmin if < 40 yo, consider biopsy

Duration < 3 months
Elevation < 3 fold
Asymptomatic
Preserved synthetic function

Repeat tests in 3 months
General Approach to Abnormal LFTs

Cholestasis (Alk Phos ± bilirubin)

Liver fraction and/or GGT abnormal

US

Dilated ducts → MRCP/ERCP

Liver mass → CT, tumor markers, biopsy

Liver fraction and GGT normal

Pursue non-hepatic causes

Normal

Pursue intrahepatic causes
Drug history
AMA
Biopsy, MRCP/ERCP?
# Historical Clues

<table>
<thead>
<tr>
<th>History Component</th>
<th>Disease Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remote history of jaundice</td>
<td>Viral hepatitis</td>
</tr>
<tr>
<td>Medical history of autoimmune diseases</td>
<td>AIH</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>AIH, PBC</td>
</tr>
<tr>
<td>History of liver disease as a newborn</td>
<td>Alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td>Family history of liver disease</td>
<td>HBV, hemochromatosis</td>
</tr>
<tr>
<td>History of alcohol abuse, DUI</td>
<td>Alcohol</td>
</tr>
<tr>
<td>History of IVDA, blood transfusion prior to 1990</td>
<td>HCV</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Hemochromatosis, NAFLD</td>
</tr>
<tr>
<td>Components of Metabolic Syndrome</td>
<td>NAFLD</td>
</tr>
<tr>
<td>Medications, CAM therapy</td>
<td>Drug induced liver injury</td>
</tr>
<tr>
<td>Pruritis</td>
<td>PBC</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>PSC</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Hemochromatosis, HCV</td>
</tr>
</tbody>
</table>
## Physical Clues

<table>
<thead>
<tr>
<th>Physical Exam Findings</th>
<th>Disease Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spider angiomas</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Palmar erythema</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Cirrhosis, Biliary obstruction, hemolysis, Gilbert’s</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Kayser-Fleisher rings</td>
<td>Wilsons disease</td>
</tr>
<tr>
<td>Emphysema/Lung disease</td>
<td>Alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td>Ascites</td>
<td>Portal hypertension, cirrhosis</td>
</tr>
<tr>
<td>Asterixis</td>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Xanthelasma</td>
<td>PBC</td>
</tr>
</tbody>
</table>
Patient Characteristics

- **Sex:**
  - Female (AIH, PBC)
  - Male (PSC)

- **Age:**
  - Neonatal (A1AT)
  - < 40 (Wilson’s, AIH)
  - > 40 (viral, HFE)

- **Medications:**
  - Antiepileptics
  - HAART
  - INH

- **Risk factors HCV:**
  - IVDA (viral, EtOH)
  - Blood transfusions
  - Tattoos

- **Comorbidities:**
  - DM/obesity: NASH
  - CHF: HFE

- **Family Hx**
  - A1AT deficiency
  - Hemachromatosis

- **Country of Birth**
  - HBV
Liver Disease

A clinician is better able to understand the evaluation of liver disease with a basic understanding of each individual disease.

The next section will focus on serology of chronic liver diseases.
# Hepatocellular causes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>+ (liver failure w/pregnancy)</td>
<td>(rare)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Alpha-1 AT deficiency</td>
<td>(neonatal)</td>
<td>+</td>
</tr>
<tr>
<td>NAFLD</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Alcohol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Medication/Toxin</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
**Immune Tolerance:**
Normal ALT
DNA > 20,000,000 IU/ml
Low grade on biopsy

**Chronic HBV:**
Elevated ALT
E Antigen Positive
DNA > 20,000 IU/ml

**Inactive Carrier:**
HBeAg-/Anti-HBe+
Normal ALT
HBV DNA < 2,000
## Diagnosis of HBV

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>HBc</th>
<th>HBe</th>
<th>HBsAb</th>
<th>HBV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>HBsAg</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td>HBsAg</td>
<td>HBcIgG</td>
<td>HBeAg+ or eAg-</td>
<td></td>
<td>&gt;10^4-10^5</td>
</tr>
<tr>
<td>(immune tolerant or active)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inactive Carrier</strong></td>
<td>HBsAg</td>
<td>HBcIgG</td>
<td>eAb+</td>
<td></td>
<td>&lt;10^4</td>
</tr>
<tr>
<td><strong>Immune</strong></td>
<td></td>
<td>HBcIgG</td>
<td></td>
<td>HBsAb</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccinated</strong></td>
<td></td>
<td></td>
<td></td>
<td>HBsAb</td>
<td></td>
</tr>
</tbody>
</table>
### HCV lab tests

<table>
<thead>
<tr>
<th>HCV test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HCV</td>
<td>Seropositive in past and current infection</td>
</tr>
</tbody>
</table>
| HCV RIBA       | Seldom used  
Can distinguish false positive AB from past infection                |
| HCV RNA        | Viremia indicates current infection  
Viral load does not correlate with severity of liver disease            |
| HCV genotype   | Measure if considering interferon based therapy  
Genotype 1 predominates in US                                             |
Hemochromatosis

- **LABS:** iron/TIBC, ferritin, genotype

- **Clinical suspicion**
  - Fatigue, arthralgia, diabetes mellitus, hyperpigmentation, impotence

- **Transferrin saturation and ferritin**
  - TS > 45%
    - Sensitivity >97%
    - Specificity 45%
  - Ferritin > 1000 mg/ml marker of significant disease

- **Genotype**
  - C282Y (prevalence 5/1000 if Northern European descent)
    - Accounts for 80-85% of typical hemochromatosis
    - Only 10% of C282Y homozygotes will have end organ damage
  - Other mutations: ie H63D, S65C controversial
Autoimmune Hepatitis

- **LABS:** ANA, ASMA, anti-LKM (kids), immunoglobulins

- **Type 1 AIH**
  - Women (4:1), peak 20’s to 40’s
    - All ages and ethnic groups susceptible
  - ANA (67%), SMA (87%)
    - ANA found in PBC, PSC, viral hepatitis, drug related hepatitis, NASH, ETOH
  - pANCA common
  - Hyperglobulinemia (high IgG)

- **Type 2 AIH (young women)**
  - Anti-LKM1
  - Less hyperglobulinemia
  - Tends to be more severe at onset and more likely to progress to cirrhosis
## Wilson’s

**LABS: ceruloplasmin, 24 urine copper, serum copper, genetic testing**

<table>
<thead>
<tr>
<th>Test</th>
<th>WD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceruloplasmin</td>
<td>&lt;20 mg/dl</td>
<td>95% homozygotes 20% heterozygotes</td>
</tr>
<tr>
<td>Slit-lamp</td>
<td>KF rings</td>
<td>Absent early F(+) cholestatic disease</td>
</tr>
<tr>
<td>24 hour urine</td>
<td>&gt;100 ug</td>
<td>F(-) early F(+) cholestatic disease</td>
</tr>
<tr>
<td>Hepatic copper</td>
<td>&gt;250 ug/g</td>
<td>F(+) cholestatic disease F(-) sampling error</td>
</tr>
</tbody>
</table>

Genetic testing by whole-gene sequencing exists, but can be difficult as most persons with WD are compound heterozygotes and there are roughly 300 mutations.
Alpha-1 Antitrypsin Deficiency

- **LABS:** alpha1-antitrypsin level, phenotype
  - Serine protease inhibitor for which liver disease results from failure to export
  - **History**
    - 10% develop neonatal hepatitis or obstructive jaundice
  - **Serum levels**
    - Low
  - **Phenotyping**
    - PiZZ most severe (10-15% of normal levels)
  - **Liver histology**
    - A1AT globules in ER of periportal hepatocytes
NAFLD

- NAFLD
  - 20-30% in US

- NASH
  - 3% of general population
  - 20% of obese individuals

- Disease associations
  - Metabolic syndrome
    - Visceral obesity, insulin resistance, dyslipidemia (HDL, TG), elevated blood pressure

- Asymptomatic transaminase elevation
  - ALT > AST
  - GGT may be increased
  - Alk phos usually < 2x ULN
  - Elevated ferritin—60% (marker for IR)
normal

[[image: normal.png]]

steatohepatitis

[[image: steatohepatitis.png]]

steatohepatitis w/ mild fibrosis

[[image: steatohepatitis_mild_fibrosis.png]]

steatohepatitis w/ established cirrhosis

[[image: steatohepatitis_cirrhosis.png]]
Alcoholic Hepatitis

- **Diagnosis-History**
  - Ask about DUI
  - AST>>ALT (both typically < 300 U/L)
  - Elevated bilirubin and prolonged PT
  - Alkaline phosphatase often normal

- **Calculate discriminant function**
  - Serum bilirubin + 4.6*(patient PT - control PT)

- **DF > 32 is important**
  - Designates poor prognosis, high mortality
  - Marker for therapy consideration
    - Prednisolone, pentoxifylline
Hepatotoxic Medications

- Commonly prescribed Medication
  - Augmentin
  - Anti-Epileptics
  - Azole (antifungal)
  - Isoniazid
  - Anesthetics
    - Halothane
  - Nicotinic acid
  - Nitrofurantion
  - Propylthiouricil
  - Oral hypoglycemics
    - Glyburide
    - TZDs
  - HMG CoA reductase inhibitors
  - Protease inhibitors

- OTC, CAM, illicit
  - Acetaminophen
  - NSAIDs
  - Ephedra
  - Kava
  - Chaparral
  - Black Cohosh
  - Ecstasy
  - Hydrofluorocarbons
  - Chloroform
  - Toluene
LFT’s and Statins

• Chronic aminotransferase elevation and histological injury has never been convincingly proven

• Significant hepatotoxicity attributable to statins is very rare

• Use of lower doses and highly lipophilic (cerivastatin, lovastatin, simvastatin) may reduce hepatotoxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly Lipophilic</td>
<td>1.58</td>
<td>0.81, 3.05</td>
</tr>
<tr>
<td>Mildly Lipophilic</td>
<td>3.54</td>
<td>1.72, 5.58</td>
</tr>
</tbody>
</table>

Argo et al Hepatology 2008;48:662
# Cholestatic Liver Disease

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBC</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>PSC</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Obstructive Jaundice</td>
<td>+(pain)</td>
<td>+</td>
</tr>
<tr>
<td>Medications/Toxins</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Primary Biliary Cholangitis

LABS: AMA, immunoglobulins

- Serologic
  - Anti-mitochondrial antibody (AMA)
    - 95% positive in PBC
    - 1% general population
    - 5% PBC patients AMA negative
    - Targets mitochondrial specific complexes
  - High levels of IgM
  - Alkaline phosphatase elevation > aminotransferases
  - Increased bilirubin associated with worsened disease severity
  - High cholesterol (especially HDL)
Primary Sclerosing Cholangitis

More common in men
UC coexists in 90%
pANCA common
Check IgG4-exclude autoimmune pancreatitis
If dominant stricture check Ca 19-9
Medicines that Cause Cholestasis

- Anabolic steroids
- Allopurinol
- Amoxicillin-clavulanic acid
- Atazanavir
- Diltiazem
- Erythromycin
- Estrogens
- Indinavir
- Nevirapine
- Methyltestosterone
- Quinidine
- Total parenteral nutrition
- Trimethoprim-sulfamethoxazole
Surveillance for HCC

AASLD recommends US (and AFP*) every 6-12 months for surveillance

- Hepatitis B carriers
  - Asian males ≥ 40
  - Asian females ≥ 50
  - Cirrhosis at any age
  - Positive family history
  - Africans ≥ 20
- For those not listed above HCC risk varies; consider HBV viral load and grade of inflammation

- Non-hepatitis B Cirrhosis
  - Hepatitis C
  - Alcohol
  - Hemochromatosis
  - PBC
  - Alpha-1 antitrypsin
  - NASH
  - Autoimmune hepatitis

Bruix Hepatology 2010 (AASLD position paper)
*AFP was dropped from 2010 guidelines
Fetoprotein

- AFP is a marker of liver regeneration
  - It is often elevated in viral hepatitis
- AFP can be used for surveillance and diagnosis
- AFP > 20 ug/dl
  - Sensitivity 41-65%
  - Specificity 80-94%
  - Positive LR 3.1-6.8
  - Negative LR 0.4-0.6
    - Gupta Ann Intern Med 2003

HCV with Cirrhosis
2% HCC

- AFP > 20
  - Positive LR 5
  - Post-test probability = ~10%

- AFP < 20
  - Negative LR 0.5
  - Post-test Probability = 1%
Clinical scenario

A 45 year old woman sees you in follow up.
She has HCV and alcohol cirrhosis, but stopped drinking 2 years ago
Her labs include CR 0.8, TB 0.9 and INR 1.1, AST 66, ALT 48
She recently saw hepatology and was told she did not need transplant
As her primary care doctor she asks if you agree
Severity of Liver Disease

- Child-Turcotte-Pugh System (CTP)
  - Not formally validated as prognostic tool
  - Useful means to rapidly assess prognosis
  - Also useful for pre-operative risk assessment
  - Semi-Subjective

- Model for End stage Liver Disease (MELD)
  - Currently used for transplant listing
  - Based on creatinine, INR, total bilirubin (Cr and INR more heavily weighted)
  - Objective values comprise score
  - Validated to predict survival
    - 3 month survival for a MELD of
      - 6 >90%
      - 40 < 7%
    - Malinchoc Hepatology 2003
OUR Scenario: MELD Score of 5

Estimated 3-month survival as a function of the MELD score in patients with cirrhosis

MELD: Model for End-Stage Liver Disease.


Graphic 77732 Version 4.0
MELD Score

- $3.8 \cdot \log_e(\text{serum bilirubin}) + 11.2 \cdot \log_e(\text{INR}) + 9.6 \cdot \log_e(\text{serum creatinine}) + 6.4$

**MELD – Na**
- Increase in mortality by 5% per mmol decrease in serum Na between 125 - 140
- If initial MELD score >11, the score is then re-calculated as the MELD-Na score
- $\text{MELD-Na} = \text{MELD} + 1.32 \cdot (137-\text{Na}) - [0.033 \cdot \text{MELD} \cdot (137-\text{Na})]$
- For example, a patient with a MELD score of 12, but a serum sodium level of 125 mmol/L, will have a MELD-Na score of 23
  - elevates the transplant priority for about 12% of listed patients
  - may be vulnerable to alterations by diuretic use and IVF

**OUR Scenario: MELD Score of 5**
## CTP score

<table>
<thead>
<tr>
<th>Grade encephalopathy</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ascites</th>
<th>Absent</th>
<th>Slight</th>
<th>Moderate or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bilirubin (for PBC patients)</th>
<th>1-2</th>
<th>2-3</th>
<th>&gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albumin</th>
<th>&gt;3.5</th>
<th>2.8-3.5</th>
<th>&lt;2.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8-3.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INR</th>
<th>&lt;1.7</th>
<th>1.7-2.3</th>
<th>&gt;2.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Score ≤6 Class A, 7-9 Class B, ≥10 Class C
Important Disease Associations

- Emphysema and Liver disease
- Cirrhosis, DM, arthritis, AFIB
- IBD and elevated alkaline phosphatase
- Viral hepatitis associated with liver failure in pregnancy
- Liver disease, with anemia and psychosis
- ALT greater than 5000 in someone with alcoholism
- Elevated alkaline phosphatase with itching and fatigue seen in a 50 year old woman
Case 1

A 25 year old presents 3 days after a significant acetaminophen ingestion

There is AMS and they are intubated early in the course- NAC is started

<table>
<thead>
<tr>
<th>Lab</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>3.2</td>
<td>4.1</td>
<td>4.8</td>
</tr>
<tr>
<td>AST</td>
<td>12000</td>
<td>13000</td>
<td>9000</td>
</tr>
<tr>
<td>ALT</td>
<td>9000</td>
<td>10000</td>
<td>8500</td>
</tr>
<tr>
<td>INR</td>
<td>3.0</td>
<td>4.1</td>
<td>5.3</td>
</tr>
</tbody>
</table>

By Day 3 is the course better, worse or stable?
Case 2

A person is referred for initial elevation in ALT (52)- synthetic function is normal and there are no prior available liver tests

Ultrasound one year prior suggested a fatty liver

Clinical history includes a blood transfusion in 1988 for a trauma, DM, BMI 29 and a family history of cancer in the liver but might have been metastatic

Medications include metformin, losartan and atorvastatin
Conclusions

When evaluating suspected liver disease

- Realize that aminotransferases are imperfect markers of disease state
- Following synthetic function is of vital importance
- Remember medications and complementary medicines
- Approach patients based on risk factors and pattern of liver injury (hepatocellular or cholestatic)
- Use models to assess severity of liver injury