

Evaluation of Elevated Liver Enzymes:

What does this mean and what do I do next?

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Speaker has no relationship to disclose.

Objectives

- Able to discuss most common reasons for elevations in liver enzymes (20 mins)
- Able to evaluate elevations of liver enzymes and determine hepatic etiology (30 mins)
- Develop a methodical approach to evaluation of the patient with elevated liver enzymes (20 mins)

Outline

- Get to know the liver!
- Look at the liver labs in detail:
ALT/AST, bilirubin, alkaline phosphatase, GGT, PT/INR, albumin
- An organized way to evaluate the patient

Let's get to know the Liver

"Job Description" of the Liver

- Metabolizes drugs
- Converts glucose to glycogen
- Produces bile
- Produces proteins for blood plasma, clotting
- Produces proteins immune functions
- Produces cholesterol, blood fats
- Converts ammonia to urea
- Processes hemoglobin
- Clears bilirubin

Liver Function Tests

- ALT/AST
- Bilirubin, ALP, GGT
- PT/INR/Albumin

So, if we want to know how a liver is working, we can order LFTs...but

Liver Function Tests

- ALT/AST measure of integrity of liver
- Bilirubin, ALP, GGT measure excretory function of liver
- PT/INR/Albumin measure synthetic function of liver

Quiz: About how many different liver enzymes are there?

1. Fewer than 10
2. About 10
3. Hundreds
4. Thousands

Background

There are THOUSANDS of Liver Enzymes!!!

Generally grouped in to 2 Categories:

- Enzymes that indicate damage to hepatocytes (ALT, AST)
- Enzymes that reflect cholestasis (Alk, bili)

A Look at the Liver Labs in Detail

Background

“Celebrity” Liver Enzymes:

AST = Aspartate aminotransferase, (SGOT)

ALT = Alanine aminotransferase, (SGPT)

Take Home Point

Who is your patient?

Liver chemistries must be interpreted in the context of the patient's risk factors for disease, symptoms, and history and physical examination findings.

What are Normal Values?

Normal ALT level in prospectively studied populations without identifiable risk factors for liver disease ranges from:

29 to 33 IU/L for males

19 to 25 IU/L for females

age specific values for children

Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112:18-35.

So, *why* do elevations in ALT, AST occur?

Elevations in ALT, AST

Liver Enzymes:

- Sensitive indicators of liver cell injury
- ALT, AST found in hepatocytes

So, *when* do elevations in ALT, AST occur?

Liver Enzymes:

- In the presence of liver cell injury
- In most liver diseases
- Elevated in disorders that involve do NOT NECESSARILY involve the liver (heart failure, metastatic carcinoma)

Quiz: Why are liver enzymes elevated in heart failure?

Quiz: Why are liver enzymes elevated in metastatic carcinoma?

Quiz: Why are liver enzymes elevated in non-liver related diseases?

ALT, AST

AST found in: Liver, heart, skeletal muscle

ALT found in: Liver primarily, small amounts in heart, kidney

26 y/o female nurse who was recently married presents with complaints of weakness and fatigue for the past 3 days. She reports a neg home pregnancy test.

CBC: normal

hCG: negative

UA: Reddish brown, hematuria, nitrites neg, leukos neg

Early Lab Results

	Patient	Normal Values
Glucose	82	70-110 mg/dL
Total Protein	7.5	6.0-8.5 g/dL
Total Bilirubin	0.4	0.1-1.2 mg/dL
Albumin Level	4.5	3.5-5.5 g/dL
Alkaline Phosphatase	82	30-120 U/L
AST (SGOT)	418 H	0-41 U/L
ALT (SGPT)	174 H	0-45 U/L

Take Home Point

ALT present primarily in the liver, so better marker of hepatocellular injury than AST.

Take Home Points

- AST present in the liver, cardiac muscle, skeletal muscle, kidney, and brain
- Increase in AST without an elevation in ALT is suggestive of cardiac or muscle disease

New Guidelines Provide a Clearer Path Forward for Abnormal Liver Tests - Medscape - Feb 01, 2018.

More Lab Results

	Patient	Normal Values
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Albumin Level	4.5	3.5-5.5 g/dL
Alkaline Phosphatase	82	30-120 U/L
AST (SGOT)	418 H	0-41 U/L
ALT (SGPT)	174 H	0-45 U/L
CK	10,000 H	22-198 U/L

What's in your differential diagnosis for this patient?

Take Home Point!

Think liver disease with elevated ALT, AST, but don't limit your differential diagnosis to *only* liver disease!

Quiz: True or False
A normal ALT, AST excludes liver disease.

Elevations in ALT, AST

- Normal ALT, AST do NOT exclude liver disease!
- Patients with cirrhosis commonly have normal ALT, AST levels *if there is no continuing injury* to hepatocytes.

Take Home Point!

ALT, AST are NOT sensitive measures of liver *disease*.

REAL Hepatocellular Injury

ALT, AST:

- Highest elevations (> 8 times ULN) usually occur secondary to hepatocellular injury [hepatitis, hepatotoxicity from acetaminophen, ischemic hepatitis (shock liver), autoimmune hepatitis]
- ALT >10,000IU/L: think acetaminophen or shock liver

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What affects ALT, AST?

- **Day to day** there are changes in ALT (5-10%)
- **Day to day** there are changes in AST (10-30%)

Desai, S. (2004). Clinician's Guide to laboratory medicine (2nd ed.). Hudson,OH: LexiComp

What else affects ALT, AST?

- **Race and gender** do!
- **AST: 15% higher** in African American males
- **NO other significant differences** in women or other races
- **Should we adjust AST** for African American males?

Desai, S. (2004). Clinician's Guide to laboratory medicine (2nd ed.). Hudson,OH: LexiComp

What else affects ALT, AST?

- **"Trunk fat"** does!
- **AST, ALT: 40-50% higher** in patients with abdominal adiposity

Desai, S. (2004). Clinician's Guide to laboratory medicine (2nd ed.). Hudson,OH: LexiComp

Quiz: Can liver injury be induced by metabolically active intra-abdominal fat?

Ruhl, C.E., Everhart, J.E. (2010). Trunk fat is associated with increased serum levels of alanine transferase in United States. Gastroenterology. 138(4):1346

Abdominal Adiposity

- **Trunk fat is a major body composition determinant of increased ALT**

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Abdominal Adiposity

- **Patients with elevated body mass index and other features of metabolic syndrome, including diabetes mellitus, obesity, hyperlipidemia, or hypertension, with mild elevations of ALT should undergo screening for NAFLD with ultrasound**

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What else affects ALT, AST?

- Exercise can!
- AST: 3-fold increase with strenuous exercise
- ALT: lower in patients who exercise at regular levels
- Enzymes increase more with strength training

Detail, S. (2004). Clinician's Guide to laboratory medicine (2nd ed.). Hudson, OH: LexiComp

How does hemodialysis affect ALT, AST?

Why do you need to know?

How does hemodialysis affect ALT, AST?

- Hemodialysis patients have falsely low ALT, AST levels
- These patients are at increased risk of liver disease, including hepatitis C
- ULN is about 50% of healthy individuals!

Elevated ALT, AST

Demonstrate injury to hepatocytes

Clinical Pearl

If AST:ALT ratio is 3:1 or greater... THINK alcoholic liver disease, especially if GGT is elevated

Clinical Pearl

In most hepatocellular injury, ALT > AST.

Background

“Celebrity” Liver Labs:

Bilirubin

Where does bilirubin
come from?

Bilirubin Level

ALL conjugated bilirubin
+ALL unconjugated bilirubin
Serum bilirubin level

Bilirubin Level

- Normal serum bilirubin levels means production = clearance of bilirubin

Production = Clearance

Bilirubin Level

Production ≠ Clearance

Elevated Bilirubin levels

- Overproduction
- Impaired uptake, conjugation, excretion
- Leakage from damaged hepatocytes or bile ducts

Bilirubin

Indirect bilirubin = unconjugated
Direct bilirubin = conjugated

- *Elevated Direct* = hepatobiliary disease
- *Elevated Indirect* = ??? Hepatobiliary disease

Wallach, J. B. (2005). *Interpretation of diagnostic tests*. (8 ed., p. 422). Philadelphia, PA: Lippincott Williams & Wilkins.

Quiz: True or False
A normal bilirubin level
excludes liver disease.

Bilirubin Level

- **Bilirubin is NOT a sensitive indicator of liver function or dysfunction**
- **Bili levels may be normal in a partially obstructed bile duct or severe liver injury**

Patient has an Elevated Serum Bilirubin Level

First Things First:
Determine whether it is conjugated or unconjugated

Here's Why:
Almost 100% of bilirubin in healthy people is unconjugated

Elevated Serum Bili: Second Step, R ratio

The "R ratio" has been proposed to assess whether the pattern of liver injury is hepatocellular, cholestatic, or mixed.

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Patient has an Elevated Serum Bili Level

The ratio is calculated using this formula:

$R = (\text{ALT value} \div \text{ALT upper limit of normal [ULN]}) \div (\text{alkaline phosphatase value} \div \text{alkaline phosphatase ULN})$

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R Ratio Interpretation

If R ratio > 5, hepatocellular injury

If R ratio < 2, cholestatic injury

If R ratio = 2-5, a mixed pattern

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Causes of Elevated Conjugated Bilirubin

Hepatocellular Disease

- Hepatitis
- Pancreatitis
- Drug induced
- Hemochromatosis
- Others

Cholestasis

- Pancreatic etiologies
- Malignancy
- Cholangitis
- Hepatitis and other intrahepatic causes

ALWAYS HEPATOBILIARY DISEASE

Causes of Elevated Unconjugated Bilirubin

- Hemolysis
- Ineffective erythropoiesis
- Neonatal jaundice
- Crigler-Najjar Syndrome
- Gilbert's Syndrome
- Decrease in hepatic uptake by drugs (rifampin)

USUALLY NOT HEPATOBILIARY DISEASE

Gilbert's Syndrome

- Characterized by elevated levels of unconjugated hyperbilirubinemia
- Effects 7% of population
- Often misdiagnosed as hepatitis
- Bilirubin levels elevated but < 3-4 mg/dL
- Benign clinical entity

USUALLY NOT HEPATOBILIARY DISEASE

Hyperbilirubinemia

Only direct bilirubin is water soluble

It can be identified on urine dipstick!

Take Home Point!

Positive urine dipstick for bilirubin signifies the presence of conjugated (direct) bilirubin.

When patients with hepatobiliary disease recover, the *urine bilirubin becomes negative before serum conjugated bilirubin.*

Background

“Celebrity” Liver Enzymes:

Alkaline Phosphatase

Alkaline Phosphatase

- An enzyme that catalyzes the hydrolysis of phosphate esters at an alkaline pH
- Found in liver, biliary tree, bone, placenta, intestine, kidney, WBCs

Alkaline Phosphatase

- ALP levels are *increased in tissues that are active in metabolism* (kidney, intestine, etc.)
- Clinical importance: most common elevations are related to liver or bone issues

Patient has an elevated ALP. What's the etiology?

Fractionation of ALP is possible but....

- Expensive
- Have to wait for it to be performed

Take Home Point!

Fractionation of ALP is possible but....

To help differentiate bone or liver:

- Order GGT, 5-nucleotidase levels
- *If normal*, likely origin is the bone
- *If elevated*, likely origin is the liver

Quiz:

A pregnant patient is found to have elevated alkaline phosphatase level. Is the etiology likely to be pathological?

Alkaline Phosphatase

- Elevations likely in pregnancy due to growth of placenta and fetal bone
- 2-3 fold increase in 3rd trimester!!!

Quiz:

An adolescent is found to have elevated alkaline phosphatase level. Is the etiology likely to be pathological?

What else affects ALP?

Elevations occur with high bone turnover:

- Healing fractures
- Osteomalacia
- Hyperparathyroidism
- Paget disease of bone
- Osteogenic sarcoma (In adolescents?)
- Bone Metastasis

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson, OH: LexiComp

What else affects ALP?

Elevations occur with liver and liver related issues:

- Cholestasis
- Infiltrative disease (lymphoma, leukemia, etc.)
- Liver lesions/masses
- Hepatitis, cirrhosis
- Many others

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson, OH: LexiComp

What else affects ALP?

Other Factors that can cause Elevations :

Race/Gender:

- 15% higher in African American males
- 10% higher in African American females

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson,OH: LexiComp

What else affects ALP?

Hemolysis

- Hemoglobin inhibits enzyme activity

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson,OH: LexiComp

What else affects ALP?

Smoking

- 10% higher

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson,OH: LexiComp

Quiz:
A 35 year old female takes oral contraceptives. What effect will this have on her ALP?

What else affects ALP?

Oral contraceptives

- 20% lower

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson,OH: LexiComp

What else causes decreased ALP?

- Wilson's disease
- Hypothyroidism
- Pernicious anemia
- Estrogen in post-menopausal females
- Theophylline
- Alendronate

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson,OH: LexiComp

Take Home Point!

Would prefer to measure ALP in a fasting state.

Non-fasting state may increase levels slightly

- If elevated non-fasting, repeat test, fasting.
- If remains elevated, investigate

Which of the following could be the cause of an elevated alkaline phosphatase level?

1. Age
2. Pregnancy
3. Recent healing fracture
4. Hyperthyroidism
5. Bone metastasis
6. Overdose with acetaminophen

Summary: What's the Etiology of Elevated ALP?

- Elevations of other LFTs highly suggestive of hepatobiliary origin
- If normal LFTs, measure 5 nucleotidase (specific for hepatobiliary tree)
- If 5 nucleotidase not available, order GGT (sensitive but not specific)
- Normal GGT or 5N indicates likely etiology is bone

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson, OH: LexiComp

Background

“Celebrity” Liver Enzymes:

Gamma Glutamyl Transferase (GGT)

GGT

- Found in hepatocytes, biliary epithelial cells, kidney, intestines, pancreas, spleen, heart, brain
- **Consequently, not specific for liver disease**

GGT

- Elevated in 80-95% of patients with acute hepatitis; regardless of type
- Not helpful in differentiating different types of liver disease
- **Most useful with elevated ALP to differentiate whether etiology is bone or liver**

Background

“Celebrity” Liver Labs:

Prothrombin Time (PT)
International Normalized Ratio (INR)

PT/INR

- PT/INR is a measure of the function of the extrinsic pathway
- The factors are made in the liver
- PT will remain normal until about 80% of liver function is compromised
- Therefore, neither sensitive nor specific for liver disease

Summary: Etiology of Abnormal PT/INR

- Decreases are seen in chronic liver disease in conjunction with other ABNORMAL liver tests
- Look at pattern of other abnormal tests

Background

“Celebrity” Liver Labs:

Albumin

Albumin

- Liver is the only organ that makes albumin
- Albumin makes up 60% of proteins in blood
- Main purpose is to regulate osmotic pressure in the blood
- Exerts osmotic effect and transports bilirubin, calcium and other electrolytes, progesterone, thyroxine, medications

Albumin

- Neither sensitive nor specific for liver disease
- Half life is about 3 weeks; so its *main use is in evaluation of the synthetic capacity of the liver in patients who have chronic liver disease*
- Many non-hepatic diseases that are associated with hypoalbuminemia: pregnancy, burns, malignancy, rapid rehydration

Etiology of Hypoalbuminemia

- Decreases are seen in chronic liver disease in conjunction with other **ABNORMAL** liver tests
- Look at pattern of other abnormal tests

Liver Function Tests

- **ALT/AST** measure of integrity of liver
- **Bili, ALP, GGT** measure excretory function of liver
- **PT/INR/Albumin** measure synthetic function of liver

Liver Function Tests	
Elevations	Differential Dx
ALT/AST <small>(liver injury)</small>	Liver injury, hepatitis, NAFLD, acute liver failure (>10x ULN)
ALP <small>(liver injury)</small>	Think bone disease, liver disease, obstructed bile ducts
Bilirubin <small>(liver function)</small>	RBC destruction, liver disease, bile duct obstruction, Gilbert's disease
PT (in setting of abnormal LFTs) <small>(liver function)</small>	Cirrhosis, cancer originating in liver
Albumin <small>(liver function)</small>	Usually normal in liver disease

**Evaluation of the Patient
with Liver Enzyme
Elevations**

Quiz:
**What's the most
important part of initial
evaluation of a patient
with elevated enzymes?**

History

1. Exposure to hepatotoxins:

- Prescription meds
- OTC, illicit
- Herbal products
- Occupational/recreational exposure to toxins

History

2. Risk for viral hepatitis

3. "Significant" EtOH consumption (difficult to get a good history)

EtOH Consumption

"Significant" EtOH consumption:

- >210 grams per week for men (15 drinks/week)
- >140 grams per week for women (10 drinks/week)

The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ, American Gastroenterological Association, American Association for the Study of Liver Diseases, American College of Gastroenterology. Gastroenterology. 2012;142(7):1592.

EtOH Consumption

14-gram (1 drink) equivalents of EtOH:

- 12 oz beer
- 5 oz wine
- 1.5 oz of 80 proof liquor

The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ, American Gastroenterological Association, American Association for the Study of Liver Diseases, American College of Gastroenterology. Gastroenterology. 2012;142(7):1592.

Take Home Point!

Look at ratio of abnormal AST, ALT

- Ratio AST: ALT > 2 => Strongly consider EtOH
- Ratio AST: ALT > 1 => Consider EtOH liver disease
- Ratio AST: ALT < 1 => Seen in fatty liver, others

History

4. Other Diseases/Conditions

- Right sided heart failure
- DM, obesity
- Pregnancy (gallstones)
- IBD
- Alpha-1 antitrypsin deficiency
- Celiac disease
- Thyroid disease

Summary of History

1. Hepatotoxins?
2. Risk of hepatitis?
3. EtOH consumption?
4. Other diseases/conditions?

Physical Exam

- Muscle wasting
- Spider nevi, palmary erythema, gynecomastia, caput medusae (engorged periumbilical veins radiating from the umbilicus secondary to severe portal hypertension)
- Ascites
- Dupuytren's contractures
- Enlarged left supraclavicular node
- Enlarged liver, tender liver
- Others

Let's Look at Abnormal Liver Function Tests

Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112:18-35.

First Step: What's Elevated?

This helps determine etiology!

- Elevated ALT, AST: think hepatocyte injury
- Elevated Alkaline phosphatase: think cholestasis
- Isolated elevated bilirubin level

Obviously...

If clues elicited in history and physical exam point to a possible etiology, work it up.

Obviously...

Exclude common conditions: DM, heart failure, thyroid disease, muscle disorders

IF No Clue about Etiology of Elevations

- Extensive testing saves time and money but more false-positives
- IF clues present, focused testing saves time and money and prevents false-positives

Tapper EB, Saini SD, Sengupta N. Extensive testing or focused testing of patients with elevated liver enzymes. J Hepatol. 2017;66:313-319

Quiz:
Asymptomatic, otherwise healthy patient with no obvious clues in history about AST/ALT elevations. How to handle?

Enzyme	Normal	Patient
AST	10-30	412
ALT	2-28	439

Previous Patient Question Lab Values?
Before initiating an evaluation of abnormal liver chemistries, repeat the panel or clarify

Quiz:
Asymptomatic, otherwise healthy patient with no obvious clues in history about AST/ALT elevations? How to handle?

Enzyme	Normal	Patient
AST	10-30	42
ALT	2-28	43

1. Work up.
2. Watch and wait for 4-6 months.

Elevations in ALT, AST

Enzyme	Normal	Mild	Moderate	Severe
AST	10-30	< 2-3 ULN	2-3 to 20	>20
ALT	2-28	< 2-3 ULN	2-3 to 20	>20

- Most common is mild to moderate elevations (< 8 times ULN)
- Refer severe elevations!!!

Desai, S. (2004). Clinician's Guide to laboratory medicine (3rd ed.). Hudson,OH: LexiComp

ALT, AST Elevation

Common Causes for Mild to Moderate Elevations:

- Infectious
- Metabolic
- Alcohol or hepatotoxic drug use
- Autoimmune
- Hereditary liver disease

ALT, AST

Mild to Moderate Elevations

Initial Workup: Screen for Infectious Hepatitis:

- Serology for Hepatitis A, B, C
- HBsAg, Anti-HBs, anti-HBc, anti-HCV

Nonalcoholic Fatty Liver Disease (NAFLD)

Steatosis = fatty liver

NAFLD: hepatic steatosis present without evidence of significant hepatic inflammation

NASH: hepatic steatosis associated with hepatic inflammation (may look just like alcoholic steatohepatitis)

ALT, AST

Mild to Moderate Elevations

Initial Workup: Screen for Nonalcoholic Fatty Liver Disease (NAFLD):

- Typically, ALT, AST 2-5 times ULN
- ALP may be 2-3 times ULN
- Serum albumin, bili: usually normal
- Symptoms of metabolic syndrome, central obesity, T2DM, dyslipidemia

O'Shea RS, Dasarthy S, McCullough AJ. Practice Guideline Committee of the American Association for the Study of Liver Diseases, Practice Parameters Committee of the American College of Gastroenterology. Hepatology. 2010;51(1):307.
Lazo M, Hernaez R, Eberhardt MS et al. Prevalence of Nonalcoholic Fatty Liver Disease in the United States: The Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol 2013;178:38-45.

Imaging with Ultrasound

Imaging for Nonalcoholic Fatty Liver Disease (NAFLD):

- **Ultrasound:** sensitivity 85%, specificity 94%
- Least expensive
- Less sensitive in morbidly obese
- **US:** increased echogenicity; diffuse fatty infiltration

Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54(3):1082.

Imaging with US vs CT, MRI

Imaging for Nonalcoholic Fatty Liver Disease (NAFLD): Detection of steatosis

	US	CT without contrast	CT with contrast	MRI
Sensitivity	85%	33	50	88
Specificity	94%	100	83	63

Rofsky NM, Fleishaker H. CT and MRI of diffuse liver disease. Semin Ultrasound CT MR. 1995;16(1):16.

Vibration Controlled Transient Elastography (VCTE)

Used to grade fibrosis based on liver stiffness (quantitative and reproducible)

Hernaiz R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54(3):1082.

Diagnosis

Nonalcoholic Fatty Liver Disease (NAFLD):

- Demonstration of hepatic steatosis by imaging or biopsy
- Exclusion of other causes of steatosis
- Exclusion of "significant" EtOH consumption

O'Shea RS, Dasarathy S, McCullough AJ. Practice Guideline Committee of the American Association for the Study of Liver Diseases, Practice Parameters Committee of the American College of Gastroenterology. Hepatology. 2010;51(1):307.

ALT, AST
Mild to Moderate Elevations

Initial Workup: Screen for Hemochromatosis:

- Serum iron, TIBC
- Fe/TIBC > 45% (*then*, get a serum ferritin)
- Serum Ferritin > 200 ng/mL in men
- Serum Ferritin > 150 ng/mL in women supports diagnosis

Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and Management of hemochromatosis: 2011 practice guideline by American Association for the Study of Liver Diseases. Hepatology. 2011;54(1):328.

Quiz:

Why don't you order a serum ferritin initially?

1. It costs too much.
2. Serum ferritin is an acute phase reactant.

Suppose Initial Workup:

- Inf hepatitis: Negative
- Hemochromatosis: Negative
- Fatty liver disease: Negative

Now what???

What again?

- Review medication list (again)
- Assess EtOH use (again)

ALT, AST Elevation

Remember Common Causes:

- Infectious
- Metabolic
- Autoimmune
- Hereditary liver disease
- Alcohol or hepatotoxic drug use

ALT, AST Elevation

Second Level of Workup:

Consider an autoimmune hepatitis

- Clue might be co-existence of other diseases with autoimmune features: hemolytic anemia, ITP, DM type 1, thyroiditis, celiac sprue, ulcerative colitis

Björnsson E, Talwalkar J, Treeprasertsuk S, Neuhauser M, Lindor K. Patients with typical laboratory features of autoimmune hepatitis rarely need a liver biopsy for diagnosis. Clin Gastroenterol Hepatol. 2011;9(1):57.

Autoimmune Hepatitis

Common Presentation

- ALT, AST usually elevated
- Usually normal bili, ALP but can have very high bili and ALP if cholestatic presentation

Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis, American Association for the Study of Liver Diseases. Hepatology. 2010;51(6):2193.

Cholestatic Injury

Flow of bile is blocked

- Elevations in ALP, glutamyl transferase, bilirubin
- Elevations < 8 fold
- Patient symptoms: pruritis, jaundice, dark urine

Autoimmune Hepatitis

Workup

- Total IgG or gamma globulin level
- Positive ANA (most common circulating autoantibodies in Type 1 disease)
- Positive ASMA (antismooth muscle antibodies) 1:320 or greater; common in Type 1 disease
- Anti-liver/kidney microsomal-1 (anti-LKM-1) antibodies (Type 2 disease)

Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis, American Association for the Study of Liver Diseases. Hepatology. 2010;51(6):2193.

ALT, AST Elevation

Second Level of Workup:

Consider Thyroid disease

- Hypothyroidism/Hyperthyroidism can cause elevations (constellation of symptoms and findings)
- TSH, free T4, T3 concentrations
- Might also be a clue to autoimmune hepatitis

ALT, AST Elevation

Second Level of Workup:

Consider Celiac Disease

- Clue might be a history of diarrhea, IDA
- Anti-tTG antibodies
- Moderately sensitive, highly specific for untreated celiac disease

Hopper AD, Hadjivassiliou M, Hurlstone DP, Lobo AJ, McAlindon ME, Egner W, Wild G, Sanders DS. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. Clin Gastroenterol Hepatol. 2008;6(3):314.

Suppose Second Line Workup:

- Autoimmune Hepatitis: Negative
- Thyroid disease: Negative
- Celiac disease: Negative

Now what???

ALT, AST Elevation

What Other Causes?

- Infectious
- Metabolic
- Autoimmune
- Hereditary liver disease
- Alcohol or hepatotoxic drug use

ALT, AST Elevation

Third Level of Workup:

- Consider Wilson's Disease: abnormal copper transport=>hepatolenticular degeneration (1 in 30,000 people)
- Alpha-1 antitrypsin deficiency
- Adrenal insufficiency
- Muscle disorders (Increased CK/aldolase levels)

Wilson's Disease

Abnormal LFTs

- Serum cerulplasmin level (low, < 20 mg/dL)
- Kayser-Fleischer rings (slit lamp eval): considered pathognomonic for Wilson's Disease

Still Stumped???

Liver Biopsy

Suppose Alk Phos is Elevated?

This helps with determining etiology!

- Elevated ALT, AST: think hepatocyte injury
- Elevated Alkaline phosphatase: think cholestasis
- Isolated elevated bilirubin level

Elevated Alkaline Phosphatase Level

Hepatic in Etiology?

Quiz:
Is the elevated ALP of hepatic origin?

Enzyme	Normal	Patient
AST	10-30	42
ALT	2-28	43
ALP	30-100 u/L	350

Ultrasound?
Yes!

Quiz:
Is the elevated ALP of hepatic origin?

Enzyme	Normal	Patient
AST	10-30	28
ALT	2-28	26
ALP	30-100 u/L	350

Ultrasound?

Quiz:
How would you determine if ALP is of hepatic origin?

Enzyme	Normal	Patient
AST	10-30	28
ALT	2-28	26
ALP	30-100 u/L	350

GGT? Serum 5-nucleotidase?

5 Nucleotidase, GGT elevated: Interpretation?

Liver or Bone?

Enzyme	Normal	Patient
AST	10-30	28
ALT	2-28	26
ALP	30-100 u/L	350
GGT	1-70 u/L	140
5 nucleotidase	0-11 U/L	33

5 Nucleotidase, GGT WNL: Interpretation?

Liver or Bone?

Enzyme	Normal	Patient
AST	10-30	28
ALT	2-28	26
ALP	30-100 u/L	350
GGT	1-70 u/L	40
5 nucleotidase	0-11 U/L	3

Suppose Bili is Elevated?

This helps with determining etiology!

- Elevated ALT, AST: think hepatocyte injury
- Elevated Alkaline phosphatase: think cholestasis
- Isolated elevated bilirubin level

Patient has an Elevated Serum Bili Level

First Things First:

Determine whether it is conjugated or unconjugated

Here's Why:

Almost 100% of bilirubin in healthy people is unconjugated

Causes of Elevated Conjugated Bilirubin

Hepatocellular Disease

- Hepatitis
- Pancreatitis
- Drug induced
- Hemochromatosis
- Others

Cholestasis

- Pancreatic etiologies
- Malignancy
- Cholangitis
- Hepatitis and other intrahepatic causes

ALWAYS HEPATOBILIARY DISEASE

Gilbert's Syndrome

- Characterized by unconjugated hyperbilirubinemia
- Effects 7% of population
- Often misdiagnosed as hepatitis
- Bilirubin levels elevated but < 3-4 mg/dL
- Benign clinical entity

USUALLY NOT HEPATOBILIARY DISEASE

Wrap Up!
Remember your Liver Enzymes!!!!

- ALT/AST measure of integrity of liver
- Bili, ALP, GGT measure excretory function of liver
- PT/INR/Albumin measure synthetic function of liver

Wrap Up!
Remember Most Common Causes!

- Infectious
- Metabolic
- Autoimmune
- Hereditary liver disease
- Alcohol or hepatotoxic drug use

Wrap Up!
Remember to Look at what's Elevated?

This helps to determine etiology!

- Elevated ALT, AST: think hepatocyte injury
- Elevated Alkaline phosphatase: think cholestasis
- Isolated elevated bilirubin level

Thank you!

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