What to Do with the Patient With Abnormal Liver Enzymes?

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Elevated liver enzymes is often not a clinical problem by itself. However it is a warning sign of potential future problem.
Hepatic Fibrosis is a Natural Response to Chronic Injuries

- Inherited Metabolic Disorders
- Schistosomiasis
- Hepatitis Viruses
- NASH
- Cholestatic Disorders
- Immune Disorders
- Alcohol
- Drugs

FIBROSIS
The Problem...
Clinically...
The Three most important Clues!

- Liver enzyme or liver function
- Acute or chronic
- Hepatocellular or cholestatic
# Hepatic Panel

## Liver Enzymes
- ALT
- AST
- Alkaline Phosphatase
- GGT

## Liver Function
- Bilirubin
- Albumin
- Prothrombine Time
Liver Enzymes

- Sensitive for hepatic injury
- Not very specific to identify the cause of liver injury
### The Child-Turcotte-Pugh classification

<table>
<thead>
<tr>
<th></th>
<th>1 point*</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albumin</strong></td>
<td>&gt; 3.5 g/dL</td>
<td>2.8-3.5 g/dL</td>
<td>&lt;2.8 g/dL</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td>&lt; 1.7</td>
<td>1.7-2.25</td>
<td>&gt;2.25</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>&lt;2 mg/dL</td>
<td>2-3 mg/dL</td>
<td>&gt;3 mg/dL</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
<td>Stage I-II</td>
<td>Stages III-IV</td>
</tr>
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</table>
Acute vs. chronic?

- Traditionally chronic: elevation of liver test for six months
- It could be a new onset elevation of LFT in a chronic condition.
<table>
<thead>
<tr>
<th><strong>Acute</strong></th>
<th><strong>Chronic</strong></th>
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<tbody>
<tr>
<td>• Viral infection (HAV)</td>
<td>• NAFLD</td>
</tr>
<tr>
<td>• Drug-induced injury</td>
<td>• Hemochromatosis</td>
</tr>
<tr>
<td>• Autoimmune liver disease</td>
<td>• A1AT deficiency</td>
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<tr>
<td>• Ischemic</td>
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Biochemical patterns

Hepatocellular injury:
- Predominantly ALT/AST elevation

Cholestatic injury:
- Predominantly AP elevation (+/- elevated bilirubin)

Mixed pattern
What to do?

- **Assessment of etiology**
  - Laboratory tests:
    - Biochemical
    - Serological
    - Virological
    - Genetic testing
  - Imaging studies (US, CT, MR, nuclear)

- **Assessment of degree of liver injury**
  - Liver biopsy
  - Endoscopy
Liver biopsy

A small slender core of tissue is removed with a biopsy needle.
Utility of Liver Biopsy

Confirm Clinical Diagnosis

Assess Severity of Necroinflammation

Evaluate Possible Concomitant Disease Processes

Assess Fibrosis

Assess Therapeutic Intervention

However...

- Cost
- Complications
- Patient do not like it and may refuse it.
- Not all patients are candidates.
Non-invasive Prediction
The Non-invasive Tools

- **Routine Laboratory Tests**
  - ALT, AST, ALT/AST ratio, Platelet...
  - Examples: Forns tests, APRI, Metwally

- **Specialized tests**
  - Fibrotests
  - PGA index
  - CK 18

- **Imaging**
Routine Lab Tests

- Prediction model used three simple lab value to design the model:
  - Platelet count (score 0-4)
  - Serum albumin (score 0-2)
  - Serum AST (score 0-3)

- Total maximum score is 9

Zein NN et al. DDS, 2006
Nonsevere fibrosis
Severe fibrosis

Number of patients

Score 0-1
Score 2-3
Score 4-8
ROC Curve of a Model to Predict Hepatic Fibrosis

Zein NN et al. DDS, 2006
Specialized Tests: Fibrotests

- Alpha 2 macroglobulin
- Haptoglobin
- GGT
- Apolipoprotein A1
- Total bilirubin

Acute Inflammation
Gilbet’s
Hepatocyte Apoptosis Correlates with Stage of Fibrosis in NASH

Specialized Tests

• In Vivo Assessment of Liver Cell Apoptosis as a Novel Biomarker of fibrosis stage

M30 Apoptosense ELISA Kit

Quantitative measurement of caspase-generated CK-18 fragments in serum

Imaging-based techniques

- Promising
- Good reproducibility and low inter-observer variability
- Difficult to use in obese patients
- May not differentiate fat from fibrosis...
Elastography (Liver Stiffness)
Reversibility of Cirrhosis Following Treatment of Hepatitis C

Poynard et al, Gastroenterology 2002; 122:1303-1313
Making the case for perusing workup of patients with elevated liver enzymes: The HCV example
Mortality from Hepatitis C: US

Number of Deaths

Calendar Year

UNOS: United Network for Organ Sharing
Predicted HCV-Related Mortality

Natural History of HCV Cirrhosis

Survival probability (%)

Deaths
Liver-related (70%)
Other causes (30%)

Compensated
After 1st complication

Time (years after diagnosis)

Early Identification and Monitoring


El Serag H, et al. NEJM, 1999
Outcome of Current Therapy (SVR)

Overall Response

- IFN-2b 3 MIU/RBV: 47% (n = 505, P = 0.01)
- PEG-IFN-2b 1.5 µg/kg/RBV: 54% (n = 511)
- IFN-2b 3 MIU/RBV: 44% (n = 444, P = 0.001)
- PEG-IFN-2a 180 µg/RBV: 56% (n = 453)

Cumulative Incidence of Cirrhosis and HCC According to Response to IFN Therapy

### 20 Year Risks, Life Expectancy, and Quality Adjusted Life Expectancy: Treated vs. Untreated HCV

<table>
<thead>
<tr>
<th>Event</th>
<th>No Antiviral Treatment</th>
<th>PegIFN Plus Wt-Based RBV</th>
</tr>
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<tbody>
<tr>
<td><strong>20-Year Risk (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>62</td>
<td>25</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>9.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Liver transplantation*</td>
<td>2.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Liver-related death</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td><strong>Life expectancy (years)</strong></td>
<td>25.8</td>
<td>30.5</td>
</tr>
<tr>
<td><strong>Quality Adjusted Life Expectancy (QALY)</strong></td>
<td>22.8</td>
<td>27.7</td>
</tr>
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</table>

*Only first transplantations included (no retransplantations).
Novel Agents

Dropped Out
- Ribozymes
- Anti-sense therapy
- Several polymerases
- Toll-like receptor antagonists

Still In The Race
- VX-950
- Infliximab
- Nitazoxanide
- Albuferon
Conclusions

- Approach to patients with elevated liver enzymes is evolving with newer molecular assays and diagnostic techniques.
- Advances in diagnostics has primarily been driven by improved therapeutic modalities in patients with acute and chronic liver diseases.