Approach to Abnormal Liver Tests

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Conflicts of Interest

- None relevant to declare
Outline

- Properties
- Clinical value of different patterns & levels
- Pattern of liver test abnormalities in drug development

Liver enzymes vs. LFTs

- Serum aminotransferase levels and alkaline phosphatase levels are liver enzymes. Their elevations indicate hepatocyte and bile duct epithelial injury.

- Albumin, bilirubin, prothrombin time are measures of hepatic function. But these are affected by extrahepatic factors such as nutrition, hemolysis, antibiotic use.
Liver enzymes vs. LFTs

- Special liver function tests: GEC, ICG, MEGX, and various breath tests. Depend on metabolic function of hepatocytes and are dependent on liver blood flow.
- Child-Pugh score is perhaps the best indicator of liver function in patients with cirrhosis.
- MELD score measures more than liver function.

Aminotransferases are not specific to liver

<table>
<thead>
<tr>
<th><strong>AST</strong></th>
<th><strong>ALT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (9000:1)</td>
<td>Liver (7600:1)</td>
</tr>
<tr>
<td>Muscle (5200:1)</td>
<td>Muscle (750:1)</td>
</tr>
<tr>
<td>Heart</td>
<td>Kidney</td>
</tr>
<tr>
<td>Kidney</td>
<td>Red cells</td>
</tr>
<tr>
<td>Red cells</td>
<td>Brain</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
</tr>
</tbody>
</table>
Aminotransferases: Properties

- Source of normally circulating AT is unclear.
- AST and ALT activity in liver is 7000 and 3000 times higher than in serum.
- AT are released either due to cell destruction or leaky cell membrane.
- Increased synthesis

Aminotransferases: Properties

- ALT is exclusively in cytoplasm whereas AST is both cytoplasm and mitochondrial.
- Half life of total AST $17 \pm 5$ hours; ALT $47 \pm 10$ hrs
- AST/ALT ratio depends on gender and age; men with higher levels than women.
**Aminotransferases elevations: Non-Hepatic etiology**

- Hemolysis
- Myocardial infarction
- Acute renal injury
- Infarcted bowel
- Brain injury
- Muscle injury
- Macroenzymes

**Alkaline Phosphatase**

- Also present in bone, placenta, intestine, and kidney.

- Alkaline phosphatase can be fractionated - bone fraction is heat labile and liver fraction is heat stable.

- Elevated GGT or 5' nucleotidase can help hepatic vs. non-hepatic source for elevated alkaline phos.

- Alkaline phos elevation is physiological in those who are less than 18 years old, or in women who are pregnant.
**Characterization of elevated liver enzymes**

- Acute vs. Chronic
- Hepatocellular vs. Cholestatic vs. mixed

R-value: ALT/AP (both x ULN)
- > 5 is hepatocellular
- < 2 is cholestatic

**Hepatocellular Liver Disease**

**Only Acute**
- Viral Hepatitis A, E*
- Toxins
- Ischemia
- Pregnancy-related
- Herpes simplex hepatitis
- Acetaminophen

*Chronic in immunocompromised patients

**Only Chronic**
- Fatty liver
- Hemochromatosis
- A-1 antitrypsin deficiency

**Both acute & Chronic**
- Autoimmune
- Wilson’s Disease
- Hepatitis B
- Budd-Chiari Syndrome
- Alcoholic liver disease
- Medications
**Cholestatic Liver Disease**

**Extrahepatic**
- Stones
- Cancer
- Sphincter dysfunction
- Choledochal cysts
- Trauma

**Intrahepatic**
- PBC
- Sepsis
- Drugs
- Metastases
- Granulomas
- TPN

**Both intra & extra hepatic**
- PSC
- Cholangiocarcinoma
- Radiation

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**Clinical value of different patterns**

- In almost all liver diseases, ALT is higher than AST except in alcoholic liver disease and in advanced fibrosis.

- In alcoholic hepatitis, AST is greater than ALT
  - Alcohol increases mitochondrial AST and decreases cytoplasmic ALT.
  - ALT is also low due to pyridoxine deficiency.

- AST and ALT are significantly lower in patients with renal failure.
Clinical value of different levels

- Normal AT in patients with HCV and NAFLD may still be associated with abnormal hepatic histology.
- Levels < 300 U/L in chronic HCV/HBV, NAFLD, and hemochromatosis.
- ALT > 150 or AST > 300 U/L is uncommon in alcoholic liver disease.

Clinical value of different values

- **Very high values in thousands**
  - Ischemic injury
  - Drug or toxin injury
  - Viral Hepatitis
  - Autoimmune
  - Budd-Chiari syndrome
  - CBD Stones
AT elevation in the context of other abnormalities

- **Elevated bilirubin**: severity of injury, hemolysis, Gilbert’s, Obstruction
- **Very high levels with hemolysis**: Wilson’s
- **Very high levels with new onset ascites**: cardiac etiology or Budd-Chiari
- **Very high LDH**: ischemia
- **High CPK**: Rhabdomyolysis
- **APAP phenotype**: High AT and INR but not as high bilirubin

Pattern of recovery

- Dramatically improving AT indicate ischemia or toxic injury.
- Fluctuating at high levels – congestive heart failure, surreptitious APAP intake, and arrhythmias.
Macro AST

- Normal enzymes complexed with Ig G and Ig A
- High AST, but normal ALT, alk phos, CPK
- Immunoprecipitation and electrophoresis confirmed AST enzyme complex
- Can be seen in liver disease, malignancy, IBD

Keep in Mind

- Isolated asymptomatic increase in AST: Macro AST
- Jaundice or high liver tests with hemolysis: Wilson’s
- Alk phos/bili < 2: Wilson’s disease
- Acute liver disease + ascites: Budd-Chiari
- Pregnancy + ALF: HSV, HEV, AFLP
Additional terminology

- **Hy’s rule in drug development:**
  - ALT > 3 ULN and TB > 2 ULN with no other etiology
  - Prognostic significance of Hy’s rule has been validated in recent studies (~10% mortality)

- **Temple corollary:** Excessive number of cases with ALT > 10 ULN in the active group

Child-Turcotte-Pugh Classification

<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
- Class A = 5 to 6 points (least severe liver disease)
- Class B = 7 to 9 points (moderately severe liver disease)
- Class C = 10 to 15 points (most severe liver disease)

http://depts.washington.edu/hepstudy/mgmt/mgmt/ascitesMgmt/discussion.html
MELD Score

\[
\text{MELD} = 3.78 \times \log_e \text{serum bilirubin} (\text{mg/dL}) + \\
11.20 \times \log_e \text{INR} + \\
9.57 \times \log_e \text{serum creatinine} (\text{mg/dL}) + \\
6.43 \text{ (constant for liver disease etiology)}
\]

NOTES:
If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0.
Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result).

http://depts.washington.edu/hepstudy/mgmt/mgmt/ascitesMgmt/discussion.html

Post-operative Mortality Risk in Patients with Cirrhosis

To determine the risk of post-operative mortality for all types of major surgery, especially gastro-intestinal, orthopedic and cardiac surgery (includes open heart procedures), please enter the following variables:

What is the age? [enter value]
What is the MELD score? [enter value]
What is the bilirubin? [enter mg/dL]
What is the creatinine? [enter mg/dL]
What is the INR? [enter value]
What is the etiology of cirrhosis? [select option: Alcoholic or Cholestatic, Viral or Other]

Compute | Reset form

Probability of Mortality

Post-operative Interval:
- 7 days
- 30 days
- 90 days
- 1 year
- 5 years

Take home messages

- Liver biochemistries are among the most widely ordered tests in clinical practice.
- Aminotransferases and alk phos are not liver function tests.
- Patterns of their elevation are of significant utility at the bedside.
- Child’s score is most widely used for assessing the liver function.