LIVER FUNCTION TESTS

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LFTs
DO NOT MEASURE FUNCTION

• Aspartate aminotransferase (AST)
• Alanine aminotransferase (ALT)
• Alkaline phosphatase (ALP)
• Should be referred to as liver chemistries or enzymes
# LIVER TESTS

## Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Aspartate aminotransferase (AST)</td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase (ALT)</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Alkaline phosphatase (ALP)</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Serum albumin</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Pro-thrombin (INR)</td>
</tr>
<tr>
<td>Other</td>
<td>Platelet count</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine</td>
</tr>
</tbody>
</table>

## Liver Enzymes

### Location of Transaminases

- **ALT**
  - **Cytoplasm**

- **AST**
  - **Mitochondria**

Injury: ALT > AST  
Alcohol: AST > ALT  
Cirrhosis: AST > ALT
SERUM ALT NORMAL DISTRIBUTION

Eliminate patients with:
- BMI > 25
- Increased cholesterol
- Hypertension
- Heart disease
- Diabetes mellitus
- Any medications

LIVER TESTS
ORGANS CONTAINING AST AND ALT

<table>
<thead>
<tr>
<th></th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Yes</td>
<td>Small amounts</td>
</tr>
<tr>
<td>Heart</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Brain</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Kidney</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
HEPATOTOXICITY OR MYOPATHY
AST and ALT

![Graph showing AST and ALT levels over weeks with Medication A highlighted.](chart1)

LIVER TRANSAMINASES
AST/ALT RATIO AND HISTOLOGY

![Bar chart showing AST/ALT ratio across different fibrosis stages and cirrhosis.](chart2)

ML Shiffman et al.
NON-INVASIVE MARKERS OF FIBROSIS

APRI

- APRI = \( \frac{\text{AST}/(\text{ULN}_{\text{AST}})}{\text{platelet count}} \) \times 100
- AST increases with cirrhosis
- Platelet count declines with cirrhosis
- Can differentiate cirrhosis from patients with none-mild fibrosis


NON-INVASIVE MARKERS OF FIBROSIS
FIBROTEST

- Utilizes 5 serum biochemical markers to predict fibrosis
  - Alpha-2 macroglobulin
  - Haptoglobin
  - Gamma glutamyl transpeptidase
  - Total bilirubin
  - Apolipoprotein A1
- Markers of inflammation NOT fibrosis
ASSESSMENT OF LIVER HISTOLOGY
SERUM TESTS

1.0
0.0
0.2
0.4
0.6
0.8
1.0

FIBROTEST

ACTITEST

FIBROSIS STAGE
ACTIVITY GRADE

T Poynard, et al.
Hepatology 2003;38:481-492.

NON-INVASIVE MARKERS OF FIBROSIS
COMPARISON OF TESTS

- All noninvasive markers of fibrosis provide similar information
- All separate mild disease from advanced fibrosis
- No test can tell you which patients have no fibrosis and will not progress

L Castera, et al.
ALKALINE PHOSPHATASE
SITES OF PRODUCTION

<table>
<thead>
<tr>
<th>Site</th>
<th>Site Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hepatocyte canaliculc membrane, NOT bile duct cell</td>
</tr>
<tr>
<td>Bone</td>
<td></td>
</tr>
<tr>
<td>Intestine</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Placenta</td>
<td></td>
</tr>
<tr>
<td>Tumors</td>
<td>Lung, Ovary</td>
</tr>
</tbody>
</table>

ALKALINE PHOSPHATASE
VARIATION WITH AGE

Bone ALP during rapid growth and osteoporosis associated with advanced age.

PL Wolf
ALKALINE PHOSPHATASE
EFFECTS OF PREGNANCY

Walker et al. 

ALKALINE PHOSPHATASE
CONFIRMATION OF LIVER ORIGIN

- Fractionate ALP:
  - Liver I
  - Liver II
  - Bone
  - Intestine

- Obtain an alternative test:
  - Only helpful when liver transaminases are normal
  - Gamma-glutamyl transferase (GGT)
  - 5’ nucleosidase
CHOLESTASIS
CLINICAL FEATURES

<table>
<thead>
<tr>
<th></th>
<th>Obstructive Jaundice</th>
<th>Intrahepatic Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Elevated</td>
<td>Normal-Elevated</td>
</tr>
<tr>
<td>Large bile ducts</td>
<td>Dilated</td>
<td>Normal</td>
</tr>
<tr>
<td>Small bile ducts</td>
<td>Proliferation</td>
<td>Normal-Abnormal</td>
</tr>
<tr>
<td>Histology</td>
<td>Bile lakes</td>
<td>Bilirubin stasis</td>
</tr>
</tbody>
</table>

CHOLESTASIS
OBSTRUCTIVE JAUNDICE

Large bile duct obstruction
CHOLESTASIS
OBSTRUCTIVE JAUNDICE

- Large bile duct obstruction

- Bile duct proliferation

- Elongation of bile duct

- Observed with:
  - Large bile duct obstruction
  - Primary biliary cirrhosis
  - Sclerosing cholangitis
  - Hepatic regeneration following hepatectomy

- Not found with:
  - Drug induced cholestasis
  - Infiltrative disorders

CHOLESTASIS
BILE DUCT PROLIFERATION

- Observed with:

- Not found with:
DRUG INDUCED CHOLESTASIS
BILIRUBIN STASIS

- Direct effect on canalicular membrane by:
  - Toxins, metabolites
  - Drugs
  - Interleukins, TNF
  - EtOH
- ALP translocates to basolateral membrane of hepatocyte
- Lost to serum
CHOLESTASIS
EXCRETION OF SUBSTANCES IN BILE

Bilirubin
Cholesterol
Copper
Bile salts

Increased in serum
Fat malabsorption

INTRAHEPATIC CHOLESTASIS
ETIOLOGIES

- Medications
- Infiltrative disorders
- Hepatic metastasis
- Alcoholic hepatitis
- Benign recurrent cholestasis
- Primary bile duct disorders
INTRAHEPATIC CHOLESTASIS

INFLTRATIVE DISORDERS

• Sarcoidosis
• Amyloidosis
• Tuberculosis
• Fungal infections
• Lymphoma/small cell carcinoma

INFLTRATIVE DISORDERS

SARCOIDOSIS
DRUG INDUCED HEPATOTOXICITY
CHOLESTASIS

- NSAIDs
- H₂ blockers
- Proton pump inhibitors
- Phenytoin and other anti-seizure medications
- Oral hypoglycemic agents
- Lipid lowering drugs
- Anti-fungal agents
- Sulfonamides
- Erythrocycin
- Anti-depressants
- Haldol, thorazine and other anti-psychotic agents
HEPATOTOXICITY
PURE CHOLESTASIS

AST
ALT
ALP

Itching
Medication D
Itching Resolves

WEEKS

HEPATOTOXICITY
CHOLESTASIS WITH JAUNDICE

AST
ALT
ALP
Tbili

Medication E

WEEKS

T BILI (mg/dl)
BENIGN RECURRENT CHOLESTASIS FEATURES

- Episodic pruritus and jaundice
- First episode always prior to age 30 years
- Liver histology:
  - Cholestasis during attacks
  - Normal between attacks
- Normal cholangiography
- Autosomal dominant trait of FIC-1 protein
  - Positions proteins within cell membrane

VA Luketic and ML Shiffman

BENIGN RECURRENT CHOLESTASIS LABORATORY PATTERN

Adapted from VA Luketic and ML Shiffman
CLOTTING FACTORS SYNTHESIZED BY THE LIVER

<table>
<thead>
<tr>
<th>Clotting</th>
<th>Anti-clotting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K Dependent</td>
<td>II, VII, IX, X</td>
</tr>
<tr>
<td>Vitamin K Independent</td>
<td>I, V, VIII</td>
</tr>
</tbody>
</table>

PROLONGATION IN PRO-THROMBIN TIME ETIOLOGIES

<table>
<thead>
<tr>
<th>Vitamin K Decreased</th>
<th>Vitamin K Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged cholestasis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Obstructive jaundice</td>
<td></td>
</tr>
<tr>
<td>Malabsorption</td>
<td></td>
</tr>
<tr>
<td>Fat malabsorption</td>
<td></td>
</tr>
<tr>
<td>Chronic antibiotic use</td>
<td></td>
</tr>
</tbody>
</table>
LIVER FUNCTION TESTS

COAGULATION PROTEINS

- Vitamin K dependent and independent
- Clotting and anti-clotting factors
  - Normally in balance
  - Cirrhosis may alter this balance
- Factor VII shortest half-life - 6 hours
- Pro-thrombin time (INR) is the most sensitive of all liver function tests

COAGULATION PROTEINS
BALANCING CLOTTING FACTORS

- Clotting Factors
- Anti-clotting Factors
- Measurable (PT/INR)
- Not Measurable
BALANCING CLOTTING FACTORS
CLOTTING IN CIRRHOSIS

<table>
<thead>
<tr>
<th>Clotting Factors</th>
<th>Anti-clotting Factors</th>
<th>INR</th>
<th>Coagulation Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>1.0</td>
<td>Normal</td>
</tr>
<tr>
<td>-2</td>
<td>-2</td>
<td>2.0</td>
<td>Normal</td>
</tr>
<tr>
<td>-2</td>
<td>Normal</td>
<td>2.0</td>
<td>Hypocoagulable</td>
</tr>
<tr>
<td>-4</td>
<td>-2</td>
<td>2.0</td>
<td>Hypocoagulable</td>
</tr>
<tr>
<td>Normal</td>
<td>-2</td>
<td>1.0</td>
<td>Hypercoagulable</td>
</tr>
<tr>
<td>-2</td>
<td>-4</td>
<td>2.0</td>
<td>Hypercoagulable</td>
</tr>
</tbody>
</table>

BILIRUBIN CONJGATION AND EXCRETION

Conjugation UDP Glucuronyltransferase

Secretion into bile is the rate limiting step
### LIVER FUNCTION TESTS

#### BILIRUBIN

<table>
<thead>
<tr>
<th></th>
<th>Water Soluble</th>
<th>Bound to Albumin</th>
<th>Excreted into</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated</td>
<td>Yes</td>
<td>No</td>
<td>Urine Bile</td>
</tr>
<tr>
<td>Unconjugated</td>
<td>No</td>
<td>Yes</td>
<td>Bile</td>
</tr>
<tr>
<td>Delta</td>
<td>Yes</td>
<td>Irreversible</td>
<td></td>
</tr>
</tbody>
</table>

### HYPERBILIRUBINEMIA MECHANISMS

- Excessive production
  - Unconjugated hyperbilirubinemia
- Inefficient conjugation
  - Unconjugated hyperbilirubinemia
- Defective secretion into bile
  - Conjugated hyperbilirubinemia
HYPERBILIRUBINEMIA ETIOLOGIES

CONJUGATED
- Hepatocellular dysfunction
  - Acute
  - Chronic
  - Cirrhosis
- Cholestasis
- Genetic disorders:
  - Dubin-Johnson
  - Rotor

UNCONJUGATED
- Hemolysis
- Reabsorption of hematoma
- Genetic disorders:
  - Gilberts syndrome
  - Crigler-Najjar I
  - Crigler-Najjar II

CONJUGATED HYPERBILIRUBINEMIA GENETIC DEFECTS

<table>
<thead>
<tr>
<th>Dubin-Johnson Syndrome</th>
<th>Rotor’s Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bilirubin fluctuates between ULN and 5mg/dl</td>
<td></td>
</tr>
<tr>
<td>• No signs or symptoms of liver disease</td>
<td></td>
</tr>
<tr>
<td>• ALP and GGT are always normal</td>
<td></td>
</tr>
<tr>
<td>• Symptoms of cholestasis are absent</td>
<td></td>
</tr>
<tr>
<td>• Transport of bile and other substances into bile is normal</td>
<td></td>
</tr>
<tr>
<td>• Dark heavily pigmented liver</td>
<td></td>
</tr>
<tr>
<td>• Gallbladder not visualized on oral cholecystogram</td>
<td></td>
</tr>
<tr>
<td>• Liver histology normal</td>
<td></td>
</tr>
<tr>
<td>• Oral cholecystogram is normal</td>
<td></td>
</tr>
</tbody>
</table>
UNCONJUGATED HYPERBILIRUBINEMIA
CRIGLER-NAJJAR SYNDROME

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Autosomal recessive</td>
<td>?</td>
</tr>
<tr>
<td>UDP GT activity</td>
<td>Absent</td>
<td>50% of normal</td>
</tr>
<tr>
<td>Bilirubin levels</td>
<td>~20 + mg/dl</td>
<td>~ 5 mg/dl</td>
</tr>
<tr>
<td>Kernicterus</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Treatment</td>
<td>Plasmapheresis</td>
<td>Hepatocyte/liver transplant</td>
</tr>
</tbody>
</table>

GILBERT’S SYNDROME
CHARACTERISTICS

- The most common cause of jaundice in otherwise healthy persons:
  - Total bilirubin 2-7 mg/dl
  - Nearly all unconjugated bilirubin
- Autosomal dominant
- Reduced conjugation of bilirubin
- Jaundice worsens during fasting
- Bilirubin can be reduced with phenobarbital
GILBERT’S SYNDROME
FASTING AND TREATMENT

![Graph showing bilirubin levels with data from M Black, et al., Lancet 1970;1:1359-1363.]

LIVER FUNCTION TESTS
“NON-LIVER” TESTS

- **Platelets**: A platelet count of <125/cc is the most sensitive test for identification of patients with cirrhosis

- **Serum creatinine**: The single most important predictor of 30 day mortality in patients with cirrhosis. Serum creatinine > 2.5 mg/dl doubles 30 day mortality
“NON-LIVER” FUNCTION TESTS

PLATELET COUNT


MODEL OF END STAGE LIVER DISEASE
SERUM CREATININE

▪ MELD Score based upon:
  ▪ Total bilirubin
  ▪ INR
  ▪ Serum creatinine
▪ Creatinine has the strongest weight on mortality in the MELD score calculation.