Practical Approach to Abnormal Liver Chemistries

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CONTRA COSTA REGIONAL MEDICAL CENTER
NOON CONFERENCE SERIES

DISCLOSURE OF CONFLICT OF INTEREST

- Speaker has nothing to disclose
“Liver Function” Tests

• Aminotransferases: ALT/AST
• Bilirubin
• Alkaline phosphatase
• GGTP (Gamma-glutamyltransferase)
• Albumin
• Prothrombin time
• Platelet count
“Liver Function” Tests

• A misnomer
  – Elevated aminotransferases/alkaline phosphatase are markers of liver injury, not liver function
  – Albumin/Bili/PT can be affected by extrahepatic factors
    • nutritional state
    • hemolysis
    • antibiotic use
  • Poor sensitivity and specificity for liver disease
Three Categories

• Markers of Hepatocyte Injury/Necrosis
  – AST/ALT

• Markers of Cholestatic Liver Disease
  – Bilirubin/AP/GGTP

• Markers of Liver Functional Reserve
  – Albumin/INR/Platelet Count
Markers of Hepatocellular Injury: Aminotransferases

- Serum aminotransferases are sensitive indicators of liver cell injury
- **AST** - (aspartate aminotransferase) liver >> heart > skeletal muscle > kidneys, brain, RBCs
- **ALT** – (alanine aminotransferase) more specific to liver, low concentrations also in kidney and skeletal muscles.
- Normal AST/ALT = 0.8
- AST > ALT occurs in setting of ETOH excess and advanced fibrosis/cirrhosis
- ALT elevation is a scalable indicator of increased liver and general mortality
Marker of Cholestasis: Alkaline Phosphatase

- **ALP** – predominate source = liver and bone (placenta, kidneys, intestines)
- Hepatic ALP present on surface of bile duct epithelia
- Elevated in the setting of infiltrative disease, biliary obstruction, or rising bile acids
- Takes time for induction of enzyme levels so may not be first enzyme to rise with acute biliary obstruction: half-life is 1 week.
- Gamma GT may be useful to evaluate the origin of ALP
Markers of Hepatocellular Injury: Gamma-GT

- **Gamma-GT** – hepatocytes and biliary epithelial cells, pancreas, renal tubules and intestine.
- Not present in bone
- Raised in virtually *ANY* liver disease, hepatocellular, cholestatic, and drug-induced
- Very sensitive but non-specific
  - A twofold elevation of the GGT in patients whose AST/ALT ratio is greater than 2:1 strongly suggests alcohol abuse
- Isolated GGT increase does not require any further evaluation, monitor periodically and investigate only if other LFT’s become abnormal
Bilirubin

- Bilirubin is formed by breakdown of heme present in hemoglobin, myoglobin, cytochromes, catalase, peroxidase and tryptophan pyrrolase.
- Poorly soluble in water and highly toxic, transported in serum bound to albumin
- Glucuronidation occurs within hepatocytes prior to active secretion into bile cannulicili
- Normal serum bilirubin concentration in children and adults is less than 1 mg/dL
- In normal plasma, about 4 percent of bilirubin is conjugated
Urinary diphosphoglucuronate glucuronosyltransferase (UGT)

Diagram:
- Extravascular or intravascular hemolysis
- Blood
  - Unconjugated bilirubin + albumin
  - Urobilinogen
- Hepatic sinusoid
- Hepatocyte
  - Unconjugated bilirubin (transported with ligandin or Z protein, conjugated to glucuronic acid)
  - Conjugated bilirubin
  - Urobilinogen
- Biliary system
- Portal vein
- Small intestine
  - Conjugated bilirubin (bacterial proteases)
  - Urobilinogen
  - Feces
- Kidney
  - Urobilinogen excreted in urine
  - Feces

10% of urobilinogen in urine
90% of urobilinogen in feces
Hyperbilirubinemia

• The bilirubin normally present in serum reflects a balance between production and clearance.
• Elevated serum bilirubin concentrations can be due to three causes which can sometimes coexist:
  – Overproduction of bilirubin
  – Impaired uptake, conjugation, or excretion of bilirubin
  – Backward diffusion from damaged hepatocytes or obstructed bile ducts
Bilirubin

- Total serum bilirubin is not a sensitive indicator of hepatic dysfunction.
- Concentrations of serum bilirubin may be normal despite moderate to severe hepatic parenchymal injury, including cirrhosis, or a partially or transiently obstructed common bile duct.
- This lack of sensitivity can be explained in part by the reserve capacity of the human liver to remove bilirubin
  - In patients who have hemolysis, the normal liver can remove at least twice the normal daily bilirubin load without the development of hyperbilirubinemia
What is a True Normal Aminotransferase Value?
Determining the Definition of Normal ALT Values

• **Statistical definition**
  - Standard practice to define normal lab values
  - Middle 95% of healthy subjects
    - Abnormal: > 97.5th percentile
  - Influenced by reference population

• **Biological definition**
  - Risk of developing disease or complication
    - Cholesterol, glucose
  - Abnormal ALT: level associated with disease
Updated Limits for Normal ALT

- 9221 first-time blood donor candidates
- 57% determined to be ‘low risk’ for liver disease
  - Negative viral serology
  - BMI < 25
  - Normal serum cholesterol, triglycerides, and glucose levels
  - Absence of concurrent medication use
- Updated healthy ALT ranges determined from the group of low-risk individuals
  - **Males:** 30 IU/L
  - **Females:** 19 IU/L

Biologic Definition of Normal ALT

- Cohort study of 142,055 S. Korean health insurance participants
  - Aged 35-59 years
  - Baseline ALT measured 1990-1992
  - Follow-up through 2000
  - Death certificates used to determine date of death and cause of death
  - Limitation: hepatitis B diagnosis unknown

ALT and Subsequent 10-Year Mortality in Men

Relative Risk of Mortality

ALT (IU/L)

< 20 20-29 30-39 40-49 50-99 ≥ 100

All cause Liver

ALT and Subsequent 10-Year Mortality in Women

ALT and 11-Year Mortality in Olmsted County Cohort

- Adults from Olmsted County, Minnesota, who came to Mayo Clinic in 1995 included (N = 6823)
  - Followed from January 1995 to April 2006

![Graph showing relative risk of death vs. ALT (IU/L) for women and men.]

Disadvantages of Using a Lower ALT ULN Cutoff

• Unclear health benefit
  – i.e., NAFLD with minimally elevated ALT

• Potential unnecessary testing and consultation

• Rejection of blood donors

• Anxiety

• Medico-legal

Evaluation of Liver Abnormalities
History

• Systemic symptoms
• Family Hx
  – Hemochromatosis, Wilson’s Disease, alpha₁ antitrypsin deficiency
  – Gilbert’s syndrome, Dubin-Johnson Syndrome, Rotor’s syndrome
• Infectious risk
  – Sexual History
  – Tattoos
  – Illicit drug use
  – Travel history
History

• **Occupational exposures**
  – Chemicals (vinyl chloride, dimethylformamide, 2-Nitropropane, Trichloroethylene)

• **Other co-morbid illnesses**
  – Autoimmune diseases, Thyroid disease, Celiac disease, IBD, Diabetes Mellitus

• **Medications**
  – Prescription
  – OTC
  – Herbals, Vitamins
**Drug-Induced Liver Injury**

<table>
<thead>
<tr>
<th>Hepatocellular injury (serum aminotransferase elevations)</th>
<th>Cholestatic injury (serum ALP and bilirubin elevations)</th>
</tr>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>Androgenic anabolic steroids</td>
</tr>
<tr>
<td>Alpha-methyldopa</td>
<td>Captopril</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Estrogenic steroids</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Floxuridine</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Gold salts</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Methimazole</td>
</tr>
<tr>
<td>Heparin</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tolazamide</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Tolbutamide</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Mixed hepatocellular-cholestatic injury</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Flutamide</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Phenytoin</td>
</tr>
</tbody>
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Acetaminophen Can Cause Aminotransferase Elevation Among Healthy Adults

- Placebo controlled study of 145 healthy volunteers given acetaminophen (4 g daily for 14 days)
- An increase from 1 to 2 times the upper limit of normal was observed in 50 to 70 percent of patients.
- An increase > 3 times the upper limit of normal was observed in 33-41 percent of patients.
- About 20 percent experienced an ALT elevation more than five times the upper limit of normal (compared with 3 percent taking placebo)

JAMA. 2006;296(1):87.
Routine Monitoring of LFTs no Longer Considered Necessary for Statin Use

- Clinical studies have found ALT elevations in 0.5% to 3% of patients who take statins.
- No case reports of chronic liver damage (i.e. cirrhosis) from statin use.
- Acute liver failure resulting from statin therapy is idiosyncratic and exceedingly rare (0.2/million).
- Routine LFT monitoring is not necessary.
- Statins should not be withheld in patients with preexisting liver disease or baseline abnormal LFTs (mostly due to NAFLD).
Herbal and Dietary Supplement Hepatoxicity

- 42% of American use some form of alternative medical therapy
- Approx. 19% use dietary supplements (DS)
- 20-40% of chronic liver patients use herbal supplements
- 21% of adults taking prescriptions use DS
- 69% do not disclose DS use to their primary care provider
Hepatotoxic Herbals

- Black Cohosh
- Buckthorn (Rhamnus cathartica).
- Callilepsis laureola (Impila)
- Cascara Sagrada
- Celandine
- Chaparral
- Comfrey and other herbs containing pyrrolizidine alkaloids (heliotropium, senecio, crotalaria, symphytum)
- Doxidan
- Germander (Teucrium chamaedryis).
- Green tea leaf
- Groundsel (Senecio vulgaris).
- Impila root
- Jin Bu Huan.
- Kava
- Kombucha
- Lobelia (Lobelia inflata).

- Ma huang (ephedra).
- Mate
- Mistletoe (Viscum album).
- Nutmeg (Myristica fragrans).
- Pau d’arco (La pachol).
- Pennyroyal (Mentha pulegium).
- Poke root (Phytolacca americana).
- Ragwort (Senecio jacoboea).
- Sarsparilla (Smilax species).
- Sassafras (Sassafras albidum).
- Saw palmetto –
- Senna (Casio acutifolia).
- Skullcap (Scutellaria laterifolia).
- Soy phytoestrogen
- Sweet clover (Melilotus officinalis).
- Tansy (Tanacetum vulgare).
- T’u-san-chi.
- Valerian (Valeriana officinalis).
- Woodruff (Galium odorata).
How Prevalent Are Aminotransferase Elevations?

Very, and increasing significantly over the last two decades.
# Prevalence of Diseases Associated with Elevated ALT

<table>
<thead>
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<th>Disease</th>
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<tr>
<td>NASH</td>
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<td>Drugs/Herbs</td>
<td>???</td>
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<tr>
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<td>AIH</td>
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Prevalence and Etiology of Elevated Aminotransferases in USA 1988-1994

• Data on adults ages 17 yr and older (n = 15,676) from the Third National Health and Nutrition Examination Survey (1988–1994).

• Participants were classified as having elevated aminotransferase levels if either AST or ALT was elevated above normal.
  – Men: ALT >40 AST > 37
  – Women ALT > 31 AST > 31

• “Unexplained” ↑ALT defined as the absence of HBV, HCV, abnormal iron saturation, and no alcohol excess

The prevalence of aminotransferase elevation in the United States was 7.9%.

Aminotransferase elevation was more common in men compared to women (9.3% vs 6.6%, $p = 0.002$), in Mexican Americans (14.9%) and non-Hispanic blacks (8.1%) compared to non-Hispanic whites (7.1%), $p < 0.001$.

Hepatitis B or C infection, high transferrin saturation, and/or alcohol use accounted for only 31.0% of cases.
Aminotransferase elevation was “unexplained” in the majority (69.0%).

In both men and women, unexplained aminotransferase elevation was significantly associated with higher body mass index, waist circumference, triglycerides, fasting insulin, and lower HDL; and with type 2 diabetes and hypertension in women (all $p < 0.05$).

I.e. Metabolic Syndrome/NAFLD
Prevalence of Elevated Aminotransferases in USA 1988-94

- Male: 9.3%
- Female: 6.6%
- White: 7.1%
- Black: 8.1%
- Hispanic: 14.9%

Etiology of Elevated Aminotransferases in USA 1988-94

“Known” Etiologies of Elevated Aminotransferases in USA: NHANES 1988-94

- ETOH: 44%
- HCV: 23%
- IRON: 11%
- HBV: 3%
- Any Combo: 19%
Ten Years Later...
Prevalence and Etiology of Elevated Aminotransferases in USA 1999-2002

- Prevalence of elevated ALT (> 43 IU/L: men and women) from 1999-2002 NHANES database evaluated (N = 6823)

Prevalence and Etiology of Elevated Aminotransferases in USA 1999-2002

• In NHANES 1999–2002, the prevalences of elevated ALT, AST, or either ALT or AST were 8.9%, 4.9%, and 9.8%,

• In NHANES 1988–1994, which employed a different assay methodology, the prevalences of elevated aminotransferases were approximately half of the prevalences described in NHANES 1999–2002, but the predictors of elevated ALT activity were similar. (i.e. BMI, DM, hyperlipidemia, visceral fat, metabolic syndrome)

Prevalence of “Unexplained” Elevated Transaminases

After exclusion of viral hepatitis and more than one alcoholic drink per day

Trunkal Fat is a Major Body Composition Determinant of Increased ALT

When BMI, waist circumference, and trunk fat were considered together, only trunk fat remained independently associated with increased ALT.

Gastroenterology. 2010;138(4):1346-1356
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Prevalence of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among a Largely Middle-Aged Population Utilizing Ultrasound and Liver Biopsy: A Prospective Study

Christopher D. Williams, Joel Stengel, Michael I. Asike, Dawn M. Torres, Janet Shaw, Maricela Contreras, Cristy L. Landt and Stephen A. Harrison

Gastroenterology
Volume 140, Issue 1, Pages 124-131 (January 2011)
DOI: 10.1053/j.gastro.2010.09.038
High Prevalence of NAFLD/NASH in Urban Population

- Brooke Army Medical Center Primary Care Clinic in Dallas: include all active duty personnel, their dependents, and military retirees (to include spouses)
- 328 pt underwent a right upper quadrant ultrasound.
- Mean age: 54.6 ± 7.35 years; range, 28–70 years
- 50.9% were female.
- Caucasian (62.5%), Hispanic (22%), African American (11.3%), and other (4.3%).
- The mean body mass index was 29.8 ± 5.64 with 45.4% of the patients meeting criteria for obesity (BMI ≥ 30)
400 enrolled
- 5 disqualified (2 known NAFDL, 3 over ETOH limit)
  - 67 failed to get ultrasound
328 completed ultrasound

156 positive US
22 refused biopsy
134 liver biopsies performed

5 normal
89 not NASH
40 NASH
   9 advanced fibrosis

Source: Gastroenterology 2011; 140:124-131 (DOI:10.1053/j.gastro.2010.09.038)
NAFLD and NASH prevalence

<table>
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<th>Condition</th>
<th>Prevalence (%)</th>
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<tr>
<td>NAFLD overall</td>
<td>46</td>
</tr>
<tr>
<td>NAFLD Hispanic</td>
<td>58.3</td>
</tr>
<tr>
<td>NAFLD Caucasian</td>
<td>44.6</td>
</tr>
<tr>
<td>NAFLD African American</td>
<td>35.1</td>
</tr>
<tr>
<td>NASH overall</td>
<td>12.2</td>
</tr>
<tr>
<td>NASH among diagnosed NAFLD</td>
<td>29.9</td>
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Source: Gastroenterology 2011; 140:124-131 (DOI:10.1053/j.gastro.2010.09.038)
NASH prevalence among ethnic groups

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<th>Ethnic Group</th>
<th>Prevalence (%)</th>
<th>N</th>
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<tr>
<td>Overall</td>
<td>12.2</td>
<td>40/328</td>
</tr>
<tr>
<td>Hispanic</td>
<td>19.4</td>
<td>14/72</td>
</tr>
<tr>
<td>Caucasian</td>
<td>9.8</td>
<td>20/205</td>
</tr>
<tr>
<td>African American</td>
<td>13.5</td>
<td>5/37</td>
</tr>
<tr>
<td>Other</td>
<td>6.7</td>
<td>1/14</td>
</tr>
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P = .03

Source: Gastroenterology 2011; 140:124-131 (DOI:10.1053/j.gastro.2010.09.038)
• Although US is an acceptable first-line screening procedure for NAFLD in clinical practice, it underestimates the prevalence of hepatic steatosis when there is < 20% fat.

• For the presence of macrovesicular hepatic steatosis of any degree had a sensitivity of 60.9% and a specificity of 100%.

• The sensitivity increased to 100% and the specificity to 90% when there was > 20% of fat.

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Alcohol
“Known” Etiologies of Elevated Aminotransferases in USA: NHANES 1988-94

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- HCV: 23%
- HBV: 3%
- IRON: 11%
- Any Combo: 19%

Prevalence and Etiology of Elevated Aminotransferases: Role of ETOH

Effect of BMI and Alcohol on Relative Risk of Liver-Related Death

Prospective cohort study of 9558 men followed for average of 42 years.

![Graph showing the effect of BMI and alcohol on relative risk of liver-related death](image-url)
Hepatitis C
HCV Prevalence Varies by Race, Sex, and Age

B, Blacks; F, female; H, Hispanic; M, male; W, Whites.

Prevalence of HCV 1988-2002

- Estimated 3.2-3.4 million Americans chronically infected with Hepatitis C
Prevalence of HCV in Males
1999-2002

Annals Internal Medicine 2006; 144:705
Prevalence of HCV in Females 1999-2002

Annals Internal Medicine 2006; 144:705
Hepatitis B
**Estimated Prevalence of HBsAg-Positive Persons in the US by Population Segment**

<table>
<thead>
<tr>
<th>Population Group</th>
<th>CHB Prevalence, %&lt;sup&gt;[1,2]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-born API</td>
<td>1.40</td>
</tr>
<tr>
<td>Foreign-born API</td>
<td>8.90</td>
</tr>
<tr>
<td>Non-Asian Americans</td>
<td>0.42</td>
</tr>
<tr>
<td>Correctional institutions</td>
<td>2.00</td>
</tr>
<tr>
<td>Other group living quarters</td>
<td>0.50</td>
</tr>
</tbody>
</table>

- Age-adjusted prevalence of anti-HBc and HBsAg in the US statistically similar during 1999-2006 vs 1988-1994<sup>[3]</sup>
- ~40,000 persons with chronic HBV infection immigrate to US each yr<sup>[4]</sup>

HBV Seroprevalence Among Asian Americans

  - Chinese
  - Korean
  - Vietnamese
- Median age
  - 43 yr (12-80)
- HBsAg+, overall
  - 558/5341 (10.4%)

Proportion of HBsAg+ Individuals

- Philadelphia: 11%
- San Francisco: 14%
- Boston: 10%
- Chicago: 11%
- New York City (1): 15%
- New York City (2): 11%
- Overall: 10.4%

# Phases of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>Immune Tolerance</th>
<th>Immune Active/ HBeAg-Positive CHB</th>
<th>Nonreplicative (Inactive Carrier)</th>
<th>HBeAg-Negative CHB</th>
</tr>
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<tbody>
<tr>
<td>Typical HBV DNA, IU/mL</td>
<td>&gt; 200,000 and often &gt; $10^{7-8}$</td>
<td>200,000 - $2 \times 10^9$</td>
<td>&lt; 2000</td>
<td>2000 - $2 \times 10^7$</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated or fluctuating</td>
<td>Normal</td>
<td>Elevated or fluctuating</td>
</tr>
<tr>
<td>Other observations</td>
<td>Liver biopsy typically normal or minimal findings</td>
<td>Active inflammation on liver biopsy</td>
<td>HBsAg may become undetectable</td>
<td>Active inflammation on liver biopsy</td>
</tr>
<tr>
<td>Treatment candidate?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
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</table>

1IU = ~5 copies/mL

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(17/100,000)
Prevalence of Inherited Liver Diseases

<table>
<thead>
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<th>Disease</th>
<th>Homozygote Frequency</th>
<th>Gene Frequency</th>
<th>Heterozygote Frequency</th>
</tr>
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<tbody>
<tr>
<td>Haemochromatosis</td>
<td>1:400</td>
<td>1:20</td>
<td>1:10</td>
</tr>
<tr>
<td>α₁AT Deficiency</td>
<td>1:1600</td>
<td>1:40</td>
<td>1:20</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1:2500</td>
<td>1:50</td>
<td>1:25</td>
</tr>
<tr>
<td>Wilson's Disease</td>
<td>1:30,000</td>
<td>1:170</td>
<td>1:85</td>
</tr>
</tbody>
</table>

Leggett et al Brit J. Haem. 1990
The natural history and disease burden of HH

Mutant HFE → Raised SF ± TS → Increased liver iron → Hepatic fibrosis → Iron overload related disease

1 in 200 N. Europeans C282Y +/-

Biochemical Expression 75%

50%

25%

↑ALT Arthritis Cirrhosis HCC

28% 1%

5.6% 1.9%
(Cirrhosis)

Hemochomatosis

• Screening should begin with a fasting serum iron and total iron binding capacity (TIBC), which permits the calculation of the iron or transferrin saturation (serum iron/TIBC).

• An iron saturation of greater than 45 percent warrants obtaining a serum ferritin.

• Ferritin should not be obtained as an initial test because it is an acute phase reactant and therefore less specific than the iron saturation.
Prevalence of ANA in Liver Disease

% Positive

- AIH
- PBC
- PSC
- NAFLD
- HCV
- HBV
- ALD

Positive

0 20 40 60 80 100
ANA Testing in Patients with Elevated Transaminases Has Low Specificity

A useful screening test for AIH is IgG or serum protein electrophoresis (SPEP). More than 80 percent of patients with autoimmune hepatitis will have hypergammaglobulinemia.

Prevalence of ANA in Liver Disease

- Low titers of ANA positivity are seen in up to a third of patients with NASH/NAFLD
- Low titers of anti-smooth muscle antibody (ASMA) and AMA have also been reported in patients with NASH/NAFLD
- In patients with suspected NAFLD, if ANA or ASMA titers are greater than 1:160 and 1:40 respectively, SPEP of total IgG and/or liver biopsy should be considered to exclude the presence of autoimmune hepatitis
Initial Evaluation of Mild-Moderate Transaminase Elevation 2-5x

- Review possible link to medications, herbal therapies or recreational drugs
- Screen for alcohol abuse (screening instruments, AST/ALT ratio >2:1)
- Obtain serology for hepatitis B and C (HBsAg, HCV Ab)
- Screen for hemochromatosis (FE/TIBC >45 percent)
- Evaluate for fatty liver (obtain a RUQ ultrasound)
- If the above serologies are negative, the ultrasound is consistent with NAFLD, and the patient fits the profile for metabolic syndrome, no further work up indicated
Initial Evaluation of Mild-Moderate Transaminase Elevation 2-5x

- Positive HCV antibody
  - Hepatitis C viral load (Genotype optional)
  - Ultrasound
  - INR/CBC/platelets
- Positive HBsAg
  - Hepatitis B quantitative DNA
  - HB-E Antigen/ anti-E antibody
  - Ultrasound/AFP optional, based on age/HCC risk
Alkaline Phosphatase
Mild-Moderate AP Elevation

• Mild-moderate elevation in alkaline phosphates activity, up to three times the upper limit of normal, are nonspecific and occur in all types of liver disease, including viral hepatitis, chronic hepatitis, cirrhosis, infiltrative diseases of the liver, and congestive heart failure.

• Elevations in hepatic alkaline phosphatase of this magnitude can also occur in disorders that do not directly involve the liver, such as Hodgkin lymphoma, myeloid metaplasia, intra-abdominal infections, and osteomyelitis.
Marked/Predominant AP Elevation

- **Biliary Obstruction**
  - Pancreatic or cholangio-carcinoma
  - CBD stones
  - Sclerosing Cholangitis
  - Primary Biliary Cirrhosis

- **Infiltrative diseases**: metastatic carcinoma, amyloidosis, sarcoidosis, hepatic abscesses, tuberculosis

- **Drug-induced cholestasis**
Evaluation of elevated serum alkaline phosphatase

Rule out physiologic causes: pregnancy, post prandial increase (up to 1.5 to 2X ULN), repeat fasting

Determine the source
Gamma glutamyl transpeptidase or 5' nucleotidase

Normal    Increased

Alkaline phosphatase likely of bone origin    Alkaline phosphatase likely of hepatobiliary origin

Test for bone disorders    Check AMA
Right upper quadrant ultrasound

AMA positive, ultrasound normal or AMA negative, hepatic parenchyma abnormal    Dilated bile ducts

Liver biopsy    ERCP

AMA negative and ultrasound normal    Assess the degree of elevation of the alkaline phosphatase

>50 percent elevated    <50 percent elevated

Liver biopsy ERCP or MRCP    Observation

AMA: antimitochondrial antibody.
Unconjugated Hyperbilirubinemia: Overproduction

- Overproduction of bilirubin
  - Extravascular or intravascular hemolysis,
  - Extravasation of blood in tissues (large hematomas)
  - Dyserythropoiesis.

- The normal liver can remove at least twice the normal daily bilirubin load without the development of hyperbilirubinemia.

- Uncomplicated hemolysis seldom causes a serum bilirubin value in excess of 5 mg/dL.
Unconjugated Hyperbilirubinemia: Impaired Hepatic Conjugation: Gilbert's syndrome

- Affects approximately 3 to 7 percent of the population, with white males predominating over females by a ratio of 2 to 7:1.
- Impaired conjugation of bilirubin is due to reduced bilirubin UDP glucuronosyl transferase activity.
- Affected patients have mild unconjugated hyperbilirubinemia with serum levels almost always less than 6 mg/dL.
- The serum levels may fluctuate and jaundice is often identified only during periods of illness or fasting.
NHANES Distribution of BMI: 1988-1994

Obesity Rate “Only” 22%!

Obesity Statistics 2007-2008: US Males

JAMA 2010;303:235
Obesity Statistics 2007-2008: US Females

- **BMI > 25**
  - White: 61.20%
  - Black: 78.90%
  - Hispanic: 76.10%

- **BMI > 30**
  - White: 33.00%
  - Black: 49.60%
  - Hispanic: 43.00%

- **BMI > 35**
  - White: 16.70%
  - Black: 27.90%
  - Hispanic: 18.90%

- **BMI > 40**
  - White: 6.40%
  - Black: 14.20%
  - Hispanic: 7.00%

*JAMA 2010;303:235*
Etiology of Elevated Aminotransferases in USA 1988-94