Approach to Elevated Liver Tests

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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
The left depicts 177 overweight patients undergoing routine surgery. The right depicts 629 patients undergoing evaluation for HCV.

For obese persons undergoing bariatric surgery, 2 SD above the mean was an ALT of 60 IU/mL. The right is the ability of ALT to discriminate the presence of fatty liver disease in patients undergoing bariatric surgery (AUC = 0.653).
Refining Normal

- Population of persons donating blood
  - Selected those at lowest risk for liver disease (normal BMI, normal lipids and glucose, no medications)
  - Median ALT was 11 U/L
  - Value at the 95th percentile for
    - Women was 19 U/L
    - Men was 30 U/L
- Applied this to a population with HCV RNA
  - Reference of lab “abnormal” was 55% sensitive and 97% specific
  - The above criteria was 76% sensitive and 89% specific


Significant disease can occur at “normal”

- Data from Italy-patients at risk for NAFLD
- 63/458 patients had a liver biopsy with an ALT < 40 U/L (long standing steatosis)
- Mean ALT was 28 ± 7 U/L
- Fibrosis ≥ 2 (moderate) was seen in 22% with “normal” ALT and 34% with increased ALT (p=ns)
- 5/63 (8%) persons had cirrhosis
- Of 37% of persons with NASH and a normal ALT, 27% met more stringent criteria for normal
  - Fracanzani Hepatology 2008 ;48:792-798
Most laboratories use > 2 SD to define abnormal
- The differences in clinical laboratories abnormal is based on the health of the reference population
- There is difficulty defining “normal” so your clinical suspicion for disease should supersede labs
- A “normal” ALT does not exclude liver disease or histologic damage

No recommendation to routinely test healthy, asymptomatic persons

Screened disease
- Medically important
  - Yes
- Relatively high prevalence
  - Yes
- Natural history of disease should be known
  - Limited data (Lack of population based data)
- Effective intervention should exist
  - Limited interventions for some diseases (NAFLD)
Prevalence of abnormal aminotransferases

- NHANES III data
- Used ALT > 40 for men and > 31 for women as abnormal
- Prevalence of abnormal aminotransferases was 7.9%
- Men 9.3%, women 6.6%
- Hispanic 14.9%, African American 8.1% and non-Hispanic white 7.1%
- Only 31% of cases had an etiology for abnormal aminotransferases (viral hepatitis, alcohol, iron overload)
- If more stringent criteria for abnormal ALT used 26% had an elevated ALT, of which 21.2% had no explanation

Clark Am J Gastroenterol 2003

Interpretation of Liver Tests

- True “liver function tests”
- Hepatocellular damage
- Cholestasis
True Liver Function Tests

- **Albumin**
  - Low albumin: edema, anasarca
  - Nephrotic syndrome, malnutrition, protein losing enteropathy
- **Prothrombin time**
  - High PT/INR: increased risk of bleeding
  - Vitamin K deficiency, consumptive coagulopathy
- **Bilirubin**
  - Jaundice (total bilirubin > 2-3 mg/dL)
- **Cholesterol**

Prolonged PT

- Machines are calibrated to activated thromboplastins for patients on warfarin
  - There is significant variation in INR from lab to lab in cirrhotic patients
- Common clinical dilemma- vitamin K deficiency, consumptive coagulopathy or cirrhosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cirrhosis</th>
<th>Vit K def</th>
<th>Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal V</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal VII</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal VIII</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**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

- **Lactate dehydrogenase (LDH)**
  - Can be markedly elevated in shock liver

**ALT/AST ratios**

- In most liver diseases ALT > AST
- Exceptions:
  - Alcoholic liver disease
  - >2:1 ratio Wilson’s disease
  - Accompanying hemolytic anemia
  - Advanced fibrosis
    - AST/ALT ratio >1 had a sensitivity of 41%, a specificity of 78% to identify advanced fibrosis
      - Unpublished data
Causes of Markedly Elevated Aminotransferase Levels (> 1,000 U/L)

- Drug/toxin induced injury
  - Acetaminophen
  - NOT alcohol alone
- Acute viral hepatitis
- Shock liver
- Autoimmune hepatitis
- Common bile duct stone

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
**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>PSC</td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>Hepatic metastasis</td>
</tr>
<tr>
<td></td>
<td>TPN</td>
<td>Severe hepatitis</td>
</tr>
<tr>
<td></td>
<td>Benign recurrent cholestasis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Vanishing bile duct syndrome</td>
<td>Vanishing bile duct syndrome</td>
</tr>
<tr>
<td></td>
<td>Dubin-Johnson syndrome</td>
<td>Benign recurrent cholestasis</td>
</tr>
<tr>
<td></td>
<td>Rotor syndrome</td>
<td>Infiltrating diseases</td>
</tr>
<tr>
<td></td>
<td></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 degredation 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 5% of population
  - Benign, unconjugated hyperbilirubinemia
  - Can be worsened by stress, fasting
First Approach

- Repeat abnormal tests
  - Many will normalize without intervention
  - 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
    - Cholestasis
    - Mixed

Worrisome?

- 20 yo male
  - TB 1.8
  - AP 180
  - AST 2789
  - ALT 6239
  - Alb 3.0
  - PT 20

- 29 yo female
  - TB 22.0
  - AP 99
  - AST 560
  - ALT 901
  - Alb 2.1
  - PT 66

Listing for fulminant hepatic failure requires onset of encephalopathy within 8 weeks of onset of liver disease symptoms and one of the following: 1) ventilator dependence, 2) requiring renal replacement therapy or 3) INR > 2.0
The “shotgun” approach

- Liver consult
  - HAV IgM → Chronic hepatitis?
  - HBV s Ag, core IgM
  - Anti-HCV
  - AMA → Is there cholestasis?
  - ANA, ASMA
  - Ceruloplasmin → Patient age?
  - Alpha-1 antitrypsin
  - Iron, TIBC, ferritin
  - Tox screen
  - RUQ US
  - Consider Biopsy

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
Cholestasis (Alk Phos ± bilirubin)

Liver fraction and/or GGT abnormal

Liver fraction and GGT normal

US

Dilated ducts

Liver mass

Normal

Pursue non-hepatic causes

Pursue intrahepatic causes

Drug history

AMA

Biopsy, MRCP/ERCP?

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
### 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>
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.

**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
- E Antigen Negative
  - DNA > 2,000 IU/ml

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

**Resolved HBV (seroclearance):**
- HBeAg- Chronic HBV

**Diagrams:**
- Vertical
- Horizontal
- Seroconversion
- Inactive carrier
- HBeAg- Chronic HBV
# 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>HBClgM</td>
<td>HBeAg+ or eAg-</td>
<td>&gt;10⁴-10⁵</td>
<td></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>HBClgG</td>
<td>eAb+</td>
<td>&lt;10⁴</td>
<td></td>
</tr>
<tr>
<td><strong>Immune</strong></td>
<td></td>
<td>HBClgG</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>
<tr>
<td>HCV RIBA</td>
<td>Seldom used</td>
</tr>
<tr>
<td></td>
<td>Can distinguish false positive AB from past infection</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>Viremia indicates current infection</td>
</tr>
<tr>
<td></td>
<td>Viral load does not correlate with severity of liver disease</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>Measure if considering interferon based therapy</td>
</tr>
<tr>
<td></td>
<td>Genotype 1 predominates in US</td>
</tr>
</tbody>
</table>
IL-28 in HCV genotype 1

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>37</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>African American</td>
<td>14</td>
<td>49</td>
<td>37</td>
</tr>
<tr>
<td>Hispanic</td>
<td>29</td>
<td>48</td>
<td>22</td>
</tr>
</tbody>
</table>

Prevalence genotype (%) SVR rate (%)

Thompson et al Gastroenterology 2010

Hemochromatosis

- 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
- Liver biopsy (HII >1.9 µmol/g dry weight)
Hemochromatosis

- Other mutations can lead to hemochromatosis
- Childhood
  - Hemojuvelin (Autosomal Recessive)
  - Hepcidin (Autosomal Recessive)
- Adult
  - Transferrin receptor 2 (Autosomal Recessive)
- Secondary iron overload and ferroportin-related (autosomal dominant)
  - Reticuloendothelial iron deposition, lower incidence of organ damage
- Remember not all iron overload is HFE

Autoimmune Hepatitis

- 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-LKMI
  - Less hyperglobulinemia
  - Tends to be more severe at onset and more likely to progress to cirrhosis
Wilson’s

<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

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Alpha-1 Antitrypsin Deficiency

- 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
- Liver histology
  - A1AT globules in ER of periportal hepatocytes
  - PAS positive, diastase-resistant
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)

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
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)
**PSC**

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

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**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

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**Alpha-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%
### Ultrasound and AFP

<table>
<thead>
<tr>
<th>Six month AFP and US (58% adherent)</th>
<th>No Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor &lt; 5 cm 45%</td>
<td>Tumor &lt; 5 cm 0%</td>
</tr>
<tr>
<td>Resection 47%</td>
<td>Resection 8%</td>
</tr>
<tr>
<td>Conservative therapy 21%</td>
<td>Conservative therapy 51%</td>
</tr>
<tr>
<td>Survival 1 year 66%</td>
<td>Survival 1 year 31%</td>
</tr>
<tr>
<td>Survival 5 year 46%</td>
<td>Survival 5 year 0%</td>
</tr>
<tr>
<td>HCC mortality rate 83.2/100,000</td>
<td>HCC mortality rate 131.5/100,000</td>
</tr>
</tbody>
</table>

Zhang J Cancer Res Clin Oncol 2004. 18,816 persons enrolled in prospective study

### 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%
      - 10: 7%
  - Malinchoc Hepatology 2003
Cirrhosis ≠ Transplant

<table>
<thead>
<tr>
<th>MELD</th>
<th>Hazard Ratio</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11</td>
<td>3.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-14</td>
<td>2.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15-17</td>
<td>1.21</td>
<td>0.1</td>
</tr>
<tr>
<td>19-20</td>
<td>0.62</td>
<td>0.5</td>
</tr>
<tr>
<td>21-23</td>
<td>0.38</td>
<td>0.8</td>
</tr>
<tr>
<td>24-26</td>
<td>0.22</td>
<td>1.0</td>
</tr>
<tr>
<td>27-29</td>
<td>0.18</td>
<td>0.7</td>
</tr>
<tr>
<td>30-39</td>
<td>0.07</td>
<td>0.9</td>
</tr>
<tr>
<td>≥40</td>
<td>0.04</td>
<td>0.9</td>
</tr>
</tbody>
</table>

CTP score

<table>
<thead>
<tr>
<th>Score</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade encephalopathy</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate or more</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1-2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Bilirubin (for PBC patients)</td>
<td>1-4</td>
<td>4-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

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