Evaluation of the Inpatient with Abnormal Liver Tests

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Overview

- General approach
- Cholestatic liver test pattern
  - Post-op jaundice
    - Cholestasis of sepsis
- Hepatitis liver test pattern
  - DDx of severe ALT abnormalities
    - Drug-induced liver injury (DILI)
    - Acute cardiac hepatopathy
    - Viral hepatitis – reactivation
- Pre-op evaluation of patient with cirrhosis
Frequency of “Abnormal Liver Tests” as Inpatient Consultation

• Among inpatient consults, the evaluation of the patient with abnormal liver tests accounts for up to 15% of consults.
• This may be an underestimation, as there may be even more informal, “curbside” consults and a shift to deferring the consults to outpatient follow-up.
• This is likely to occur more often for abnormal liver tests than symptoms that warrant an endoscopy.

General Approach

• Mirrors that done in the outpatient setting, except work-up done more rapidly, as findings often influence management of other conditions.
• Components of the initial evaluation include:
  1. Confirmation that the test abnormality is of liver origin
  2. Determination if whether abnormalities are new versus chronic
  3. Establishment of cause
  4. Evaluation of severity of disease, in particular, if any evidence of decompensation
**Isolated Liver Test Abnormality**

**ALKP**
- (Alkaline Phosphatase)
  - Sources: bone, intestinal or placental origin
  - Fractionation ALKP
  - GGT or 5-nucleotidase

**AST**
- Sources: cardiac muscle, skeletal muscle, kidney, brain, pancreas and RBCs
- Exclude hemolysis, cardiac ischemia, rhadomyolysis, inflammatory muscle dz. based on history and other labs

**Step 1: Diagnostic Evaluation**

**History Essentials**
- Are liver test abnormalities new (with the current hospitalization) or preexisting
- Time course of liver test abnormalities and rate of increase
- Prior drug, alcohol, over-the-counter, herbal/health products use prior to admission and of prescription medications given in the week prior to and during hospitalization
- Concurrent conditions, especially the presence of fever or signs of infection, any documented periods of significant hypotension or other cardiac events, or recent surgeries or endoscopic procedures is important
- Recent surgeries
Step 2: Diagnostic Evaluation
Physical Examination

• Clinical signs of cirrhosis:
  • Splenomegaly, spider angiomata, palmar erythema, firm liver edge
• If suspected or known cirrhosis, signs of decompensation:
  • Encephalopathy, ascites, and edema are important prognostically.
• Plus evidence of systemic diseases that may include liver manifestations (lymphadenopathy, heart failure, etc)

Step 3: Evaluation of Liver Enzyme Profile

Cholestatic
- ↑ ALKP alone or to greater fold increase than AST and ALT
- GGT elevation if liver origin
- ± Bilirubin elevation
- Significant ALKP elevation w/o bilirubin more common with:
  - Partial biliary obstruction
  - Infiltrative diseases

Hepatitic
- ↑ ALT and AST usually elevated similarly and greater fold than ALKP
- AST >> ALT
  - Alcohol: 2-fold higher
  - Wilson’s: due to concurrent hemolysis
  - Cirrhosis any cause
- ± Bilirubin elevation
- Prognostic importance
Diagnostic Approach for Patient with Cholestatic Enzyme Profile

US Abdomen or CT scan

Abnormal Biliary Tree
- Stones, Tumors
- Strictures (including PSC)

Normal Biliary Tree
- Drugs/toxins
- Infiltrative Dz e.g. Lymphoma
- Granulomatous Dz e.g. Mycobacterium, sarcoidosis
- Chronic Cholestatic Liver Dz e.g. PBC, cystic fibrosis, small duct PSC
- Sepsis

Cholangiography

Autoimmune markers, cultures, more imaging, liver biopsy

Cholestatic Liver Diseases
Elevated Alkaline Phosphatase ± Bilirubin

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Clues</th>
<th>First Order Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary</td>
<td>Fever, abd pain, weight loss</td>
<td>US or CT scan</td>
</tr>
<tr>
<td>Drug-toxicity</td>
<td>History of exposure</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Malignancy: lymphoma, HCC</td>
<td>Hepatosplenomegaly, adenopathy B symptoms</td>
<td>Biopsy Tumor markers</td>
</tr>
<tr>
<td>Infectious</td>
<td>Fever, abnormal abdominal imaging</td>
<td>Cultures other sites, liver biopsy</td>
</tr>
<tr>
<td>Chronic granulomatous dz</td>
<td>Lung, lymph node, other systems involvement</td>
<td>Biopsy</td>
</tr>
<tr>
<td>PSC/PBC</td>
<td>Presence of ulcerative colitis; other autoimmune diseases</td>
<td>Cholangiogram, usually MRCP for PSC AMA, ANA, IgM/G</td>
</tr>
</tbody>
</table>
Post-Op Jaundice

- New onset jaundice post-operatively is usually multifactorial
- More frequent in patients with underlying cirrhosis than those with normal livers or non-cirrhotic chronic liver disease
- Fractionation of bilirubin will help to delineate broad categories of cause for jaundice
- Pattern and severity of the liver test abnormalities help to narrow the differential diagnosis
- Abdominal sonography is best initial test to assess for extrahepatic causes of jaundice

### Jaundice Post-Op: Differential Dx

<table>
<thead>
<tr>
<th>Categories</th>
<th>Specific Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconjugated Hyperbilirubinemia</td>
<td>Hemolysis (all causes)</td>
</tr>
<tr>
<td>Isolated ↑ bilirubin</td>
<td>Hematoma reabsorption</td>
</tr>
<tr>
<td>Conjugated Hyperbilirubinemia</td>
<td>Gilbert’s syndrome</td>
</tr>
<tr>
<td>-- Hepatocellular Dysfunction</td>
<td>Drug toxicity</td>
</tr>
<tr>
<td></td>
<td>Anesthesia</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Ischemic hepatitis</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Benign intrahepatic cholestasis</td>
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<tr>
<td></td>
<td>Total parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td>Acute viral hepatitis</td>
</tr>
<tr>
<td>Conjugated Hyperbilirubinemia</td>
<td>Bile duct stone/stricture</td>
</tr>
<tr>
<td>-- Extrahepatic Disorders</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>ALKP also ↑</td>
</tr>
</tbody>
</table>

Faust TW, Clinics in Liver Disease 2004;8:151-66
Cholestasis of Sepsis

- Described by Osler: pneumonia can lead to jaundice
- Related to endotoxin and endotoxin-induced cytokines (mainly TNFα, IL-1β, IL-6) or microbial TLR2 or TLR4 agonists

Underlying Mechanisms of Hyperbilirubinemia in Sepsis

1. Hemolysis
   a. In normal red cells
   b. In RBCs with red cell enzyme defects (G6PD)
   c. Pathologic changes to RBCs secondary to infection
d. Drug-induced hemolysis
2. Hepatic dysfunction
   a. Decreased bilirubin uptake
   b. Decreased canalicular transport
c. Decreased clearance of conjugated bilirubin
d. Hepatic ischemia
   i. Hypotension
   ii. Prolonged Hypoxia
e. Hepatocellular injury (mild reactive hepatitis to overt hepatocellular necrosis)
3. Cholestasis

Clinical Features
- Onset within days of bacteremia
- Can occur before other clinical features of underlying infection
- Conjugated bilirubin 2-10 mg/dL range, rarely higher
- ALKP 2-3x ULN, minimal AST/ALT elevations
- Pruritus not typical

Cause and Natural History
- Gram-neg most common but gram-positive also causative
- Intraabdominal most common but also UTI, PNA, endocarditis meningitis
- Presence of jaundice or cholestasis does not influence prognosis
- Resolution mirrors that of infection

**Benign Intrahepatic Cholestasis**

- Described first in 1975
- Jaundice appearing 1-12 days post-op
- Typically in patients who received transfusions and post-op course complicated by sepsis
- Marked total bilirubin elevation (both conjugated and unconjugated) with normal to moderate ALKP elevation
- Imaging normal and biopsies normal or mild non-specific abnormalities
- Resolves without treatment

Prandi D, Nouv Presse Med 1975;20:2165-8

**Management of Cholestasis of Sepsis**

**Diagnosis**
- Always in DDx of patient with cholestatic profile
- Often part of a “mixed picture” post-op
- Exclude all other cholestatic causes

**Treatment**
- Antibiotics
  - Consider empiric antibiotics once cultured
  - Drain abscesses
  - Replace lines, etc
- Consider early introduction of enteral nutrition
- No established role for URSO

Hawker F Anaesth Intensive Care 1991
Chronic “Hepatitis” Pattern
Elevated ALT (and AST)

- Sporadic, isolated ALT elevations need no further work-up
- Persistent or rapidly rising ALT elevation warrant work-up
  - ALT slightly > AST or approximately same
  - If AST>ALT = consider alcohol (usx. 2:1 ratio)
- Acute vs chronic distinguished by history
- High of ALT (AST) elevation can help in DDx

Severe (>2000 U/L) ALT Elevation
“Short-List” of Causes

1. Acute viral hepatitis
2. Drug induced hepatotoxicity
3. Vascular: ischemia/congestive
4. Autoimmune (infrequent)
5. Acute biliary obstruction (infrequent)
**DDx Mild to Moderate Hepatitis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Clues</th>
<th>First Order Testing</th>
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<tbody>
<tr>
<td>NAFLD</td>
<td>Metabolic syndrome</td>
<td>Abdominal imaging to look for fatty liver</td>
</tr>
<tr>
<td>HCV</td>
<td>Risk factors: Injection drug use, blood transfusion, occupational</td>
<td>Anti-HCV</td>
</tr>
<tr>
<td>Alcohol, drug-toxicity</td>
<td>History of exposure</td>
<td>Abstinence or removal</td>
</tr>
<tr>
<td>HBV</td>
<td>Risk factors: sex, injection drug use, + family hx</td>
<td>HBsAg, anti-HBc</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>Female, other autoimmune conditions</td>
<td>ANA&gt;1:160, anti-smooth muscle Ab &gt;1:40</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>pseudogout, DM, heart dz, + family history</td>
<td>Transferrin saturation &gt;45%, ferritin &gt;200</td>
</tr>
<tr>
<td>Wilson's dz</td>
<td>&lt;40 yrs, neuro or Psy sx, hemolytic anemia, pseudogout</td>
<td>Low ceruloplasmin, high 24 hr Urine copper</td>
</tr>
</tbody>
</table>

**Drug-Induced Liver Injury Classification**

- **Predictable reactions:**
  - Result from direct, dose-related toxicity of the drug or its metabolites; the best example is acetaminophen

- **Idiosyncratic reactions:**
  - Not necessarily dose-related, occur with latencies of weeks to more than a year
  - Can be immune-mediated (allergic) or non-allergic
DILI: Pattern Recognition

<table>
<thead>
<tr>
<th>Pattern of Injury</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Hepatitic         | Immune-mediated: minocycline, phenytoin, dihydralazine, allopurinol  
Non-immune: isoniazid, statins, fibrates, methotrexate |
| Cholestatic       | Immune-mediated: ACE inhibitors, amoxicillin-clavulanic acid, sulfas, sulindac, tricyclic antidepressants  
Non-immune: azathioprine, estrogens, anabolic steroids |
| Steatosis         | Microvesicular: valproate, NRTIs  
Macrovesicular: amiodarone |
| Granulomas        | Allopurinol, amoxicillin-clavulanic acid |
| Vascular          | Estrogens (Budd-Chiari)  
Cyclophosphamide (sinusoidal obstructive syndrome) |

Diagnostic Approach: Suspect DILI

- Careful history taking
  - Med list, over-the-counter drugs, herbs
  - Current and recent exposures
  - Excellent up-to-date resource for DILI: [livertox.nih.gov](http://livertox.nih.gov)

- Diagnosis made by removing suspected drug → resolution of liver test abnormalities
  - Rechallenge establishes causality but rarely done *(and not without risk)*
  - Liver biopsy may be helpful in the evaluation
Management of DILI

- Discontinuation of possible offending drugs
- Laboratory monitoring
  - Including INR, renal function, acid-base status
- Administer specific antidote if available
- Supportive management
  - Monitor of hepatic encephalopathy
- Evaluate for liver transplantation if signs of progressive liver failure/ HE
Cardiac Hepatopathy

- Acute or chronic hepatic injury resulting from cardiopulmonary dysfunction
- Congestive hepatopathy is the consequence of primarily backward heart failure
- Ischemic hepatitis (also called “shock liver” or “hypoxic hepatitis”) is the consequence of forward heart failure

Rabie R. The liver in heart failure. Handbook Liver Disease

Typical Biochemical Profile in Acute vs. Chronic Cardiac Hepatopathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute N=12</th>
<th>Acute on Chronic N=18</th>
<th>Chronic N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST X ULN</td>
<td>30 (1-100)</td>
<td>7.5 (1-150)</td>
<td>1 (1-8)</td>
</tr>
<tr>
<td>ALT X ULN</td>
<td>19 (1-120)</td>
<td>8.0 (1-150)</td>
<td>1 (1-6)</td>
</tr>
<tr>
<td>ALKP X ULN</td>
<td>1.9 (1.7-5)</td>
<td>1.2 (0.5-6)</td>
<td>1.5 (1-13)</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>2.4 (0.8-18.9)</td>
<td>3.4 (0.8-18.1)</td>
<td>1.05 (0.4-7.0)</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.7 (3.3-4.2)</td>
<td>3.3 (2.5-5)</td>
<td>3.5 (2.5-4.8)</td>
</tr>
<tr>
<td>PT (% of N)</td>
<td>53 (10-89)</td>
<td>35 (10-100)</td>
<td>60 (26-100)</td>
</tr>
</tbody>
</table>

- In ischemic and congestive liver injury, AST is typically higher than the ALT

Myhers RP. Hepatology 2003;37:393-400
### Congestive Hepatopathy

- Severity of AST/ALT depends on severity of RHF
- Those with cardiac index <1.5 L/min, 80% have AST/ALT ↑
- In acute congestion, ↑ INR may be seen, that rapidly corrects once congestion resolves
- Hepatomegaly, splenomegaly, ascites and edema may all be present and HE (likely multifactorial) is present in up to 25% with acute heart failure
- Signs of chronic liver disease unless patient has underlying cardiac cirrhosis

### Ischemic Hepatitis = “Shock Liver”

- A well-documented hypotension episode lacking in up to 50% of cases → need high index of suspicious
- Consistent with circulatory compromise, renal dysfunction is commonly seen
- Most cases accompanied by signs of heart failure; renal dysfunction is commonly seen
- Jaundice, is present, is mild (usually <4.5 g/dL)
Ischemic Hepatitis = “Shock Liver”

- ALT/AST ↑ rapidly (within 24-48 hrs of hypotensive event)
- Rapid return once circulatory function restored (3-11 d)
- If ALT >> AST or if there is a significant (>2 X ULN) ALKP, an alternative diagnosis likely
- INR and bilirubin elevations usually mild
- Markedly elevated LDH also

Outcome of Ischemic/Congestive Hepatopathy

- Prognosis dependent upon correction of underlying cardiac compromise
- Jaundice (prolonged elevation bilirubin) is poor prognostic sign in acute and chronic heart failure settings
- Fulminant hepatitis failure with asterixis may occur, typically 2-3 days post circulatory failure, with a lower likelihood of short-term survival
Acute Viral Hepatitis in the Inpatient Setting

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic Testing</th>
<th>Specific Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>HAV IgM</td>
<td>Supportive</td>
</tr>
<tr>
<td>HBV/HDV</td>
<td>HBsAg, HBV DNA</td>
<td>HBV antivirals</td>
</tr>
<tr>
<td>HCV</td>
<td>Anti-HCV, HCV RNA</td>
<td>Supportive, early antiviral therapy if no spontaneous clearance</td>
</tr>
<tr>
<td>HEV</td>
<td>anti-HEV IgM</td>
<td>Supportive, ribavirin</td>
</tr>
<tr>
<td>EBV</td>
<td>Monospot, EBV DNA PCR</td>
<td>Supportive, acyclovir</td>
</tr>
<tr>
<td>CMV</td>
<td>CMV DNA PCR</td>
<td>Valganciclovir</td>
</tr>
<tr>
<td>HSV</td>
<td>HSV DNA PCR</td>
<td>Acyclovir (IV)</td>
</tr>
</tbody>
</table>

Others: dengue, yellow fever, adenovirus, paramyxovirus

Typical Course of HBV Reactivation With Chemotherapy

- HBsAg (+), (n.d.), (+), (+)
- HBeAg (-), n.d., (-), (-)
- HBeAb (+), n.d., (-), (-)
- HBV DNA log.<sub>10</sub> c/mL: Und, 6.0, 8.7, 6.9

"Risk" is highest when immune suppressive therapy is withdrawn

Risks of HBV Reactivation in Patients Receiving Immuno-Modulatory Drugs

- Chemotherapy, includes rituximab
  - HBsAg(+) --> rates of reactivation range from 30-80%
  - HBsAg(-) but anti-HBc(+) --> rates of reactivation = 3-4%
- Anti-TNF drugs – less frequent
  - Incidence not well defined – case reports only
  - Infliximab and adalimumab most frequently reported – reporting bias?

Factors Linked with Risk of HBV “Flare”
During Chemotherapy

- HBV DNA levels
  - Higher risk of flare when serum HBV DNA is detectable
- Type of chemotherapy
  - Rituximab-containing chemotherapy risky
  - Black box warning regarding HBV for anti-TNF drugs
- Age, sex, HBeAg, liver enzymes not consistently predictive

Efficacy of Pre-Emptive Antivirals

HBsAg +ve pts with NHL treated with CHOP
Randomized ‘Pre-emptive’ vs ‘On-Demand’ Lamivudine

- Pre-emptive group - start LAM 1 day prior to CHOP
- On-demand - start LAM if ALT>1.5 x ULN
Prophylactic Antiviral Therapy

- **Initiation of treatment**
  - Should be started at same time or 1 week before initiating immune modulatory drug
  - Choice of drug should be guided by HBV DNA level and anticipated duration of use
    - Use ETV or TDF if high viral load
    - LMV can be used if HBV DNA low (≤10^3 IU/mL)

- **Duration of treatment**
  - Continue for 6-12 months after last dose of immune modulatory drug
  - If active HBV disease → treatment per usual guidelines

Management of HBV Reactivation

1. Start antiviral therapy as soon as diagnosis made
   - Entecavir or tenofovir good choices
     - Adjust to renal function
     - Follow HBV DNA levels to assess response

2. Monitor liver function (INR, total bilirubin) and mental status
   - If rising INR or HE, consider evaluation for LT

3. Advise on schedule of subsequent IMS treatment to liver status and achievement of viral load decline
Pre-Op Evaluation of Patient with Cirrhosis

- Provide assessment of morbidity and mortality risk to guide discussions with patients and their families
- If elective surgery, determine need for LT evaluation pre-procedure or deferral until post-LT
- Determine need for prophylactic therapies
  - Beta blockers or EGD for varices
- Advise on cytopenia management, fluids and infection monitoring
- Coordination with anesthesia for optimization of intraoperative management

Cirrhotic Patient Undergoing Surgery

- Risk of mortality predicted by severity of cirrhosis
- Mortality associated with portosystemic shunts and other intraabdominal surgery in cirrhotics:
  - 10% if CP-A, 17-30% if CP-B and 63-82% if CP-C
- Other factors:
  - Cardiopulmonary comorbidities
  - Higher ASA physical status classification
  - Type of surgery, emergency (vs elective surgery
  - Older age
- Mayo Post-Operative Mortality Risk
Operative Risk in Cirrhosis

- ASA is best predictor of early (<7 d) mortality
  - ASA class V likely will die within 7 d of surgery
- MELD is best predictor of mortality > 7 days
  - For each 1-point increase in MELD (> 8), 30 and 90-day mortality increases by 14%
  - If MELD < 8, risk is low and pre-op LT evaluation probably not necessary
  - If MELD ≥16, risk is high (55% at 90 d) and elective surgery should be deferred until post-LT

Predicting Post-Op Mortality In Cirrhotic Patients

## Cirrhosis Severity and Estimated Post-Operative Mortality

<table>
<thead>
<tr>
<th>MELD</th>
<th>7 day Mortality (%)</th>
<th>30-day Mortality (%)</th>
<th>90-day Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7</td>
<td>1.9</td>
<td>5.7</td>
<td>9.7</td>
</tr>
<tr>
<td>8-11</td>
<td>3.3</td>
<td>10.3</td>
<td>17.7</td>
</tr>
<tr>
<td>12-15</td>
<td>7.7</td>
<td>25.4</td>
<td>32.3</td>
</tr>
<tr>
<td>16-20</td>
<td>14.6</td>
<td>44.0</td>
<td>55.8</td>
</tr>
<tr>
<td>21-25</td>
<td>23.0</td>
<td>53.8</td>
<td>66.7</td>
</tr>
<tr>
<td>≥26</td>
<td>30.0</td>
<td>90.0</td>
<td>90.0</td>
</tr>
</tbody>
</table>

*Source: Gastroenterology 2007;132:1261-9.*

### Inpatient with Abnormal Liver Tests

**Key Aspects**

- Acute or pre-existing chronic
- Hepatitic or cholestatic pattern or mixed
- Severity and rate of change
- Presence of co-morbidities
- Presence or absence abnormal imaging
- Presence or absence of decompensation
  - Especially hepatic encephalopathy