Approach to Abnormal Liver Tests
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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.

Case 1: Abnormal liver tests
- 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.

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.
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

Classify the Abnormality

• Primarily hepatocellular or biliary injury?
  – AST & ALT v. Alk phos, GGT, bilirubin

• Is there massive hepatocellular injury?
  – AST & ALT > 1000

• Is there evidence of functional abnormality?
  – Symptoms/signs, INR, albumin, bilirubin

Classify the Abnormality

• 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

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.
**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)

- **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

**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
Case 2: Abnormal Liver Tests

- 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.

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.

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:
Severe acute hepatitis.
Needs prompt assessment of liver function.

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
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.

Prognosis in Fulminant Hepatic Failure

- Acetaminophen induced
  - Arterial pH < 7.3
  OR
  - Creatinine > 3.4, INR > 6.5, and Grade 3-4 Encephalopathy
- Non-Acetaminophen induced
  - INR > 6.5
  OR
  - 3 of following
    - INR > 3.5, > 1 wk jaundice to HE, TB > 18, age (< 10, > 40), indeterminate/drug induced etiology

Then 95% mortality without transplantation

Consider Differential Diagnosis:

AST & ALT > 1000

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

Consider Differential Diagnosis:

AST & ALT > 1000

“Rule of 5”
- Viral Hepatitis (A, B, C, D, E, other)
- Medications/Toxins
- Hepatic vascular compromise
  - Autoimmune hepatitis
  - Acute biliary obstruction
Diagnosis Specific Evaluation: AST & ALT >1000

- Viral Hepatitis (A, B, C, other)
  - Risk factors for exposure
  - HAV IgM, HBsAg, HBcIgM, 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

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.
Case 3: HBV

- 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.

What single test would most help your management?

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

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 (HBV DNA and eAg)
- 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.
**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.

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**A Few Corollary Points**

- 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.

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**Case 4: Advanced Liver Disease**

- 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, 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.

Classify the Abnormality

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, INR 1.5, Platelets 75 & alb 3.2. Please assess candidacy for liver transplantation.

- Primarily hepatocellular injury
- Modest hepatocellular injury
- Evidence of functional abnormality

Interpretation:
Chronic liver disease with probable decompensated cirrhosis.

Diagnosis of Cirrhosis

- Liver histology remains the gold standard for the diagnosis of cirrhosis.
- However, obtaining liver tissue is invasive, and contraindicated in many patients with cirrhosis.
- Therefore, cirrhosis is frequently a clinical diagnosis.

Consider Differential Diagnosis: Cirrhosis

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

- Fulminant liver failure
- Complications of end-stage liver disease
- Hepatocellular carcinoma
- Hepatopulmonary syndrome
- Polycystic liver disease
- Metabolic diseases
  (Familial amyloidosis, primary oxaluria, glycogen storage disease)

Contraindications for Liver Transplantation

Absolute Contraindications

- Extrahepatic malignancy
- 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

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
MELD: Model for End-stage Liver Disease

- MELD Risk Score = 10 \times [0.957 \times \log e (\text{creatinine mg/dL}) + 0.378 \times \log e (\text{bilirubin mg/dL}) + 1.120 \times \log e (\text{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 Score

Google: MELD calculator

www.unos.org/resources/MeldPeldCalculator.asp

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MELD Based Allocation

- 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

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
