

Pennsylvania Academy of Family Physicians Foundation

## Pittsburgh CME Conference

November 7 - 9, 2014

### **Abnormal LFT's...Now What? *(Patient Safety)***

Bruce Gebhardt, MD


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#### **Disclosures:**

Speaker has no disclosures and there are no conflicts of interest.

The speaker has attested that their presentation will be free of all commercial bias toward a specific company and its products.

The speaker indicated that the content of the presentation will not include discussion of unapproved or investigational uses of products or devices.



Allegheny Health Network

**Saint Vincent  
Hospital**

**Abnormal Liver Tests**

Bruce C. Gebhardt, MD  
Residency Program Director  
Saint Vincent Family Medicine  
Residency Program

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**Or.....Alternative Title**

Why did I order that darn test???



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**Disclosure**

Dr. Bruce Gebhardt has no conflict of interest, financial agreement, or working affiliation with any group or organization.



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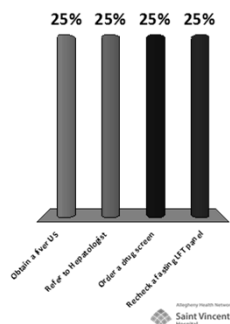
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You receive lab work from a patient that was obtained for a life insurance policy. The Alkaline Phosphatase is mildly elevated. Your next step should be:

- A. Obtain a liver US
- B. Refer to Hepatologist
- C. Order a drug screen
- D. Recheck a fasting LFT panel




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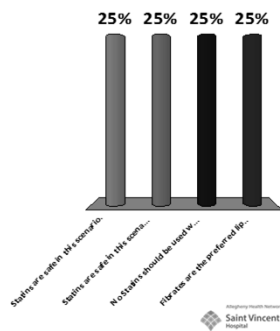
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You are recommending Statin initiation in a patient with suspected NASH after a thorough work-up. The AST/ALT are consistently 2x normal. Your best advice to the patient is:

- A. Statins are safe in this scenario.
- B. Statins are safe in this scenario and may improve AST/ALT
- C. No Statins should be used with abnormal AST/ALT.
- D. Fibrates are the preferred lipid agents in this scenario




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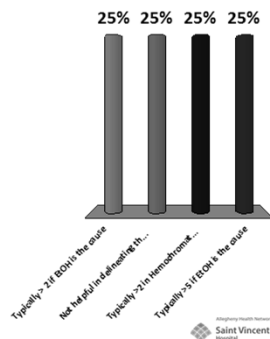
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The AST/ALT ratio when these tests are abnormal is:

- A. Typically > 2 if EtOH is the cause
- B. Not helpful in delineating the etiology
- C. Typically > 2 in Hemochromatosis
- D. Typically >5 if EtOH is the cause




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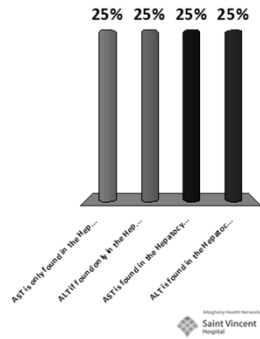
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**Pick the correct statement**

- A. AST is only found in the Hepatocyte mitochondria.
- B. ALT is found only in the Hepatocyte mitochondria.
- C. AST is found in the Hepatocyte, mitochondria and cytoplasm.
- D. ALT is found in the Hepatocyte mitochondria and cytoplasm.




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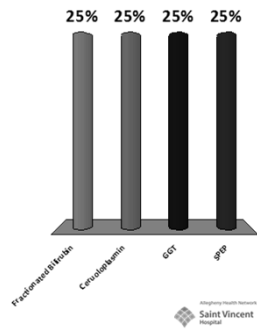
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**Which of the following would you order to determine the origin of an elevated Alkaline Phosphatase?**

- A. Fractionated Bilirubin
- B. Ceruloplasmin
- C. GGT
- D. SPEP




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**Goals**

- List the most common reasons for abnormal LFTs.
- Describe what the various LFTs actually measure.
- Clarify which liver problems affect which LFTs.
- Specify an appropriate work-up of abnormal LF's.
- Highlight the things I learned preparing for this talk.
- Discuss two common LFT scenarios in our practices

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### The Scenerio

- You, or in my case, a resident orders LFTs for some reason.
- Typically, the reason is abdominal pain, or perhaps obtained for an insurance policy.
- Typically, you don't suspect underlying liver pathology besides perhaps gallstones.
- Typically, the patient's exam is normal.
- Almost always, you are flummoxed when one or several LFTs are mildly elevated.
- Now what?



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### Abnormal LFTs

- Most are not due to bad or rare things
- But we fear missing the Primary Biliary Cirrhosis, Hemochromatosis, or tumor.



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### Abnormal LFTs

- First-as we all know, liver FUNCTION test is a misnomer.
- These tests indicate hepatobiliary disease—so really “liver tests”
- Either liver enzyme-AST,ALT,GGTP--or
- Reflect liver synthetic ability-Albumin, Bili, PT/INR
- The typical Hepatic Panel or CMP contains
  - AST/ALT
  - Alkaline Phosphatase
  - Bilirubin
  - Total Protein
  - Albumin



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### Liver Tests

- Up to 9% of patients without Sx have elevated liver enzymes—some sources say up to 30%
- 1% of all patients screened have significant liver disease.
- The incidence of abnormal liver tests is growing as our waist lines grow-obesity and metabolic syndrome.



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### General Categories How Can We Organize Liver Disease?

- Hepatocellular damage
- Cholestasis
  - Cholestasis is divided into:
    - Extrahepatic
    - Intrahepatic
- Mixed Pattern
- Acute vs. chronic
  - Chronic defined as abnormalities persisting >6 months
  - Further, one can describe; **mild, moderate, or severe** levels of abnormalities



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### Another way to categorize Liver Disease and therefore Liver Tests

1. Hepatitis-acute injury and/or necrotic lesions
2. Cirrhosis
3. Acute Biliary Obstruction
4. Space-occupying lesions
5. Passive Congestion
6. Acute Fulminant Hepatic Failure



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### AST/ALT

- AST and ALT- enzymes active in the hepatocytes
- Catalyze the transfer of alpha-amino groups from aspartate or alanine to the alpha-keto group ketoglutaric acid...more biochemistry.....gluconeogenesis.
- AST found in many other tissues, muscle for example
- ALT almost entirely found in the liver.



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### AST/ALT

- ALT more specific to liver problems.
- AST in hepatocyte cytoplasm and mitochondria
- ALT in hepatocyte cytoplasm
- Damage to the hepatocytes releases ALT and AST into the serum.



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### AST/ALT

- Absolute levels of transaminases correlate poorly with the severity or extent of damage
- Do not provide reliable prognostic information.
- Mild**-up to 5x increase
- Moderate**-6-14x increase
- Marked**->15x increase
- One can suspect various etiologies based on severity of abnormality however.



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### For Example

- EtOH-AST <8x normal, ALT <5x normal
- NAFLD-AST/ALT <4x normal
- Acute Viral Hepatitis or Toxin related->25x normal
- Ischemic Hepatitis/Shock Liver->50x normal



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### AST/ALT

Mild-can be acute or chronic

- NASH or NAFLD
- Etoh
- Medications
- Viral Hepatitis
- Hemochromatosis
- Celiac
- Hyperthyroidism
- Wilson's
- Alpha-1 Antitrypsin Deficiency
- Autoimmune

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### Hyperthyroidism

- Thought to create hepatic ischemia by increasing hepatic oxygen requirements.
- I didn't know that!



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### AST/ALT

#### Marked

- Acute viral hepatitis-A through E, HSV family (HSV, EBV, CMV)
- Ingestions-toxins/medications
- Ischemic-"shock" liver—fast elevation, fast resolution
- Acute obstruction can raise AST/ALT quite high acutely



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### AST/ALT

- Ratio of elevation of these two can help.
- Normal ratio 0.8
- AST/ALT >2.0 with ALT <300 suspicious for EtOH.
- We all know this....but why??
  
- AST/ALT >4.0 in a young patient indicative of Wilson's disease



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### Two Reasons for AST/ALT ratio increase

- EtOH is toxic to hepatocytes
- EtOH also induces hepatocyte mitochondria
- Therefore, since AST is found in the mitochondria, EtOH causes a greater elevation of AST vs. ALT
- Also, EtOHics frequently malnourished.
- B6 is a co-factor for both AST/ALT, but has a higher affinity for AST.
- Even Dr. Levy didn't know that!



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### **EtOH**

- Chronic overuse over two years
- Men >210 grams EtOH/week
- Women >140 grams EtOH/week
- Beer-12 oz
- Wine-5 oz
- 80 proof spirits-1.5 oz
- These contain 14 grams of EtOH
- 15 drinks/week—men
- 10 drinks/week-women



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### **Alk Phos**

- Alkaline Phosphatase is found in many organs.
- Primarily liver and bone
- Also, placenta, ileal mucosa, kidney, and leukocytes
- Involved in phosphate ester hydrolysis



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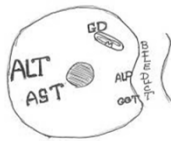
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### **Alk Phos**

Elevation due to either:

- A. Intra-hepatic biliary obstruction
  - Primary Biliary Cirrhosis
  - Primary Sclerosing Cholangitis
- B. Extra-hepatic biliary obstruction
  - Stones
  - Stricture
  - Mass
- C. Infiltrative liver process
  - Granulomatous Disease--Sarcoid
  - Malignancy-primary/metastatic



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### Alk Phos

- The elevation is not strictly from obstruction impairing bile excretion
- Obstruction leads to bile accumulation in the hepatocytes which induces the synthesis of AP
- In acute obstruction, AP may not raise immediately, may take a few days
- I didn't know that



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### Alk Phos

- High fat food can increase AP by 30%, in blood type O and B patients.
- BMI increase can raise AP by 25%
- Tobacco can raise 10%
- Third trimester pregnancy can increase 2-3 fold
- BCP's can raise 20%
- CKD can raise intestinal AP
- If high—first thing is to recheck a *fasting* lab
- Who knew that?



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### GGT

- Microsomal enzyme found on the surface of hepatocyte and biliary epithelia.
- Found in many other tissues.
- Only a 32% predictive value of hepatobiliary disease.
- GGT's **main value** is to help separate liver from bone source of AP raise.
- Cheaper and more available than AP fractionation.
- 5' Nucleotidase also mentioned in articles



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### Bilirubin

- Catabolic end product of heme breakdown
- Increase reflects an imbalance between production, conjugation, and excretion
- Direct/conjugated is water soluble
- Indirect/unconjugated is lipid soluble.
- Direct is highly specific for biliary tract obstruction
- Direct bilirubin appears in urine
- 70% of TB is usually indirect.



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### Bilirubin

- Jaundice occurs with Bilirubin  $>3.0$
- From the French-Jaune-meaning yellow
- 4mg/Kg of Bilirubin produced each day
- 80% of this from RBC catabolism



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### Indirect Bili Elevation Two Causes

- A. Bilirubin over production
  - Hemolysis-Hemolytic anemia/HbS
  - Extensive muscle injury
  - Hematoma absorption
- B. Reduced ability to conjugate
  - Impaired blood return-CHF, portosystemic shunting
  - Gilbert's
  - Crigler-Najjar syndrome



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### Conjugated Bili Elevation

- Definition-TB with DB fraction >50%
- Increase due to the inability of the hepatic mass to excrete conjugated bilirubin.
- Leads to overflow in the serum.
  - A. Hepatocellular injury
  - B. Cholestasis;
    - Intra or extra-hepatic
- TB level does provide prognostic information



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### Liver Synthetic Function

- PT/INR-reflects the extrinsic clotting pathway
- Factors II, V, VII, X
- All but VIII made in the liver
- I didn't know that.
- Albumin
  - 10 grams made and excreted daily!
- Neither PT/INR or Albumin are specific to liver dysfunction, i.e. nutrition, Vitamin K deficiency, etc. affect as well.
- But, if INR doesn't respond to Vitamin K—likely liver etiology.



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### Evaluation

Once you find increased LFT's.....

- History**-as always key.
- Symptoms and Signs**
- Hepatocellular necrosis--anorexia, N/V, fever
- Cholestasis-jaundice, pruritus, clay colored stool, dark urine.



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### Evaluation

#### PMHx:

- Obesity-90% bariatric surgery patients with NAFLD
- DM-50% DM with NAFLD
- Metabolic Syndrome-TG's, HDL

#### ***NAASH-most common cause of mild AST/ALT elevation in US***

- 30% US adults with NAFLD-Hepatic Steatosis
- 3-6% NASH-hepatitis
- Hyperthyroidism
- CHF
- Lots of others to ask about



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### Evaluation

- Medicines:** include Rx, OTC, herbs/supplements
- Some meds cause hepatocellular damage, others cholestatic abnormalities, others fatty liver.
- Acetaminophen, NSAID's, ACE, INH, Sulfa, antifungals...many more



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### Evaluation

- NIH database lists >1,000 meds/supplements that can cause liver toxicity
- Kava Kava, Valerian, Mistletoe, Comfrey
- 10% of cases of medicine induced liver injury from herbs/supplements
- Comfrey removed from the market in France



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## Evaluation

- **Etoh:** 10% of cases in one Swedish study of Asx patients with abnormal LFTs.
- **Sexual History:** Hepatitis B/C
- **Drug use:** IVDU-Hep B/C, intranasal cocaine
- **Travel:** Hep A, E
- **Country of origin:** Asia-Hep B, Northern Europe-Hemochromatosis
- **Diet:** Raw Oysters-Hep A, Mushrooms.



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## Amanita phalloides ("Death cap")



## Amanita bisporigera ("Destroying angel")



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## Evaluation

### Family Hx:

- Gilbert's-5% of US population
  - Men > women
  - Indirect bilirubin < 5
  - No other LFT abnl
- Wilson's
- Hemochromatosis
- Alpha-1 Antitrypsin Deficiency

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### USPSTF

#### Screening I have to Remember

- Hepatitis C
- Recommendation-one time screen for all born between 1945-1965
- Grade B
- HIV
- Recommendation-screen ages 15-65
- Grade A



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### Evaluation

#### •Physical Exam

- BMI
- Palmar erythema
- Spider nevi
- Jaundice
- Ascites
- Splenomegally
- Caput Medusae



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### Evaluation

- Hx, PE, biochemical liver test findings.....
- **80%** of Dx can be made from these.
- First step as always...
- **Repeat the test, fasting.**
- If mild and no other warning signs on Hx/PE
- Work on common things: weight loss, Etoh and meds/toxins removal.
- Recheck in 2-6 months, depending on clinical situation and levels.



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### Evaluation:AST/ALT

#### Viral Hepatitis

- Hep C-1.8% of general population.
- Hep B-0.2-0.9% of general population-US
- Up to 20% of Hep B patients from endemic areas
- Other risk factors—Blood transfusions before 1992, intranasal cocaine, hemodialysis
- Worldwide-most Hep B transmitted shortly after birth or at a young age.



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### Evaluation:AST/ALT

#### Hemochromatosis

- Northern European descent
- 1/10 heterozygous
- 1/200-400 homozygous
- Men-onset in 3<sup>rd</sup> and 4<sup>th</sup> decade
- Women-post menopause
- Iron studies—transferrin saturation (Iron/TIBC), ferritin



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### Hemochromatosis

- Serum Iron and TIBC first
- Transferrin Saturation= Iron/TIBC ratio
- If >45%....
- Then do ferritin.
- Ferritin is acute phase reactant, so often increased NOT because of Hemochromatosis
- >400 in men
- > 300 in women---supports Dx of Hemochromatosis



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### Evaluation:AST/ALT

#### Autoimmune Hepatitis

- Higher in Women, patients with other autoimmune diseases
- North America prevalence in patients with chronic liver disease—11-23%.
- ANA, Anti-smooth muscle antibody, SPEP.



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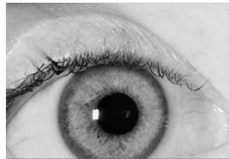
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### Evaluation:AST/ALT

#### Wilson's Disease-autosomal recessive

- Patients <40 years old
- Ceruloplasmin—would be low!
- Transaminases often->400
- AST/ALT >4
- Kayser-Fleischer Rings-iris
- Neuro/Psych problems
- JFP Photorounds



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### Evaluation: AST/ALT

**Alpha-1 Antitrypsin** levels-pulmonary findings

**Celiac testing**- GI symptoms

**Hyperthyroidism**- symptoms, on replacement, check supplements



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### Evaluation of AP

- **Check GGT**
- 5' Nucleotidase also mentioned.
- Liver US to delineate intra vs. extra-hepatic etiology.
- Biliary duct dilation indicates extra-hepatic obstruction.
- No biliary duct dilation indicated intra-hepatic obstruction.



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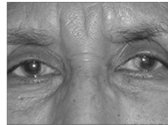
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### Elevated AP

- **Primary Biliary Cirrhosis**-Anti-mitochondrial AB
- Women 9:1 vs. Men
- **Primary Sclerosing Cholangitis**-seen with Ulcerative Colitis
- These cause intra-hepatic obstruction
- JFP Photorounds



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### What do all these tests cost?

- |                        |                           |
|------------------------|---------------------------|
| • CMP-\$88             | • Ceruloplasmin-\$50      |
| • Hepatic Profile-\$66 | • Alpha 1AT-\$58          |
| • TIBC/Iron-\$87       | • ANA-\$100               |
| • Ferritin-\$121       | • Anti-Smooth Muscle-\$58 |
| • GGTP-\$42            | • SPEP-\$91               |
| • Hep A/B/C-\$293      | • CK-\$42                 |
| • TSH-\$128            | • Celiac Screen-\$449     |
| • Free T4-\$150        | • RUQ US-\$750            |



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### So, what to do? AST/ALT

1. Repeat the test fasting.
2. Stop Etoh, toxins, lose weight
3. Recheck 6-8 weeks.
4. Viral Hepatitis screen, Hemochromatosis labs, Liver Ultrasound

Etiology found up to 30% with these tests

Add in up to 30% with NASH



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### So, what to do? AST/ALT

If no answer yet

5. Autoimmune, Thyroid, and Celiac labs

If still no answer

6. Wilson's Dz, Alpha-1 Antitrypsin, CK, and adrenal insufficiency labs

If still no answer and levels remain 2x normal for 6 months, consider referral for Bx.

Little data that Bx will provide answer or change treatment plan, but may make patient and you feel better.



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### So, what to do? Isolated AP

Alk Phos from Cholestasis typically >4x normal

1. Confirm Liver source-GGT
2. Check meds that can cause cholestasis
3. Ultrasound-intra or extra-hepatic cholestasis?
4. Extra-hepatic-may need CT, ERCP, MRCP
5. Intra-hepatic-PBC, viral hepatitis, EBV, CMV, pregnancy labs
6. Continue >50% of normal for 6 months--Bx



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## Two Common Scenarios

### One

- NASH—how to differentiate benign steatosis from steato-hepatitis?
- NASH typically benign-no long term affects
- 3-6% have inflammation that can lead to cirrhosis and hepatocellular cancer.
- Biopsy is the only way to tell for sure.
- Ultrasound-Sn-82-89%; SP-93% for fatty infiltration



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## NASH

- Liver Bx complications
- 30% transient pain
- 3% significant pain
- < 3% significant complications
- 0.03 risk of death
- Most sources recommend referral for consideration in presumed NASH if LFTs remain elevated 6 months or worsen



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## Two Common Scenarios

### Two

- Statins
- 1-3% of patients on statins have increased transaminases
- 70% are transitory
- Testing for transaminases q6-12 months estimated to cost 3 billion \$/year.
- Severe/fatal liver injury is rare and **idiosyncratic**



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## Statins

- Prescribers Letter 2012
- Check LFTs prior to starting a statin
- Do NOT follow LFTs while on statins if normal baseline
- Ok to start and maintain statins if  $< 3x$  normal
- Statins may decrease transaminases in NASH, likely due to anti-inflammatory affect
- STOP statins in acute hepatitis or decompensated cirrhosis



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## Goals

- List the most common reasons for abnormal LFTs.
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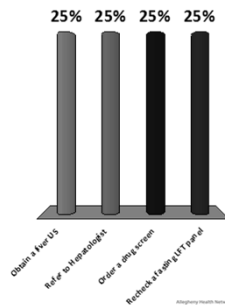
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- B. Refer to Hepatologist
- C. Order a drug screen
- D. Recheck a fasting LFT panel



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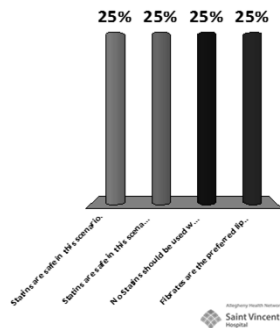
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You are recommending Statin initiation in a patient with suspected NASH after a thorough work-up. The AST/ALT are consistently 2x normal. Your best advice to the patient is:

- A. Statins are safe in this scenario.
- B. Statins are safe in this scenario and may improve AST/ALT
- C. No Statins should be used with abnormal AST/ALT.
- D. Fibrates are the preferred lipid agents in this scenario




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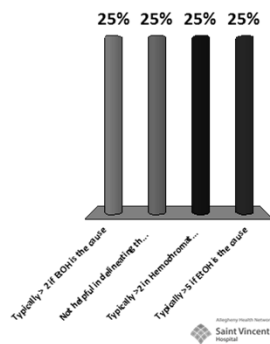
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- B. Not helpful in delineating the etiology
- C. Typically >2 in Hemochromatosis
- D. Typically >5 if EtOH is the cause




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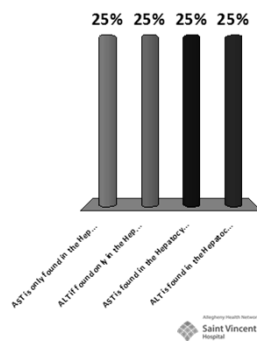
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Pick the correct statement

- A. AST is only found in the Hepatocyte mitochondria.
- B. ALT is found only in the Hepatocyte mitochondria.
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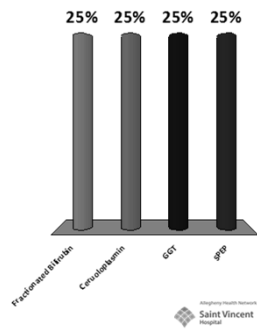
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Which of the following would you order to determine the origin of an elevated Alkaline Phosphatase?

- A. Fractionated Bilirubin
- B. Ceruloplasmin
- C. GGT
- D. SPEP



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