The ABCs of Liver Disease
HIV and Hepatitis Management
The New York Course

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Note on references

References listed in the syllabus are cited by number in the text of slides.
Outline

1. Why we need our livers: LIVER FUNCTION
2. Usual presentations of LIVER DYSFUNCTION
3. Interpretation of LIVER function TESTS
4. GARDEN-VARIETY LIVER DISEASE: what we should expect, what we should fear
5. The importance of STAGING chronic liver disease
Normal liver function

The liver is a metabolically active filter\textsuperscript{1}
Normal liver microanatomy
Abnormal liver function

<table>
<thead>
<tr>
<th>Injury</th>
<th>Impaired Filtration</th>
<th>Impaired Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td>Chronic</td>
<td>X</td>
<td>O</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Disease discovery: liver function tests

| Cell Integrity: | • AST  
<table>
<thead>
<tr>
<th></th>
<th>• ALT</th>
</tr>
</thead>
</table>
| Bile Excretion:| • Bilirubin  
|                | • Alkaline phosphatase  
|                | • Cholesterol |
| Metabolic Capacity: | • Bilirubin  
|                    | • Prothrombin time  
|                    | • Albumin  
|                    | • Cholesterol |
| Immune Surveillance: | • Serum globulin |
Types of liver injury: hepatocellular

- **Cell Integrity:**
  - AST
  - ALT

- **Bile Excretion:**
  - Bilirubin
  - Alkaline Phosphatase
  - Cholesterol

- **Metabolic Capacity:**
  - Bilirubin
  - Prothrombin time
  - Albumin
  - Cholesterol

- **Immune Surveillance:**
  - Serum Globulin
Types of liver injury: cholestatic

**Cell Integrity:**
- AST
- ALT

**Bile Excretion:**
- Bilirubin
- Alkaline Phosphatase
- Cholesterol

**Metabolic Capacity:**
- Bilirubin
- Prothrombin time
- Albumin
- Cholesterol

**Immune Surveillance:**
- Serum Globulin
Hepatocellular vs cholestatic disease

\[
\frac{\text{ALT}}{\text{Alk Phos}} \quad \text{(expressed as multiples of ULN)}
\]

**Hepatocellular disease:** Ratio >5

**Cholestatic disease:** Ratio <2

**Mixed disease:** Ratio = 2-5
Etiologic diagnosis

1. The **TYPE** of test abnormality: *cellular*, *cholestatic*, or *mixed*

2. The **TIME COURSE** of the test abnormality: *acute*, *chronic*, or *acute on chronic* (lice & fleas)

3. The **CONTEXT** of the test abnormality: viral exposure, new medications, alcohol abuse

4. The **PATTERN** of the test abnormality: many etiologies cause characteristic patterns of test results (fingerprints)
Patterns of liver injury

**Fatty liver:**
- AST & ALT <100
- Often fluctuate
- Normal bilirubin, INR

**Hepatic ischemia:**
- AST & ALT >1,000
- AST >ALT
- Normal bilirubin, INR
- Progressive resolution

**Autoimmune:**
- AST & ALT >100
- Looks like viral hepatitis
- May have negative markers

The pattern of the liver-test abnormality is the fingerprint of the perpetrator.
What varieties of liver disease are we likely to encounter?³

ACUTE:
*Toxic:* DRUGS; alcohol
*Viral:* HAV, HBV
*Other:* immune, ISCHEMIA

CHRONIC:
*Metabolic:* FAT (NAFLD; NASH)
*Viral:* HBV, HCV
*Other:* immune-mediated
Drug-induced liver injury (DILI)\(^4,5,6,7,8\)

1. Usually causes primary hepatocellular liver injury (abnormal AST, ALT) but may be cholestatic or mixed

2. Vast majority of episodes are unpredictable, with variable latency (3-365 days)

3. Believed most often to be caused by immuno-allergenic reactions or abnormal metabolism

4. With continued exposure, mild injury often resolves, but severe injury usually worsens

5. Patients with chronic liver disease are generally not more susceptible than others, unless hepatic metabolism impaired

6. Although a clear dose relationship is usually absent, most episodes occur with doses >50 mg/day
# Most common causes of adult DILI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ALF Study Group&lt;sup&gt;6&lt;/sup&gt;</th>
<th>DILI Network&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>n = 137</td>
<td>n = 519</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Sulfa drugs</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Azoles</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Amox/clavulanate</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>115</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Others (psychotropics)</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td><strong>NSAIDS</strong></td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td><strong>Herbal concoctions</strong></td>
<td>14</td>
<td>59</td>
</tr>
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</table>
Diagnosis and evaluation of DILI

LiverTox® provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications, herbs, and dietary supplements. LiverTox also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. The LiverTox website provides a comprehensive resource for physicians and their patients, and for clinical academicians and researchers who specialize in idiosyncratic drug-induced hepatotoxicity.
Diagnosis and evaluation of DILI

- Guilt by association
- Other causes (viral; AIH)?
- Encephalopathy?
- Coagulopathy?
- Acidosis?
- Renal failure?
Ischemic liver injury

- Portal flow has low pressure but high volume
- Reduced by diarrhea, vomiting, hypotension
- Aminotransferases 1,000 or greater
- AST > ALT
- Daily improvement
Fatty liver disease (NAFLD)\textsuperscript{9,10,11}

**NAFL:** 25\% of US population

(99\% of the morbidly obese; 3\% of lean individuals)

**NASH:** 30\% of NAFLD

**Fibrosis:** 50\% of NASH
## Risk factors for NAFLD\textsuperscript{9,11}

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence of NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truncal obesity</td>
<td>50%-75%</td>
</tr>
<tr>
<td></td>
<td>(&gt;90% of morbidly obese)</td>
</tr>
<tr>
<td>Type-2 diabetes</td>
<td>10%-75%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>30%-50%</td>
</tr>
<tr>
<td>None recognized</td>
<td>3%</td>
</tr>
</tbody>
</table>
Diagnosis of fatty liver disease

- A diagnosis of exclusion: with a typical liver-test pattern and no virus or toxin
- Imaging corroborates impression of NAFLD
- Biopsy is necessary to diagnose NASH
- We often assume that NASH is cause in cases of cryptogenic cirrhosis
Reasons for staging in patients with chronic liver disease

- Evidence that chronic injury is causing significant liver damage
- Prognosis of liver disease
- Indication to screen for hepatocellular carcinoma
- Indication to screen for esophageal varices
Staging methods

**VALIDATED**
- Liver biopsy
- Serum markers
- Transient elastography
- MR elastography
- Combination of above

**NOT FOR STAGING**
- Ultrasound
- CT
- Standard MR
- HCV viral load
- Aminotransferase level
The ABCs of liver disease

1. Begin by noting the PATTERN and DURATION of the liver-test abnormality

2. Does the pattern make sense in terms of the HISTORY?

3. SCREEN for virus, SUSPECT drugs and fat, and BEWARE of AIH

4. Always STAGE chronic disease

5. SCREEN FOR HCC if advanced-stage fibrosis, even after HCV cured or if NASH
Question: Is life worth living?

Answer: It depends upon the liver!

William James
International Journal of Ethics, 1895

Thank you for your attention