Session 11: The ABCs of LFTs

Learning Objectives

1. Define 3 key components of the patient history that should be further evaluated when liver function testing reveals elevated aminotransferases.
2. Identify at least 3 laboratory tests that should be considered in a patient with an ALT value that is 3 times the upper normal limit.
Session 11

The ABCs of LFTs

Faculty

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Faculty Financial Disclosure Statement
The presenting faculty reports the following:

Dr Germino has no financial relationships to disclose.
Faculty Disclosures

- Dr. Germino has no financial relationships to disclose.

Learning Objectives

- Define 3 key components of the patient history that should be further evaluated when liver function testing reveals elevated aminotransferases.
- Identify at least 3 laboratory tests that should be considered in a patient with an ALT value that is 3X the upper normal limit.

Q1. Pre-Audience Response Question

Which of the following is/are TRUE?

1. Abnormal LFTs are often seen in asymptomatic patients
2. Liver damage can be present even though LFTs are within normal limits
3. 20% of normal patients have LFTs outside the normal range
4. All of the above
5. 1 and 2 only

Q2. Pre-Audience Response Question

Risk factors for non-alcoholic fatty liver disease (NAFLD) include:

1. Obesity
2. Diabetes
3. Jejuno-ileal bypass surgery
4. All of the above
5. 1 and 2 only

Q3. Pre-Audience Response Question

Which of these findings suggest alcohol abuse?

1. AST:ALT ratio >2:1
2. AST > 8X normal
3. Pyridoxal 5-phosphate deficiency
4. All of the above
5. 1 and 3 only
Case 1: Debra, 48-year-old female

- Comes to the office for routine annual checkup
- No current complaints
- Past medical history:
  - Hypertension
  - Dyslipidemia
  - Obesity
- No allergies
- Medications: HCTZ, simvastatin, acetaminophen prn joint pain

Exam:
- 144/86 mm Hg, 72 regular, 14
- BMI: 36
- HEENT: no icterus
- Lungs: clear
- Heart: regular, no murmurs
- Abdomen: soft, nontender, no organomegaly
- Extremities: no edema

Debra

- Labs:
  - ALT: 74 U/L (normal 9-52)
  - AST: 48 U/L (normal 14-36)
  - Total bilirubin: 0.3 mg/dL (normal 0.2-1.2)
  - Total cholesterol: 202 mg/dL (normal 120-199)
  - LDL cholesterol: 112 mg/dL (normal 60-129)
  - HDL cholesterol: 31 mg/dL (normal >39)
  - Triglycerides: 245 mg/dL (normal <150)
  - Fasting glucose: 119 mg/dL (normal 70-99)

Question

Which of the following causes of abnormal LFTs should be initially considered?

1. Statin hepatotoxicity
2. Alcohol use
3. Acetaminophen use
4. NASH
5. All of the Above

Prevalence of Abnormal LFTs

% of U.S. Population

Initial Evaluation of Abnormal LFTs

- Repeat the test to confirm the result
- 5% of normal patients have results outside the "normal range"
- LFTs elevations correlate with BMI
- Normal range varies among laboratories
- Physiologic changes
  - Alkaline phosphatase elevated in 3rd trimester of pregnancy
Commonly reported LFTs

- Enzymes
  - Aspartate transaminase or aminotransferase (AST, SGOT)
  - Alanine transaminase or aminotransferase (ALT, SGPT)
  - Alkaline phosphatase (ALP)
  - Gamma-glutamyl transpeptidase (GGT)
- Synthetic Function
  - Albumin
  - Prothrombin time
- Bilirubin

Initial Evaluation of Abnormal LFTs

- Physical Examination
  - Muscle wasting
  - Stigmata of chronic liver disease
    - Spider nevi, palmar erythema, gynecomastia, caput medusae
  - Lymphadenopathy
  - Jugular venous distension
  - Pleural effusion

Audience Response Question

What is the most common cause of abnormal LFTs in the U.S. primary care population?

1. Viral hepatitis
2. Fatty liver
3. Statin use
4. Strenuous exercise

Abnormal LFTs—Most Common Causes in U.S.

- Fatty liver
  - Nonalcoholic fatty liver disease (NAFLD)
    - Prevalence ~30%
  - Nonalcoholic steatohepatitis (NASH)
- Alcoholic liver disease
- Viral hepatitis (chronic HBV and HCV)

Causes of Chronically Elevated ALT Levels

- Hepatic causes
  - NASH
  - Alcohol abuse
  - Infectious hepatitis
  - Autoimmune hepatitis
  - Hemochromatosis
  - Wilson’s disease
  - Alpha1-antitrypsin deficiency
- Nonhepatic causes
  - Celiac disease
  - Inherited disorders of muscle metabolism
  - Acquired muscle diseases
  - Strenuous exercise

Evaluation of Chronic ALT Elevation

Step 1
- Review medications, herbal therapies, or recreational drugs
- Screen for alcohol abuse
- Obtain serology for Hepatitis B and C
- Screen for hemochromatosis
- Evaluate for fatty liver

Evaluation of Chronic ALT Elevation

Step 2
- Exclude muscle disorders
- Obtain thyroid function tests
- Consider celiac disease
- Consider adrenal insufficiency

Step 3
- Consider autoimmune hepatitis
- Consider Wilson’s disease
- Consider α1-antitrypsin deficiency

Step 4
- Obtain a liver biopsy
- Consider observation
  - if ALT, AST only mildly elevated

Transaminase Levels in Alcohol Abuse

- Diagnosis supported by AST:ALT of at least 2:1
  - Alcohol-related deficiency of pyridoxal 5-phosphate
  - Low serum activity of ALT
- Gamma-glutamyltransferase twice normal with AST:ALT of at least 2:1 strongly suggests diagnosis
  - GGT not specific
- Rare for AST > 8X normal value
- Rare for ALT > 5X normal value

Medications and Elevated LFTs

<table>
<thead>
<tr>
<th>Selected Drugs/Substances Associated With LFT Elevations</th>
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<tbody>
<tr>
<td>acetaminophen</td>
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<tr>
<td>omeprazole</td>
</tr>
<tr>
<td>antifungals, INH</td>
</tr>
<tr>
<td>lisinopril, losartan</td>
</tr>
<tr>
<td>glipizide</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>allopurinol</td>
</tr>
<tr>
<td>risperidone</td>
</tr>
<tr>
<td>bupropion</td>
</tr>
<tr>
<td>SSRIs, trazadone</td>
</tr>
<tr>
<td>kava kava; germander, ephedra, PCP, anabolic steroids, cocaine, shark cartilage, senna ecstasy, glues/solvents</td>
</tr>
<tr>
<td>DPH, valproate, carbamazepine</td>
</tr>
<tr>
<td>statins</td>
</tr>
</tbody>
</table>

- Almost any drug can be a cause
- Stop medication and determine if LFTs normalize

Drug-Related Transaminase Elevations

Acetaminophen
- 4 gm/day for 5-10 days caused elevated transaminases in >50% healthy non-drinkers
- Alcohol can potentiate hepatotoxic effects

Statins
- Frequently cause elevated transaminases, but significant hepatotoxicity is rare
- Transaminase elevations usually resolve spontaneously
- May be used safely in persons with chronic liver disease
Testing for Other Causes of Abnormal Transaminases

| Autoimmune Hepatitis | Serum Protein Electrophoresis  
| | ANA  
| | Anti-Smooth Muscle ABs  
| | Liver-Kidney Microsomal ABs  
| Hemochromatosis | Serum Iron  
| | TIBC  
| | HFE Genetic Testing  
| Wilson’s Disease | Serum Ceruloplasmin  
| | Ophthalmology Exam  
| | 24-hour Urine Copper Excretion  
| α1-Antitrypsin Deficiency | Serum α1-Antitrypsin Level  

Nonhepatic Causes of Abnormal Transaminases

- Celiac disease
- Muscle disorders
  - Inborn errors of metabolism
  - Polymyositis
  - Strenuous exercise
- Thyroid disorders
- Adrenal insufficiency
- Anorexia nervosa

Back to Debra

- Denies significant alcohol or acetaminophen use
- Viral serologies are negative
- Repeat LFTs after statin discontinued: unchanged
- Ultrasound: fatty liver
  - Diagnosis: NASH

The Spectrum of NAFLD

NAFLD encompasses range of liver diseases resulting from fatty infiltration in hepatocyte:
- Simple fatty liver with no inflammation
- 3-6% progress to steatohepatitis with inflammation (NASH)
- Scarring (fibrosis)
- Cirrhosis

Nonalcoholic Fatty Liver Disease
NASH

Mallory body

Pericellular Fibrosis

Liver biopsy is required to confirm a diagnosis or to stage the disease

Nonalcoholic Fatty Liver Disease

- Hepatomegaly is the most common physical finding
- Serum AST and ALT levels are often elevated to 1-4 x the upper limit of normal
- The AST:ALT ratio is usually < 1

Pathogenesis of Nonalcoholic Fatty Liver Disease

Risk Factors for NAFLD

- Most strongly associated with obesity; dyslipidemia, HTN, glucose intolerance are also risk factors
  - NAFLD may be considered hepatic component of metabolic syndrome
- Obstructive sleep apnea
- Medications (e.g., nucleoside analogs)
- Jejunoleal bypass
- Severe rapid weight loss
- Lipodystrophic syndromes

Management of NAFLD

- NASH can progress to cirrhosis in some patients
- Modification of risk factors, such as obesity, hyperlipidemia, and proper diabetic control
- Hepatitis A and B vaccinations
- Hyperlipidemia should be treated with statins
- Weight loss is the only therapy with reasonable evidence supporting benefit
- Multiple other drugs have been studied, but most trials have been too short to determine impact on important clinical outcomes

Case 2: William, 32-year-old male

- Presents to office because of abnormal LFTs on Life Insurance physical
- No current complaints
- Past Medical History: None
- Medications: None
- Social History: Prior history of IVDA; smokes 1 PPD; drinks alcohol 3-4 days/week; multiple sexual partners in past

William

- Exam:
  - 128/76 mm Hg, 72 regular, 14
  - BMI: 23
- HEENT: no icterus
- Lungs: clear
- Heart: regular, no murmurs
- Abdomen: soft, nontender, no organomegaly
- Extremities: no edema

Labs:
- ALT: 74 U/L (normal 9-52)
- AST: 64 U/L (normal 14-36)
- Total bilirubin: 0.9 mg/dL (normal 0.2-1.2)
- Total cholesterol: 184 mg/dL (normal 120-199)
- LDL cholesterol: 100 mg/dL (normal 60-129)
- HDL cholesterol: 42 mg/dL (normal >39)
- Triglycerides: 133 mg/dL (normal <150)
- Fasting glucose: 101 mg/dL (normal 70-99)

Question

Which of the following causes of abnormal LFTs should be initially considered?

1. Hepatitis B virus
2. Hepatitis C virus
3. Alcohol abuse
4. All of the above

Hepatitis B Serology

HBsAg: hepatitis B surface antigen
  - Marker of active infection
  - Chronic HBV: HBsAg positive for at least 6 months
  - Marker of immunity to hepatitis B
HBsAb: antibody to HBsAg
  - Marker of present or past infection
HBeAg: hepatitis B “e” antigen
  - Surrogate marker of high viral load
Anti-HBe: antibody to HBeAg
  - Inactive carrier state
HBV DNA: active viral replication

Worldwide Prevalence of Hepatitis B
Incidence of Acute, Symptomatic Hepatitis B by Age Group – United States, 1990 - 2008

Adapted from National Notifiable Diseases Surveillance System (NNDSS). 

Hepatitis B

Risk Factors
- Multiple sex partners
- IDU
- MSM
- Sex contact
- Household
- Other

Hepatitis C Infection

- Risk factors
  - Blood transfusions
  - IVDA
  - High-risk sexual behavior
  - Cocaine
  - Tattoos
  - Body piercing

Hepatitis B Virus Serology

Acute Hepatitis B Virus Infection with Recovery Typical Serologic Course

Hepatitis B Virus Serology

http://pathmicro.med.sc.edu/virol/hepb-cd1.gif

Hepatitis B Chemistry Profiles

<table>
<thead>
<tr>
<th>Marker</th>
<th>Immune Tolerant</th>
<th>HBeAg</th>
<th>CHB</th>
<th>Inactive HbsAg Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAg</td>
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<tr>
<td>HBeAg</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>HBV DNA (copies/mL)</td>
<td>&gt; 10^5</td>
<td>&gt; 10^5</td>
<td>&lt; 10^3</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Normal/Active</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hepatitis C – Incidence in United States

Hepatitis C - Diagnostic Testing

- Serologic Testing
  - 92-97% sensitivity
- Serum Hepatitis C Virus RNA for confirmation
- If positive – consider liver biopsy to assess severity

Hepatocellular carcinoma in chronic HCV

Case 3: Steven, 21-year-old male

- Found to have elevated total bilirubin level with fasting blood work
  - Total bilirubin: 1.9 mg/dL (normal 0.2-1.2)
  - Direct bilirubin: 0.1 mg/dL (normal 0.0-0.4)
- No current symptoms
- No significant past medical history
- Medications: none
- Social History: No T/A/D abuse

Question

Which of the following mechanisms cause unconjugated hyperbilirubinemia?

1. Overproduction of bilirubin
2. Reduced bilirubin uptake
3. Impaired bilirubin conjugation
4. All of the above

Question

Which of the following regarding cholestatic liver disease is/are TRUE?

1. Choledocholithiasis is the most common cause of extrahepatic cholestasis
2. Drug induced cholestasis usually is reversible after elimination of the offending drug
3. Viral hepatitis can present as cholestatic liver disease
4. All of the above
5. None of the above

Causes of Hyperbilirubinemia

- Unconjugated
  - Gilbert's syndrome
  - Heart Failure
  - Medications
  - Crigler-Najjar syndrome
  - Hemolysis
  - Hyperthyroidism
  - Cirrhosis
  - Wilson's Disease

- Conjugated
  - Choledocholithiasis
  - Cholangiocarcinoma
  - Sclerosing Cholangitis
  - AIDS cholangiopathy
  - Pancreatitis
  - Strictures
  - Parasitic Infections
  - Viral Hepatitis
  - Alcoholic hepatitis
  - NASH

  - Primary Biliary Cirrhosis
  - Medications
  - Sepsis
  - Infiltrative diseases
  - Total Parenteral Nutrition
  - Pregnancy
  - End-state Liver Disease

Gilbert's Syndrome

- Common genetic disorder
- 3-7% of the population
- Males > Females
- Impaired conjugation of bilirubin
  - Reduced UDP glucuronosyl transferase activity
- Mild hyperbilirubinemia (usually less than 3 mg/dL)
  - Indirect unconjugated
  - Higher with illness or fasting
- No specific therapy
Diagnosis of Gilbert’s Syndrome

- Unconjugated hyperbilirubinemia on repeated testing
- Normal complete blood count, blood smear, and reticulocyte count and normal liver function tests (plasma aminotransferrases and alkaline phosphatase concentrations)
- No changes in 12 to 18 months

Evaluation of Elevated Alkaline Phosphatase Levels

- Sources
  - Liver
  - Bone
  - Placental
    - Women in 3rd trimester of pregnancy
  - Blood type O or B
    - Levels may increase after fatty meal

Elevated Alkaline Phosphatase Levels

American Gastroenterological Association
Evaluation of Liver Chemistry Tests

AGA Recommendation: Mild Elevations of ALT or AST (<5 X Normal)

AGA Recommendation: Elevated Bilirubin
**AGA Recommendation:**

**Elevated Alkaline Phosphatase**

Adapted from *Gastroenterology*. 2002;123:1364-1366.

**Etiology is not hepatobiliary**

<table>
<thead>
<tr>
<th>Elevated ALT evaluation</th>
<th>Liver biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUQ ultrasound to assess ductal dilatation</td>
<td></td>
</tr>
</tbody>
</table>

- **Normal bilirubin, ALT, AST**
- **γ-GT or 5'-nucleotidase**
- **No ductal dilation**
- **Liver biopsy**
- **Elevated alkaline phosphatase > 6 months**

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**Post Audience Response Questions**

**Q1. Post-Audience Response Question**

Which of the following is/are TRUE?

1. Abnormal LFTs are often seen in asymptomatic patients
2. Liver damage can be present even though LFTs are within normal limits
3. 20% of normal patients have LFTs outside the normal range
4. All of the above
5. 1 and 2 only

**Q2. Post-Audience Response Question**

Risk factors for non-alcoholic fatty liver disease (NAFLD) include:

1. Obesity
2. Diabetes
3. Jejuno-ileal bypass surgery
4. All of the above
5. 1 and 2 only

**Q3. Post-Audience Response Question**

Which of these findings suggest alcohol abuse?

1. AST:ALT ratio >2:1
2. AST > 8X normal
3. Pyridoxal 5-phosphate deficiency
4. All of the above
5. 1 and 3 only