This Morning's Presentation

- Clinical vignettes representing a few of the most common reasons for an outpatient Hepatology consult request.
- Brief discussion of a suggested approach for the primary care provider.
- Summary algorithms for the primary care provider caring for patients with abnormal liver tests.

What is the most likely cause of this patient’s elevated liver transaminases?

1. Primary biliary cirrhosis.
2. Autoimmune hepatitis.
3. Non-alcoholic fatty liver (NAFL).
4. Medications or alcohol.
5. Cholelithiasis.

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Approach to the Patient with Abnormal Liver Tests

• Classify the abnormality
  – Primarily hepatocellular or biliary injury?
  – Is there massive hepatocellular injury?
  – Is there evidence of functional abnormality?
• Consider the differential diagnosis
  – Most common, most treatable
• Perform a diagnosis specific evaluation
  – History, diagnostic testing and intervention
• Refer for specialty consultation as needed

Classifying the Abnormality

• Primarily hepatocellular or biliary injury?
  – AST & ALT
  – Alk phos, GGT, bilirubin
• Is there massive hepatocellular injury?
  – AST & ALT > 1000
• Is there evidence of functional abnormality?
  – Symptoms/signs, PT INR, albumin, bilirubin

Classify the Abnormality

50 y.o. asymptomatic woman with incidental finding of ALT and AST in the 80’s. T bili, alk phos, albumin, coags, and CBC normal. Viral serologies negative. Would like assistance with diagnosis.

• Isolated hepatocellular injury
• Mild hepatocellular injury
• No evidence of functional abnormality

Interpretation:
Incidental finding, likely chronic, there is little immediate concern.

Consider Differential Diagnosis: Isolated Modest ↑ AST & ALT

Most Common
• NAFL
• Drugs and toxins
• Viral hepatitis

Less Common
• Hereditary hemochromatosis
• Autoimmune hepatitis
• Other genetic disorders
• Vascular disorders

Diagnosis Specific Evaluation: Isolated Modest ↑ AST & ALT

• Viral hepatitis (hepatitis C & B)
  – Risk factors for vertical, blood, or sexual acquisition
  – HBsAg, anti-HCV
• Drugs and toxins (EtOH & most medications)
  – Use history
  – Improvement with discontinuation
• Non-alcoholic fatty liver (10-25% of U.S.)
  – Dx of exclusion
  – Associated with obesity, lipids, & type II diabetes: BMI (>27), lipid panel, fasting glucose or Hgb A1c
  – Liver ultrasound (hyperechogenicity in ~90%)
  – Possible response to Rx of underlying risk factor(s)

Dx Specific Evaluation: Isolated Modest ↑ AST & ALT

• Hereditary hemochromatosis
  – Co-morbidities (heart disease, diabetes)
  – Family history
  – Iron saturation (>45%) & ferritin (>450)
  – HFE mutation analysis (C282Y, H63D)
• Autoimmune hepatitis
  – Other autoimmune processes
  – Anti-nuclear Ab, anti-smooth muscle Ab (>1:160)
  – Elevated serum IgG levels
What would be the single most important test to order now?
1. HCV PCR.
2. Acetaminophen level.
3. Antinuclear antibody.
4. Prothrombin time (INR).
5. Abdominal ultrasound.

A Few Corollary Points
- Advise total abstinence from ethanol.
- Metformin is not hepatotoxic, but can cause fatal lactic acidosis in patients with poor liver or kidney function.
- Cardiovascular benefits of statins almost certainly outweigh the hepatic risks.
- Recommendations for glitazones are in flux.
Classify the Abnormality

Previously healthy 35 y.o. man with 1 wk of malaise, fatigue, anorexia, and nausea. AST 1200, ALT 1400, t bili 2.0, alk phos 220. Please help with management.

- Primarily hepatocellular injury
- Massive hepatocellular injury
- Evidence of functional abnormality is uncertain

Interpretation:

Evidence of Functional Abnormality

Evidence of Functional Abnormality

Hepatic dysfunction raises concern about possible fulminant hepatic failure, a clinical syndrome characterized by:
- Rapid development of hepatocellular dysfunction.
- Encephalopathy within 8 weeks of illness.
- The absence of a prior history of liver disease.

Evidence of Functional Abnormality

- √ Mental and cardiovascular status
- √ Prothrombin time (INR)
  - liver synthesizes coagulation factors, except VIII
  - influenced by vitamin K dependent factors
  - short half-life (6 hrs for factor VII)
- √ Bilirubin
  - produced as a breakdown product of hemoglobin
  - conjugated and excreted by the liver
- √ Albumin (Alb)
  - synthesized by liver, but dependent on nutrition & pathological losses
  - 3 week half-life

Prognosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Indicator</th>
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<tbody>
<tr>
<td>Patients Without Acetaminophen Toxicity</td>
<td>1 (≥ 55%, acidosis = 95% mortality)</td>
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<tr>
<td>Location</td>
<td>Cystic or ductal origin</td>
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<tr>
<td>Age</td>
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<td>Duration of jaundice</td>
<td>&gt; 1 week before development of encephalopathy</td>
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<td>Serum bilirubin concentration</td>
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<td>Prothrombin time</td>
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<td>Patients with Acetaminophen Toxicity</td>
<td>2 (≥ 95%, acidosis = 95% mortality)</td>
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<td>Arterial pH</td>
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<td>Prothrombin time</td>
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<tr>
<td>Serum creatinine</td>
<td>&gt; 3.4 mg/dL</td>
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</tbody>
</table>

Yee and Lidsky in Sleisenger & Fordtran 2002

Consider Differential Diagnosis:
AST & ALT >1000

Hal’s “Rule of 5”
- Viral Hepatitis (A, B, C, D, E, other)
- Medications
- Autoimmune hepatitis
- Acute biliary obstruction
- Hepatic vascular compromise

Diagnosis Specific Evaluation:
AST & ALT >1000

- Viral Hepatitis (A, B, C, other)
  - Risk factors for exposure
    - √ HAV IgM, HBsAg, HBeAg, HBeAb, HCV PCR
- Medications
  - Use history
  - Dose dependent v. idiosyncratic
    - Acetaminophen level, toxicology screen
- Autoimmune hepatitis
  - Anti-nuclear Ab, anti-smooth muscle Ab (≥ 1:160)
  - Elevated serum IgG levels
**Diagnosis Specific Evaluation: AST & ALT >1000**

- **Acute biliary obstruction**
  - Primarily choledocholithiasis
  - Associated with pain, fever, jaundice
  - Biliary imaging (U/S, CT, MRCP, ERCP)
- **Hepatic vascular compromise**
  - Mainly shock liver
  - Consistent history
  - Vascular imaging (U/S, MRA, angiogram)

**A Few Corollary Points**

- Hepatitis C very rarely causes such a high elevation in AST & ALT.
- Ethanol does not cause such elevations.
- Recommended doses of acetaminophen can cause such elevations, especially in the setting of malnutrition and alcohol use.
- Resolution of AST & ALT within days suggests biliary obstruction and vascular compromise as causes.

**What single test would most help your management?**

1. Liver transaminases.
2. Prothrombin time (INR).
3. HBcIgM.
4. Abdominal ultrasound.
5. HBV viral load.

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Classify the Abnormality

32 y.o. asymptomatic woman of Chinese descent found to be HBsAg + at prenatal screening exam. Would like to refer for management during pregnancy and treatment of hepatitis B.

- Patients with hepatitis B are classified by their replication status (presence of serum HBeAg or HBV DNA).
- HBV treatment is only indicated if there is active viral replication.
- Presence of active viral replication is associated with increased infectivity and risk of developing cirrhosis or liver cancer.

HBV and Pregnancy

- HBV screening is recommended for pregnant women at the first prenatal visit.
- No HBV medications have been approved for use in pregnant women.
- Amniocentesis and chorionic villus sampling are not specifically contraindicated in patients with hepatitis B.

HBV and Pregnancy

- Infants should receive HBV vaccination shortly after birth, then at 1-2 months and 6 months.
- Babies born to women infected with HBV should also receive HBV immune globulin ideally within 12 hours of birth.
- Breast feeding is NOT contraindicated for HBV infected moms.

Viral Hepatitis

- Always consider the possibility of HIV co-infection before treating for HBV.
- ~90% of those infected with HBV as adults will clear the virus.
- ~90% of those infected with HBV perinatally will develop chronic infection.
- HBV is a “reportable” infection.
Decompensating cirrhosis

55 y.o. man with hep C & remote heavy alcohol use. New lower extremity edema. AST 75, ALT 90, Alk phos 120, bili 2.0, PT INR 1.5, Platelets 75 & alb 3.2. Please assess candidacy for liver transplantation.

How is priority for liver transplantation determined?

2. Prothrombin time (INR).
3. MELD score.
4. Liver biopsy.
5. Severity of ascites and varices.
## Consider Differential Diagnosis: Cirrhosis

**Final Common Pathway for:**
- Viral hepatitis (e.g., HBV, HCV)
- Toxin exposure (e.g., alcohol, methotrexate)
- Metabolic (e.g., NASH, HHC, Wilson’s)
- Autoimmune (e.g., AIH)
- Cholestatic (e.g., PBC, PSC, stricture)
- Vascular (e.g., CHF, Budd-Chiari)

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## Indications for Liver Transplantation

- Fulminant liver failure (acute liver failure + altered mental status)
- Complications of end-stage liver disease (variceal bleeding, hepatic encephalopathy, ascites, hepatorenal syndrome)
- Hepatocellular carcinoma
- Hepatopulmonary syndrome
- Polycystic liver disease
- Metabolic diseases (Familial amyloidosis, primary oxaluria, glycogen storage disease, MSUD)

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## Contraindications for liver Transplantation

**Absolute Contraindications**
- Extrahepatic malignancy & cholangiocarcinoma
- Untreated AIDS
- Severe, uncontrolled systemic infection
- Multiorgan failure
- Advanced cardiopulmonary disease
- Irreversible, advanced brain damage
- Active substance abuse
- Lack of psychosocial support
- Inability to comply with treatment regimen
- Lack of proper medical insurance

**Relative** Contraindications
- HIV seropositivity/AIDS on HAART
- Methadone maintenance
- Stage 3+ hepatocellular carcinoma
- Re-transplantation for end-stage recurrent hepatitis C
- Morbid obesity
- Severe physical deconditioning

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## Listing and Allocation Criteria

- Fulminant liver failure (Status I)
  - Acute, new-onset liver failure with mental status change
- End-Stage Liver Disease
  - **Listing**: Minimal listing Criteria: MELD score ≥ 10
  - **Allocation**: MELD Score
- HCC
  - **Milan Criteria** (Mod. Stage 2)
  - **MELD Exception Points**
- Metabolic and cystic diseases
  - Special petition

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## MELD: Model for End-stage Liver Disease

- **MELD Risk Score** = 10 x [0.957 x log e (creatinine mg/dL) + 0.378 x log e (bilirubin mg/dL) + 1.120 x log e (INR)] + 6.43
- Minimum values for creatinine, bilirubin and INR = 1.0. Creatinine maximum value = 4.0 (actual or default on dialysis)
- Score rounded to the nearest integer (range 6 - 40)
MELD

• Advantages
  – Objective
  – Works reasonably well to represent expected 3-month mortality

• Disadvantages
  – Under-represents risk in some patients
    • Hepatic encephalopathy, refractory ascites
  – Does not represent impact of disease on quality of life
  – Geographic disparity in average MELD score for receiving a transplant

MELD Score

Google: MELD calculator
www.unos.org/resources/MeldPeldCalculator.asp

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<th>age</th>
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</tr>
</tbody>
</table>

Management of the Cirrhotic Patient

• If feasible treat underlying disease
• Survey for progression of cirrhosis
• Symptomatic treatment of complications
• Consider screening for liver cancer
• Refer for disease-specific treatment, help with refractory complications, and evaluation for liver transplant.

A Few Corollary Points

• If you choose to screen for liver cancer with a liver ultrasound every 6 months, then AFP testing may not be necessary.
• Any patient with a history of regular heavy ethanol use should attend AA or a similar program.
• An early referral for transplant is better than a late referral.

References

• Sleisenger and Fordtran’s Gastrointestinal and Liver Disease, 8th Edition; Edited by Feldman, Friedman, and Brandt, 2006.