

# Welcome to the Webinar

## Screening for Liver Disease:

# The work-up and diagnosis of acute and chronic liver disease

Robert G. Gish MD

# Today's presentation:



**Speaker:**  
**Robert G. Gish MD**

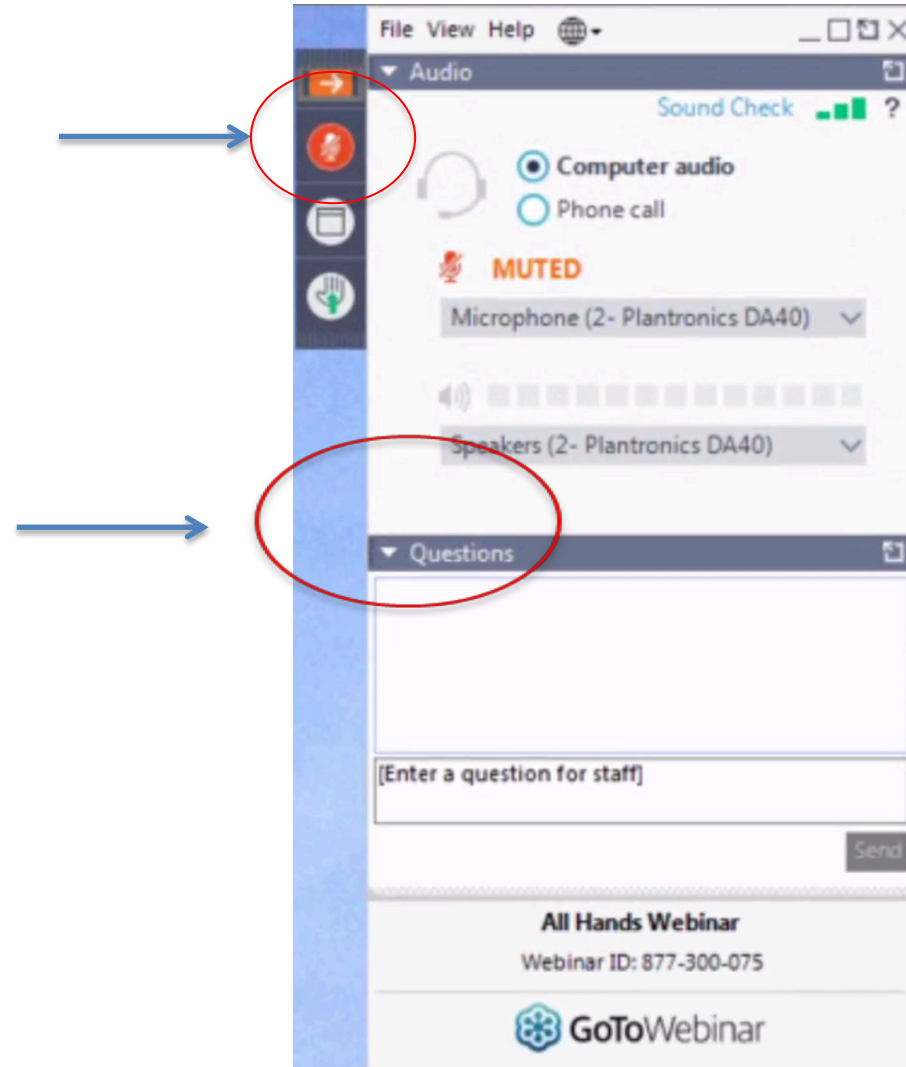
# Program Logistics

## Orange button

- Collapses window
- Expands window

## Asking questions

- Expand the window
- Type your question
- Hit “send”



# Disclosures

None



# Who should be tested for liver disease?

- Symptoms based
- Risk based
- Referral due to elevated liver tests on blood tests
- Referral due to abnormal liver imaging

# Consider Liver Disease Testing :

- All patients with metabolic syndrome
  - Test for NASH and hemochromatosis
- Patients with risk history, high risk sex or drug use, HCV HBV HIV
- Immigrant populations; HBV HCV
- Birth cohort: HCV
- All adults: HCV
- Psychiatric disorders: Wilson Disease
- Lung disease: Alpha-1
- Autoimmune disease? Do AIH work up

# Mandatory Liver Disease Testing :

- Jaundiced patient
- Large liver on physical exam
- Signs of cirrhosis/CLD
- Abnormal liver imaging
- History or current of abnormal liver tests
- RUQ pain
- Family history of liver disease

# Liver Tests “Liver Panel”

- AST, ALT
  - Alkaline Phosphatase
  - GGT
  - Bilirubin
  - Albumin
  - INR (P.T.)
- } True “liver function tests”

- Also: Lactate, glucose, cholesterol, clotting factors/TEG
- (Ammonia very poor liver function test, poor correlation with encephalopathy status)

# Evaluation of Abnormal Liver Enzyme Tests

- First step is to repeat the test!!
  - Many many things can cause a one-time elevation of liver tests
  - Mild elevations should be monitored for at least 1-6 months before a full serologic work-up is done
    - Exception is to order viral hepatitis serologies in high risk people

# Elevated ALT

- Population based survey in US 1999-2002 estimated abnormal ALT in 8.9% of population using 45 IU
  - 2015: 15% have high ALT using  $< 20$  for women and  $< 30$  men
- Symptomatic vs Asymptomatic?
- Acute vs Chronic?
- Pattern:
  - “Hepatitic” ( $ALT > AP$ ) vs Cholestatic ( $AP > ALT$ )

# The first 6 tests for a patient with confirmed elevated ALT

- Hepatitis B surface antigen
- Anti-HCV
- Iron saturation
- CAGE and alcohol history
- Medication, herbal, supplement current and history
- Metabolic syndrome: BMI, fasting blood sugar, lipid profile, waist circumference, BP

**Table 1. Etiologies of Elevated Liver Transaminase Levels**

<i>Etiologies</i>	<i>Clinical clues</i>	<i>Initial diagnostic testing</i>
<b>Common</b>		
NAFLD	Evidence of metabolic syndrome (increased waist circumference, elevated blood pressure, lipid pattern of high serum triglyceride levels and low serum high-density lipoprotein levels, elevated blood glucose levels or evidence of insulin resistance)	Fasting lipid levels, glucose (A1C) level; consider ultrasonography and NAFLD fibrosis score
Alcoholic liver disease	Excessive alcohol intake	Aspartate transaminase:alanine transaminase ratio (> 2), mean corpuscular volume (increased), alcoholic liver disease/NAFLD index
<b>Uncommon</b>		
Medications	Polypharmacy, certain herbal supplements	History
Hepatitis B	Immigrants from endemic countries, human immunodeficiency virus infection, injection drug use, men who have sex with men, household contacts or sex partners with the disease	Hepatitis B surface antigen testing
Hepatitis C	Born between 1945 and 1965, injection or intranasal drug use, blood transfusion before 1992, incarceration, hemodialysis, born to a mother with the disease, unregulated tattoo	Hepatitis C virus antibody testing
Hereditary hemochromatosis	Family history	Serum iron, total iron-binding capacity, ferritin measurements
<b>Rare</b>		
Alpha <sub>1</sub> -antitrypsin deficiency	Early-onset emphysema, family history	Serum alpha <sub>1</sub> -antitrypsin measurement
Autoimmune hepatitis	Young women with autoimmune disorders	Serum protein electrophoresis, antinuclear antibody testing*; consider smooth muscle antibody and liver/kidney microsome type 1 antibody testing
Wilson disease	Eastern Europeans younger than 35 years, neuropsychiatric symptoms, Kayser-Fleischer rings	Serum ceruloplasmin measurement

NAFLD = nonalcoholic fatty liver disease.

\*—Although antinuclear antibody testing is commonly ordered, it has lower sensitivity and specificity.

Adapted with permission from Oh RC, Husted TR. Causes and evaluation of mildly elevated liver transaminase levels. *Am Fam Physician*. 2011;84(9):1004.



# Second level testing for the Diagnosis of Elevated Liver Tests

## Hepatic:

- Viral Hepatitis: A, D, E
- Autoimmune hepatitis
  - ANA, F-actin, Quant IG
- Hemochromatosis
- Wilson disease
- Alpha-1 antitrypsin

## Either Pattern:

Drugs; take a history

Thyroid disorders; Tpanel

Celiac disease; C panel

Vascular disease: CHF, Budd Chiari syndrome,

Sinusoidal Obstructive Syndrome = SOS, imaging or bx

## Cholestatic:

- Obstruction
  - Gallstones, malignancy, parasites
- Primary Biliary Cholangitis
  - AMA
- Primary Sclerosing Cholangitis
  - MRCP
- Infiltrative diseases: metastatic cancer, sarcoidosis, amyloidosis
  - Biopsy

# Work up of acute hepatitis, new onset ALT over 200, with or without synthetic changes

- Acute hepatitis panel
  - HAV IgM
  - HBV HBsAg and anti-HBc'
    - Delta testing total Ab<sub>y</sub>
  - HEV IgM PCR
  - CMV IgM PCR
  - EBV IgM PCR
  - Herpes S, Z IgM PCR
- Wilson Disease
- Autoimmune
- Tox screen
- Blood Alc
- Drugs of abuse
- DILI, HILI, SILI history
- Acetaminophen level
- Doppler of liver for vascular assessment
- Pregnancy test

# AST, ALT

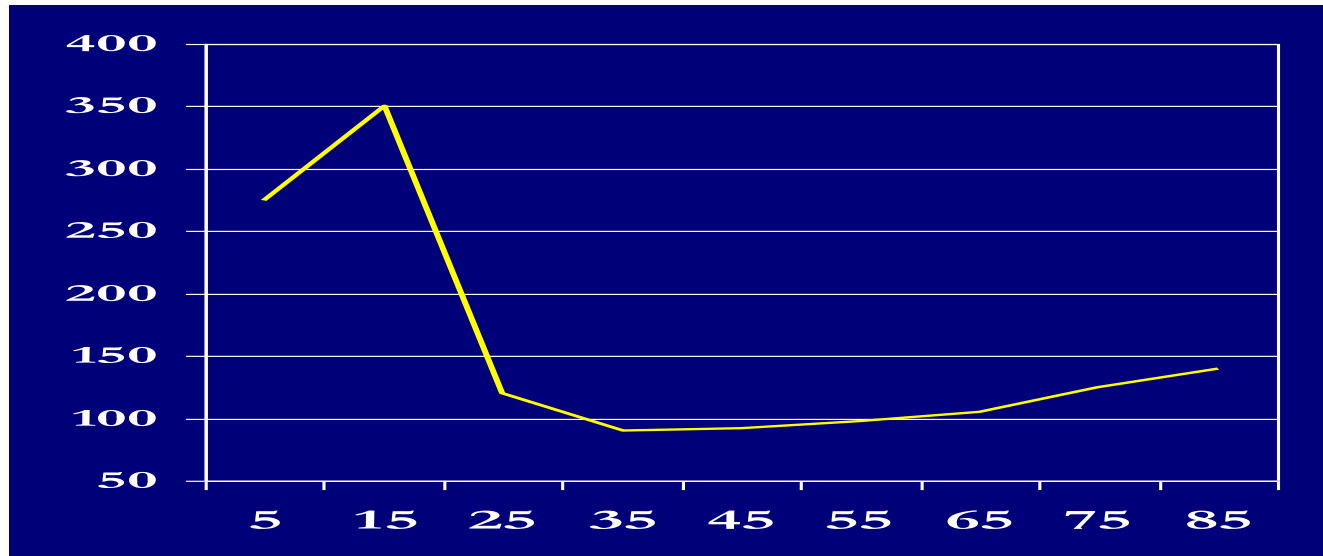
- Aspartate aminotransferase, alanine aminotransferase
  - Enzymes that are in the hepatocyte and function during gluconeogenesis
  - Leak out of the hepatocytes in times of injury and can be measured in the serum
  - AST can also come from muscle
- Normally present in serum at levels ~20-30 U/L
  - Healthy levels
    - <30 for men
    - <20 for women

# AST, ALT

- AST:
  - liver > cardiac muscle > skeletal muscle > kidney > brain > pancreas > lung > leukocytes > erythrocytes
  - Less specific for liver damage
    - Can increase with strenuous exercise, MI
  - Located in cytosol and mitochondria of hepatocytes
    - Cirrhosis; mitochondrial ratio to cytoplasm increases
  - Cleared more rapidly than ALT
- ALT
  - Mainly from cytosol of hepatocytes
  - More specific for liver damage
  - Increased from muscle : Only with severe muscle damage

# Alkaline Phosphatase

- Exists in liver in membrane of hepatocyte where it lines the canaliculus
- Liver > bone (high PTH, low Vit D) > intestine (severe ischemia)
- Placenta
- Normally changes with age, increases
- Fractionate AP to confirm source



# Other cholestatic enzymes

- GGT: gamma-glutamyltransferase
    - Found in hepatocytes and biliary epithelial cells
    - Very specific for liver injury/obstruction
    - Not paid for by MediCare since 1993
    - Very sensitive for fat and alc effect on the liver
  - 5' nucleotidase
  - Both these enzymes can be used to confirm alk phos elevation is coming from liver cells
  - GGT is also sensitive for obstruction and early autoimmune liver disease
- Can be induced by various medications, like AP



# GGT as a predictor of cardiovascular events and mortality

The MetS represent a cluster of risk factors reflecting IR [1]. It is well established that features of obesity/MetS, such as fasting hyperglycemia, hyperinsulinemia, abdominal obesity, high triglycerides/low HDL cholesterol and small dense LDL cholesterol predict CVD, independently of obesity. NAFLD, diagnosed by liver enzymes, ultrasound or a liver biopsy, has also been shown in prospective studies to predict CVD, even independently of obesity (Fig. 1).

Cohort	N	Predictor	Follow-up years	Independent of BMI	Year <sup>REF#</sup>
British	7613	GGT	11.5	Yes	1995 <sup>1</sup>
Austrian	163944	GGT	17	Yes	2005 <sup>2</sup>
Italian Type 2 DM	2103	US	5	Yes	2005 <sup>3</sup>
Finnish	28838	GGT	11.9	Yes	2006 <sup>4</sup>
Dutch	1439	ALT	10	Yes	2007 <sup>5</sup>
U.S.	3451	GGT	19	Yes	2007 <sup>6</sup>
Italian Type 2 DM	2103	US	6.5	Yes	2007 <sup>7</sup>
Japanese	1637	US	5	Yes	2007 <sup>8</sup>
Mixed U.S.	2812	ALT	20	No	2008 <sup>9</sup>
Germans	4160	GGT/US	7.3	Yes (men)	2009 <sup>10</sup>
Chinese	612	ALT/US	1.7	Yes	2011 <sup>11</sup>
NHANES, mixed U.S.	11371	US	14	No	2011 <sup>12</sup>
NHANES, mixed U.S.	11613	US	14	Yes	2012 <sup>13</sup>
Mixed U.S.	2364	GGT	13.7	Yes	2013 <sup>14</sup>

**References**

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US = ultrasound-based grading  
 ALT = serum alanine aminotransferase  
 GGT = serum γ-glutamyl transpeptidase

Figure 1. NAFLD as an obesity/MetS independent predictor of CVD events/mortality.

# Bilirubin: The BEST LIVER FUNCTION TEST

- Breakdown product of heme
  - 70-80% of normal production is from breakdown of hemoglobin in senescent RBC
- Conjugation of bilirubin occurs in ER of hepatocyte, and conjugated bilirubin is then transported into bile (rate limiting step)
- Almost 100% of bilirubin in healthy people is indirect then converted to direct bilirubin
- Chemistry **direct** /indirect confusion, due to shift from indirect to direct on the machine (conjugation)

Direct bilirubin is the foundation of assessing liver function

- Gilbert syndrome 80% indirect:
- Fractionate any elevated bilirubin



# Bilirubin

- Increased bilirubin can occur from:
  - Overproduction of bilirubin
    - Uncomplicated hemolysis (rarely levels >5 mg/dL)
  - Impaired uptake, conjugation, or excretion
    - Gilbert Syndrome, Roter, CN Syndrome, Dubin Johnsons
  - Blockage of bile duct(s)
  - Regurgitation from damaged hepatocytes of bile ducts
    - Hepatocellular damage
- Urinary bilirubin is only conjugated

# Albumin

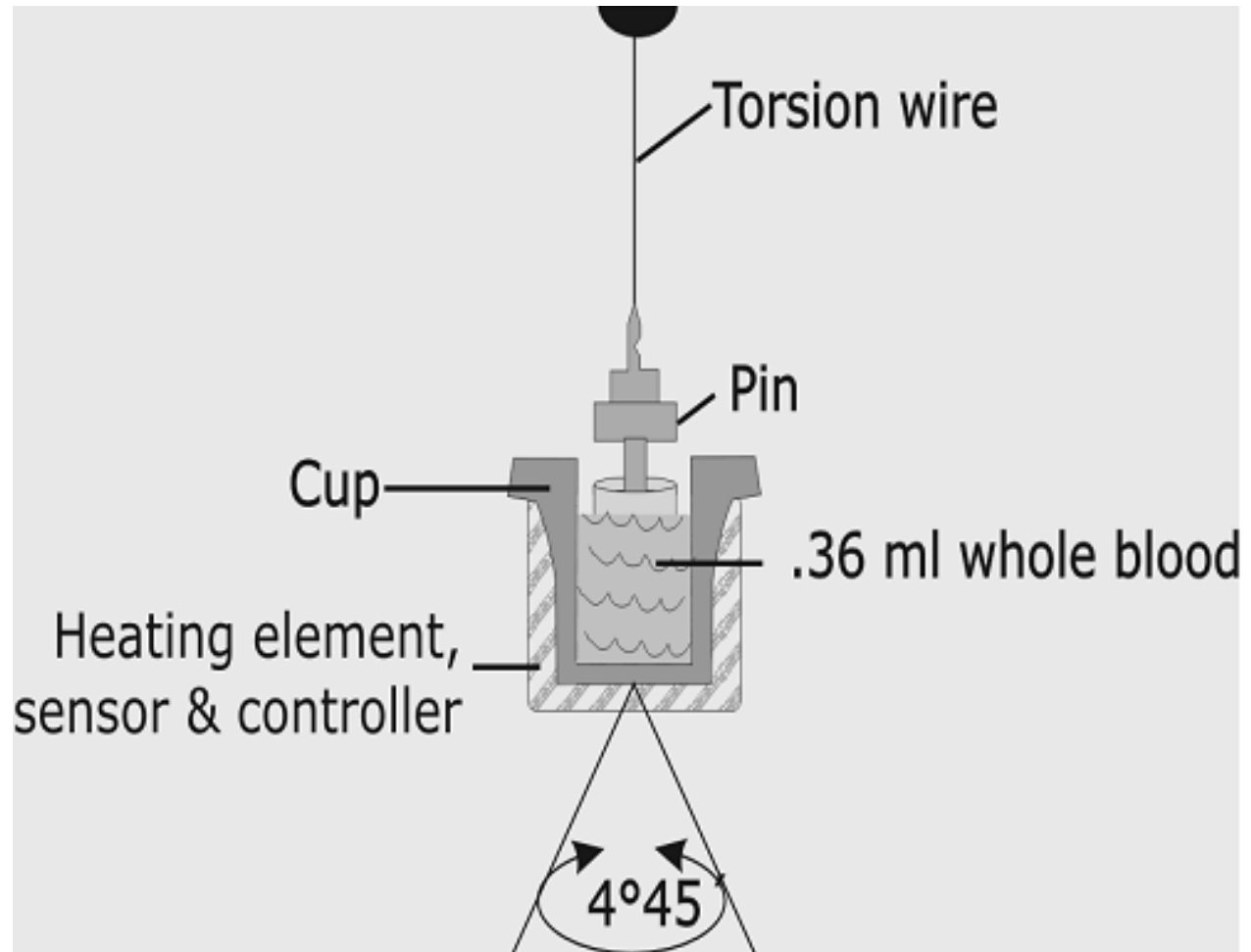
- Important plasma protein synthesized by the liver
- Half-life 20 days
- Levels <3.5-4.0 mg/dL should raise the suspicion of chronic liver disease or inflammatory disease
  - \*\*\*not specific for liver disease
- Also reduced in heavy alcohol consumption, chronic inflammation, protein malnutrition, urine loss, active HIV disease, pregnancy

# Protime/INR/TEG

- Liver synthesizes all major coagulation proteins: I, II, V, VII, IX, X, XII, XII
  - vWF is synthesized in the vascular endothelium, including the liver
- INR measures II, VII, IX, X: vitamin K dependent factors
- INR: Can be elevated in liver disease or Vitamin K deficiency
- \*\*\* one of the most important abnormalities to signify development of fulminant hepatic failure in course of acute liver disease, with bilirubin and encephalopathy
- Degree of elevation is a prognostic factor in many liver diseases, crude, poor correlation
- Best test for coagulation function / factors is **Thromboelastography (TEG)**

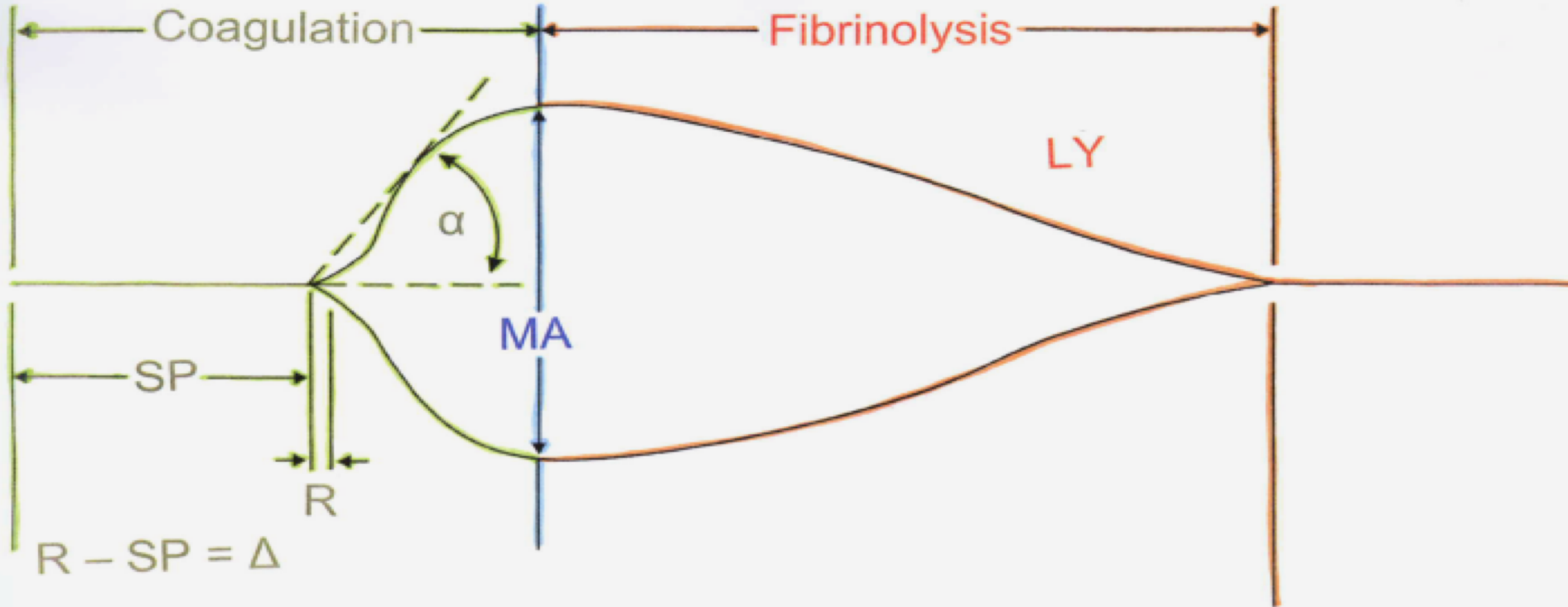
# TEG Analyzer

## Mechanics of Sample Measurement



### Key:

Green = Enzymatic System  
Blue = Platelet System  
Orange = Lytic System



SP = Split Point, time to first fibrin strands

R = Reaction time to end of thrombin burst

K = fibrin cross-linkage, fibrinogen function

Angle = fibrinogen function

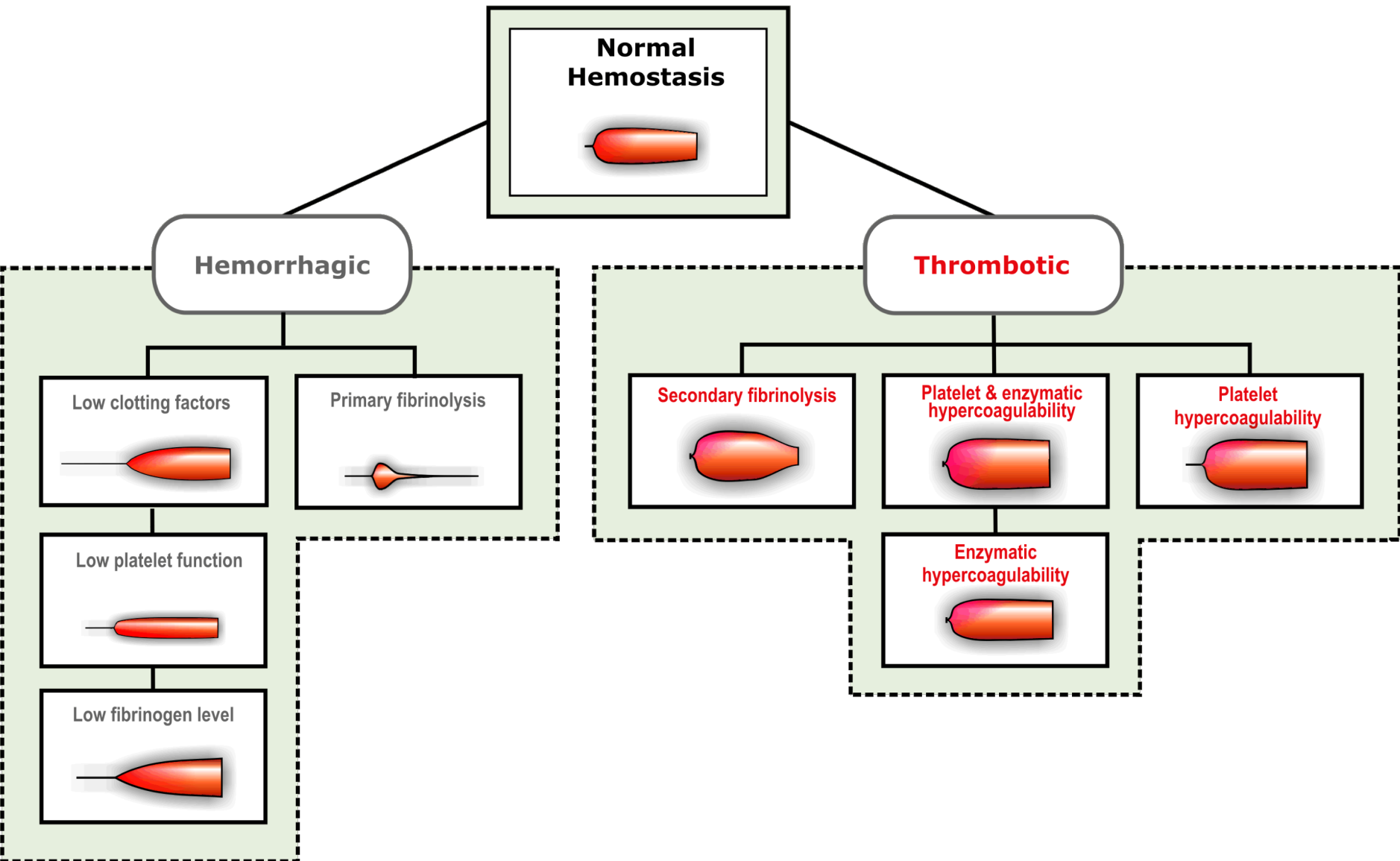
MA = platelet function in mm

G = MA converted to Kdynes/cm<sup>2</sup>

EPL = Estimated Percent Lysis, clot breakdown

LY30 = Lysis 30 minutes after MA reached

# TEG decision tree



# The work up of the pregnant patient or the patient who may become pregnant

- Hepatitis B liver panel is key
  - HBsAg indicates risk of perinatal transmission
  - Vaccinate women who are of child bearing age who are HBV panel negative
  - Vaccinate women who are sexually active

# Evaluation of Abnormal Liver Tests

- Evaluate how high the ALT or AP test is
  - Normal values are calculated from “normal” people
  - “Normal” does not mean health = 2 SD above and below the mean
    - By definition, this makes 2.5% of normal people have abnormal test!
  - Healthy ALT is <20 IU/mL in women and <30 in men
- Think of situations where a high test is “normal” or may indicate another disease, nonliver
  - Alk phos in pregnancy and hyperparathyroidism
  - AST in marathon runners



# Evaluation of Abnormal Liver Tests

- History
  - How long has elevation of liver tests been present?
  - Any symptoms: pruritus, fatigue, RUQ pain, arthralgias, myalgias, rash, anorexia, fever, weight loss, changes in urine/stool
  - Symptoms of more severe liver disease: jaundice, ascites, LE edema, GI bleeding, encephalopathy, confusion or slowed thinking
  - Risk behavior?
- Other Medical Problems?
- Family history of liver disease?
- Personal or family history of autoimmune disease or thyroid disease?
- Travel?, raw food intake?, high risk behavior? Raw pork?



# Medication History

- What medications do you take?
  - When did you start them?
  - Any change in doses?
- Over the counter medications?
- Herbals? – ask specifically!!
- Supplements
- Body building agents
- Weight loss treatments
- Vitamins



# Social History

## Essential in Eval of liver disease

- How much alcohol do you drink? – be specific!!!
- Any recent travel? Born abroad?
- Have you had any blood transfusions?
- Have you ever had hemodialysis?
- Do you work in healthcare? Any needle sticks? Medical care in developing countries?
- Any tattoos?
- Have you ever injected drugs, even once?
- Have you ever snorted drugs, even once?
- Any recent mushroom ingestion?
- Any unprotected sex? Multiple sex partners?
- Are you a war/Vietnam veteran?



# Physical Examination

- Look for signs of cirrhosis/chronic liver disease
  - Spider angiomas
  - Firm liver edge, large left lobe
  - Splenomegaly
  - Leukonychia
  - Ascites
  - LE edema
  - Abdominal wall collateral vessels
  - Proximal and temporal muscle wasting
  - Men, loss of hair and gynecomastia
- Look for signs of other diseases: acanthosis nigricans, signs of thyroid disease, xanthomas, LAD, etc
  - Check cardiac exam for JVD, hepatojugular reflex



# ABNL ALT and Elevated AP >110

## GGT >65

- US:
- Fatty liver and normal hepatobiliary imaging
  - Finish work up for metabolic syndrome
- US: Normal or heterogenous liver
  - AMA and complete work up for PBC
- AP/GGT dominant:
  - US: Normal or bright/abnl biliary system
  - MRCP to evaluate for PSC
- Alcohol history
- Biliary obstruction/ disease

**Table 3. Useful Clinical Scores for Assessing Patients with Elevated Liver Transaminase Levels**

<i>Clinical score</i>	<i>Use</i>	<i>Clinical variables needed</i>
Alcoholic liver disease/NAFLD index <a href="http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/alcoholic-liver-disease-nonalcoholic-fatty-liver-disease-index">http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/alcoholic-liver-disease-nonalcoholic-fatty-liver-disease-index</a>	Distinguish alcoholic liver disease from NAFLD	ALT level, AST level, height, mean corpuscular volume, sex, weight
NAFLD fibrosis score <a href="http://naflidscore.com">http://naflidscore.com</a>	Assess risk of hepatic fibrosis	Age, ALT level, AST level, body mass index, diabetes mellitus or glucose intolerance, platelet count, serum albumin level

*ALT = alanine transaminase; AST = aspartate transaminase; NAFLD = nonalcoholic fatty liver disease.*



# Noninvasive testing can assess fat, fibrosis and inflammation

- Elastography
  - MR scan
  - US based scans
    - VCTE>CAP, point shear-wave ARFI, 2D shear-wave
- APRI
- FIB4
- MultiScan
- Fibrosure Fibrotest Fibrospect blood test
- NAFLD NAS score

# ALCOHOL TEST

- BLOOD ALCOHOL LEVEL
- URINE ALCOHOL LEVEL
- HAIR ANALYSIS
- MCV





## What is hair alcohol testing?

A **hair alcohol test** is used to determine if a person has consumed alcohol over a certain period of time. The test works by examining the EtG (Ethyl Glucuronide) and FAEE (Fatty Acid Ethyl Esters) markers in your hair, and is one of the most accurate and established methods for testing alcohol consumption.

EtG and FAEE are both **direct markers of alcohol consumption**, and are only produced when a person has consumed alcohol or has increased blood alcohol levels. They are absorbed into the hair via sweat and diffusion, and contaminate the entire length of the hair, meaning it is not possible to segment the hair, e.g. if you haven't consumed alcohol for 5 months but then excessively drink during one month, the alcohol markers would be found throughout the entire length of the hair.

Testing for EtG markers can show a change in pattern of alcohol consumption, and is the most reliable hair test when determining the levels of alcohol consumed, and FAEE testing is designed to show the long-term alcohol consumption habit. It is advised that hair testing should be combined with another testing method, such as blood testing, in order for the results to be as accurate as possible.

## What can the results show?

Testing hair for alcohol is often used to determine alcohol abuse but it can also be required to show abstinence. The type of hair tested will determine what results are available. Testing head hair can show alcohol abuse, abstinence, or social drinking, chest or arm hair can show alcohol abuse or abstinence, and pubic hair can show abstinence. Head hair is the preferred sample.

## How much hair is needed?

Approximately 200 strands of hair are required for testing. The hair samples will be 3 or 6cm long, depending on the time period your client needs to be tested for, e.g. 3cm of hair will cover a 3-month period.

# Imaging

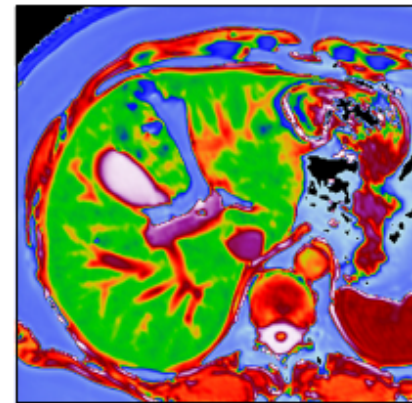
- Full abdominal US is to be considered in all patients with confirmed high ALT, as part of the work up and staging of liver disease
- Spleen size and PV diameter are key tests to look for advanced liver disease: 12:12 rule
  - 12mm for PV, 12 cm for spleen is abnl
- Liver texture: Fatty liver vs. cirrhosis
- Liver surface: smooth vs nodular
- Size of liver
  - Size of left lobe, size of caudate lobe
  - Doppler for flow in all vessels

# Liver Multiscan: MRI-based Multiparametric Tool for Characterizing Liver Tissue

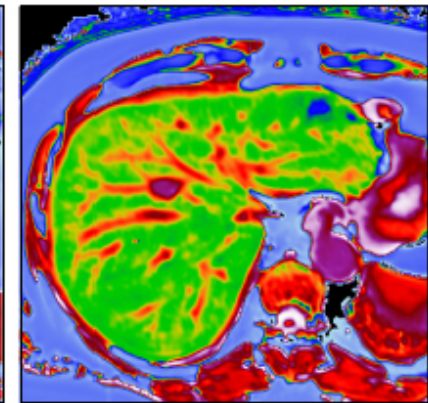
- Noncontrast MRI
  - No problem with obesity/ascites
- Components
  - $T_1$  mapping (fibrosis)
  - Proton spectroscopy (fat)
  - $T_2$  mapping (hemosiderosis)
- Measures iron and fat fraction
- Quantifies inflammation, fibrosis via

LIF score (0 to 4) from MR systems

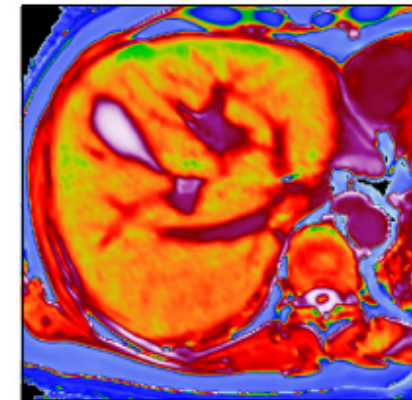
Examples of LiverMultiScan MR Data



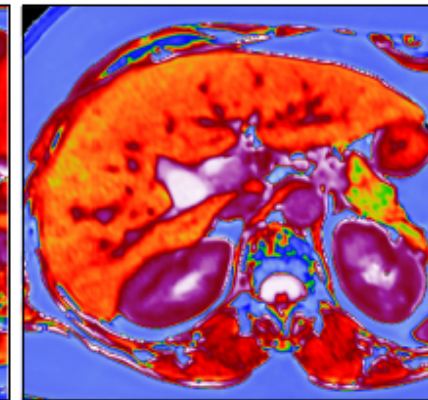
LIF = 0.8



LIF = 1.4



LIF = 2.7



LIF = 3.2

# Liver Multiscan May Be Useful in Predicting Clinical Outcomes

Liver-related Events by T1 Score  
(N=112 patients with CLD)<sup>a</sup>

T1 Score	n	Liver-related events
<1	22	None
1 to <2	34	None
2 to <3	18	Encephalopathy (1) HCC (1)
3 to 4	38	Ascites (4) Encephalopathy (2) Liver-related deaths (2)



**100% NPV for LIF<2**

<sup>a</sup>35% of patients had NAFLD, 20% had chronic HCV. 10 patients (11%) developed a liver-related event over median 27-month follow-up. CLD, chronic liver disease; LIF, Liver Inflammation and Fibrosis Score. Pavlides M et al. *J Hepatol.* 2016;64:308-315.

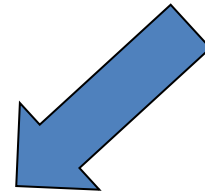
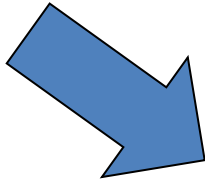
ALT < 20 women  
ALT < 30 men

# NASH Work Up

ABNL US

ABNL LT +  
DM/lipids/HTN/BMI

ABNL LT and BMI > 24



PLT < 150 000  
Or Spleen over 12 cm  
Or PV over 12 mm  
Or NFLD D Score > 0676

Yes

No

Hepatology consult  
EGD  
HCC surveillance  
Aggressive wt loss  
program

Use wt loss contract

# Other test that are surrogates for liver fibrosis

- Platelet count
  - <170 000 flag for F3
  - <100 000 flag for F4
- AST>ALT or AST/ALT Ratio > 0.8
  - Flag for F3 or F4 or recent heavy alc use

Most of the time, with the history, imaging, simple blood tests and a physical exam you should have a good idea what's the likely cause of the elevated liver tests!



# Treatment

- NASH, wt loss and exercise program, see [robertgish.com](http://robertgish.com) for wt loss contract
- HCV: cure with DAA, treat all patients
- HBV: suppress with ETV, TDF or TAF
- ALD: alcohol contract, rehab, AA, BA testing
- Hemochromatosis: Phlebotomy
- AIH: use best treatment via guidelines
- DILI < HILI > SILI, stop drug, med, herb supplement



# Case #1

- 48 year old man is found to have abnormal liver tests on routine physical examination
- No significant PMH
- On no medications, herbs, supplements
- Tried IV drugs “once in college”
- PE normal
- Labs: CBC, BMP normal
- AST 62, ALT 88, Alk phos 75, Tbil 0.7, INR 1.0, Albumin 4.1

• What is your diagnosis ?

# Case #1, continued

- Hepatitis C: Antibody positive
- What now?
  - Check HCV RNA, genotype, CBC, refer to hepatology
  - Check other viral serologies also
    - HIV , HBV and HAV
  - APRI, FIB-4

# Hepatitis C

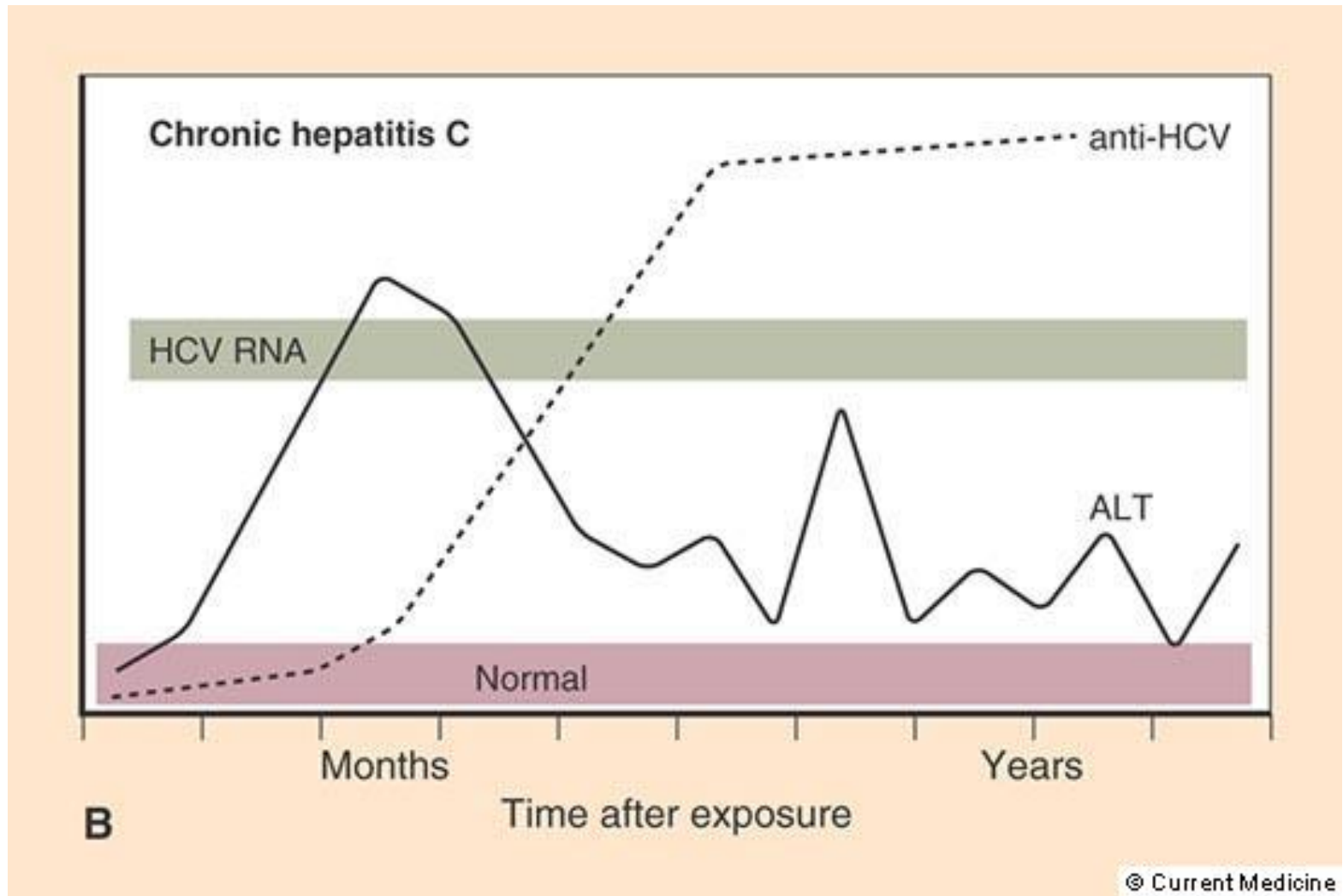
- HCV-Ab (hepatitis C antibody)
  - (+) in chronic or previous infection
  - Sensitive screening test with elevated ALT or risk or age or history of blood exposure, ? Test all adults
  - HCV Aby: Detectable 8-16 weeks after exposure to virus: RNA = at 2 – 6 weeks
  - Very very rare: False positives in autoimmune dz or hypergammaglobulinemia

- False negatives in immunosuppressed

# Hepatitis C

- Hepatitis C viral level in IU/ml not copies
- Quant and Qualitative by PCR to < 10-25 IU/ml, Abbott vs Roche assay
- Level of HCV RNA does not correlate with liver pathology
- Does not predict severity of disease

# Hepatitis C



## Case #2

### 45 year old South African man

- Presents for routine physical and found to have elevated liver tests
- PMH: hyperlipidemia
- Soc: drinks 2 beers/week, no Hx drug use
- Born in South Africa, came to US in 1985
- Family history: none (but he mentions that they don't go to the doctor)
- PE: normal

## Case #2

### 45 year old South African man

- Labs: CBC, BMP normal
- AST 50, ALT 60, Alk phos 70, Tbili 0.5
- INR, Albumin normal
- US normal
- What now?



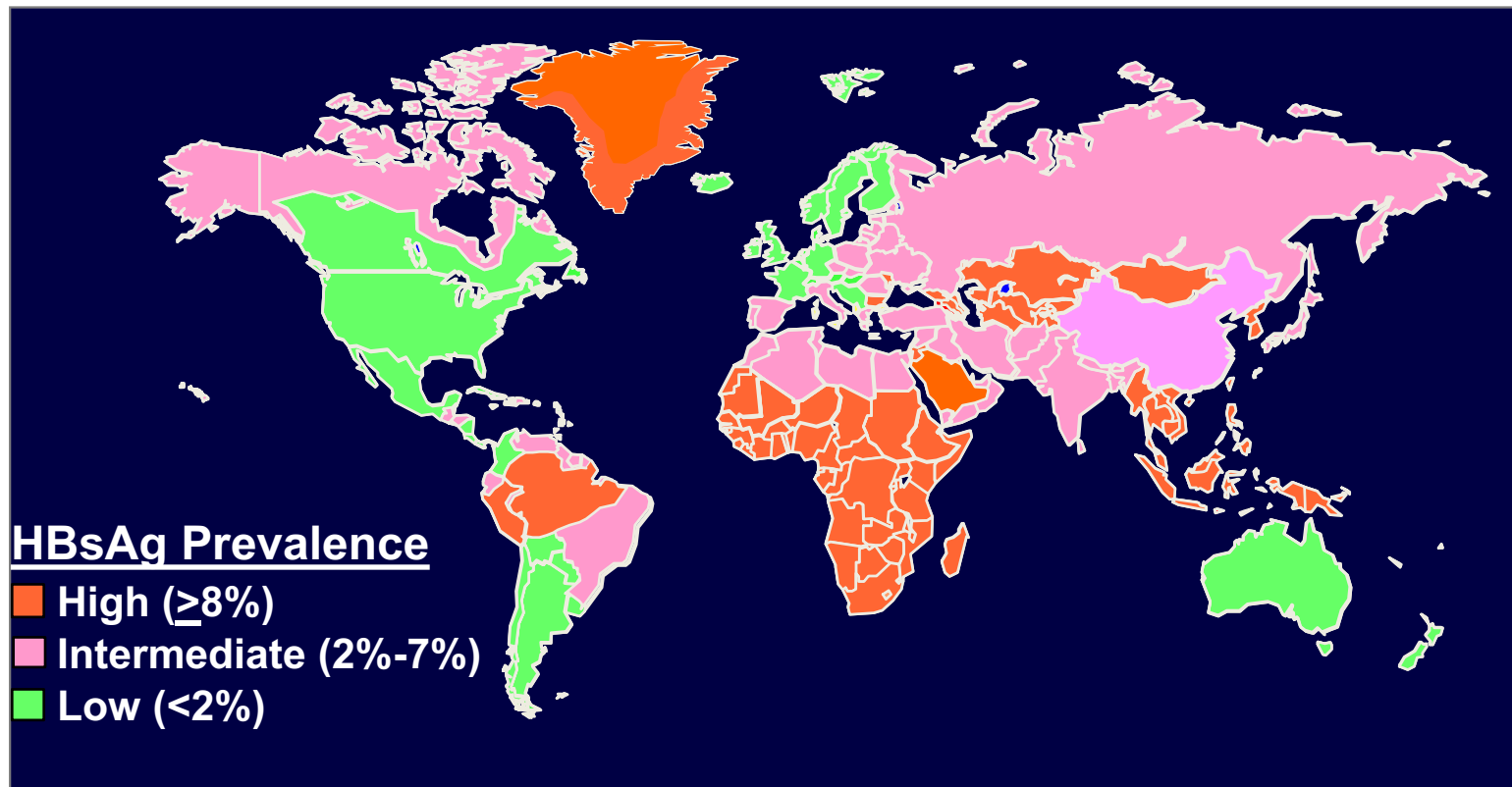
## Case #2

### 45 year old South African man

- Hepatitis BsAg: positive
  - Anti-HBs: negative
  - Anti-HBc: positive
  - What now?
- 
- HBV DNA 1.5 billion ( $10^9$ ) IU/mL, HBeAg pos, anti-HBe neg, delta antibody negative
  - Diagnosis?
    - Chronic Hepatitis B
  - What if HBV DNA was 2000 IU/mL?



# Prevalence of HBV: Global Estimates: note China < 8%; Vaccines work!



Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.

# HBV Serology Interpretation

HBsAg	Anti-HBs	Anti-HBc	HBV DNA	Interpretation
+	-	+ IgM	+	Acute infection or Highly active
+	+	+ IgG	+	Chronic infection
-	+	-	-	Immunized
-	+	+	-/+	Past Exposure, risk for reactivation, no vaccine
-	-	+	-/+	Past Exposure, risk for reactivation, no vaccine

# HBV Serologies and NAT (PCR)

- HBeAg/anti-HBe: only applicable in patients who are chronically infected or carriers
- HBeAg Positive: wild type natural infection, increased infectivity
- HBeAg Negative: core, precore mutant of virus if DNA positive, still can be infective, still has substantial risk for advancing disease
- Levels of HBV DNA important to decide if patient active or inactive with ALT level and imaging

## Case #3

### 19 year old female college student

- c/o severe fatigue of new onset, jaundice, mild pruritus of few days duration
- No EtOH
- Meds: minocycline (acne), multivitamin
- No Hx of contacts with viral hepatitis, travel
- PE: HEENT: mild scleral icterus

abdominal exam: normal bowel sounds, no organomegaly, no tenderness or palpable mass



## Case #3, continued

- Labs: alb 4.2, t bili 4.2, alk phos 248, globulins 3.9 mg/dL
- AST 180, ALT 252;
- CBC normal, lytes normal
- Acute and chronic viral hepatitis serologies neg.

What is the most likely diagnosis?

# Case #3

## 19 year old female college student

**Drug induced cholestasis secondary to minocycline.**

Symptoms resolved within 2 weeks of drug d/c, liver profile normalized in 8 weeks.



# An American Liver Foundation Webinar Program

## Hepatocellular (Elevated ALT)

## Mixed (Elevated ALP + Elevated ALT)

## Cholestatic (Elevated ALP + TBL)

Acarbose  
Acetaminophen  
Allopurinol  
Amiodarone  
Baclofen  
Bupropion  
Fluoxetine  
HAART drugs  
Herbals: kava kava  
and germander  
Isoniazid  
Ketoconazole  
Lisinopril  
Losartan  
Methotrexate  
NSAIDs  
Omeprazole  
Paroxetine  
Pyrazinamide  
Rifampin  
Risperidone  
Sertraline  
Statins  
Tetracyclines  
Trazodone  
Trovaflaxacin  
Valproic acid

Amitriptyline  
Azathioprine  
Captopril  
Carbamazepine  
Clindamycin  
Cyproheptadine  
Enalapril  
Flutamide  
Nitrofurantoin  
Phenobarbital  
Phenytoin  
Sulfonamides  
Trazodone  
Trimethoprim–sulfameth-  
oxazole  
Verapamil

Amoxicillin–clavulanic acid  
Anabolic steroids  
Chlorpromazine  
Clopidogrel  
Oral contraceptives  
Erythromycins  
Estrogens  
Irbesartan  
Mirtazapine  
Phenothiazines  
Terbinafine  
Tricyclics

**TABLE 3. MEDICATIONS, HERBS, AND DRUGS OR SUBSTANCES OF ABUSE REPORTED TO CAUSE ELEVATIONS IN LIVER-ENZYME LEVELS.**

### Medications

#### Antibiotics

Synthetic penicillins  
Ciprofloxacin  
Nitrofurantoin  
Ketoconazole and fluconazole  
Isoniazid

#### Antiepileptic drugs

Phenytoin  
Carbamazepine

#### Inhibitors of hydroxymethylglutaryl–coenzyme A reductase

Simvastatin  
Pravastatin  
Lovastatin  
Atorvastatin

#### Nonsteroidal antiinflammatory drugs

Sulfonylureas for hyperglycemia  
Glipizide

### Herbs and homeopathic treatments

Chaparral  
Chinese herbs  
Ji bu huan  
Ephedra (mahuang)  
Gentian  
Germander  
Alchemilla (lady's mantle)  
Senna  
Shark cartilage  
Scutellaria (skullcap)

### Drugs and substances of abuse

Anabolic steroids  
Cocaine  
5-Methoxy-3,4-methylenedioxymethamphetamine  
(MDMA, “ecstasy”)  
Phencyclidine (“angel dust”)  
Glues and solvents  
Glues containing toluene  
Trichloroethylene, chloroform

# Drug Induced Liver Injury

- Any drug can cause any liver injury!!!!
- Higher risks in women, older age, chronic liver disease
- Can be at start of medication, or in some cases at \*any time\* during therapy or after stopping therapy
- Should rule out other causes of liver injury





# Drug Induced Liver Injury

- A note: acetaminophen is the most common cause of DILI, and also the most common cause of acute liver failure in US
- Normal dose for acetaminophen toxicity is 6 to 12 grams/d, but toxicity can occur in much lower doses in certain circumstances, 2 gm/d
  - Alcohol use
  - Fasting state

# Case #4

## 56 year old woman

- Presents with fatigue, myalgias
- PMH: hypothyroidism, HTN
- Meds: Synthroid, Atenolol, MVI, Ca
- Soc: no drug or alc use
- FHx: father with vitiligo
- PE: appears fatigued, Abd exam with mild RUQ tenderness to deep palpation, BMI 25



# Case #4

## 56 year old woman

- CBC, BMP normal
- AST 245, ALT 280, TBili 2.0, Alk phos 207, Alb 4.0, TP 8.0
- Alb 3.8, INR 1.2, TP 8
- Viral ABC serology panels (-)
- US: mild hepatomegaly, otherwise normal
- Differential diagnosis?
- What further labs?

# Case #4

## 56 year old woman

- ANA >1:640
- F-actin >1:380
- Total globulins: 4 gm/dL
- Quantitative Ig: Elevated IgG
- Viral Hepatitis Markers negative including PCR and hepatitis E
  
- Diagnosis: Autoimmune Hepatitis

# Autoimmune Hepatitis

- Middle-aged (or teenage) woman, non-drinker without viral hepatitis
- Fatigue, arthralgias/myalgias, oligomenorrhea, jaundice
- Increased AST/ALT, gamma globulins, IgG
- Positive ANA and SMA
- All patients need liver biopsy
  - Interface hepatitis with lymphoplasmacytic infiltrate
- Responds to corticosteroids

# Case #5: 60 year old man

- Presents with new onset diabetes, found to have elevated LTs
- PMH: DM II newly diagnosed, OA in hips
- Fhx: none
- Soc: drinks 3 beers/day, no drug use
- PE: normal



# Case #5: 60 year old man

- CBC, BMP normal
- AST 80, ALT 65, Alk phos 125, TBili 0.6
- Alb 3.6, INR 1.0
- BMI 32
- Glucose 142, fasting
- US: increased echogenicity of the liver
  
- Differential?
- Tests?

# Case #5: 60 year old man

- Fe sat 70%, Ferritin 800
- Viral studies negative
- Heavy alc use
- BMI 34
  
- Differential: ETOH (ASH) vs NASH vs Hemochromatosis
- or all three ?
  
- HFE gene test: C282Y homozygote



# Hemochromatosis

- Inherited abnormality of iron absorption
- Affects 0.5% of Caucasian people
  - Rare in other races
- C282Y/H63D gene abnormalities
  - Iron overload seen in C282Y homozygotes and sometimes compound heterozygotes (C282Y/H63D)
- No role for gene testing without elevated iron tests?
  - Use for family members
- Iron tests esp ferritin can be falsely elevated in alcohol, acute inflammation, non fasting state

# Alcoholic Liver Disease

- Seen in 25% of heavy drinkers
  - >5 drinks/day in men, much lower in women
- AST>ALT in many cases
  - AST in mitochondria, and alcohol is a mitochondrial toxin
  - Also see AST>ALT when cirrhosis develops in other nonalcoholic liver diseases
- Cirrhosis can develop without LT abnormalities!
- Alcohol hepatitis rarely has AST>300s

## Case #6

A 47 year old Caucasian female presents with complaints of itching, dry mouth, and RUQ abdominal pain. She also notices some pigmentation changes on her eyelids. Her medical history includes frequent UTI's and osteopenia.

What labs are you most interested in seeing for this patient?



## Case #6

You obtain the following labs:

AST=55, ALT=75, Alk Phos=350, GGT=210,

AntiNuclear Ab. (ANA) is positive

Anti-Mitochondrial Ab. (AMA) is positive

What is the diagnosis?



# Primary Biliary Cholangitis

- Destruction of bile ducts
- Predominantly women
- Ages 30-65
- AMA positive in 95% of cases
- ANA positive in 60% of cases
- Commonly present with fatigue, pruritus
- Treatment with ursodiol can improve (slow) the course of disease

# Extrahepatic Manifestations of PBC

**Fat Soluble  
Vitamin Deficiency**

**Hyperlipidemia**

**Gallstones**

**Renal Tubular  
Acidosis**

**Pruritus**

**Sicca Syndrome**



**Xanthomata**

**Osteopenia**

**Urinary Tract  
Infections**

**Steatorrhea**

**Malignancy**

## Case #6

- A 55 y.o. male with a history of Ulcerative Colitis presents with recurrent low-grade fevers, RUQ abdominal pain, pruritus and jaundice.
- Alk Phos is high at 380
- TBili high at 4.5
- AST and ALT are both mildly elevated <100.
- What test would confirm the diagnosis?
- What cancer is this patient at risk for?

# Diagnosis of PSC

## Primary Sclerosing Cholangitis

- MRCP is most commonly used test to make the diagnosis
- ERCP and Percutaneous cholangiography are rarely used now because it is invasive
  - MRCP is sensitive, and because it is non-invasive, and cost-effective





# PSC

- Most patients will progress to liver transplant or death due to liver failure or infection
- Increased risk for cholangiocarcinoma
  - Surveillance for cancer advised with annual MRCP and biomarkers, CEA and CA19-9
- 90+% associated with inflammatory bowel disease
  - More commonly seen with UC than Crohns
- p-ANCA positive in 80%

## Case #7

- 68 year old Hispanic woman
- Elevated liver tests on routine screening
- PMH: DM, HTN, obesity
- Meds: metformin, lisinopril, ASA
- FHx: both parents died of CAD, brother with DM
- PE: acanthosis nigricans on neck, BMI 38



## Case #7

- AST 85, ALT 120, Alk phos 68, Tbili 0.8
- Alb 4.1, INR 1.1
- US: increased echogenicity, multiple gallstones
  
- Diagnosis?

# NASH

- Serologically, a diagnosis of exclusion
- Liver biopsy is the gold standard
- Abnormal buildup of fat in hepatocytes, sometimes causing inflammation
- Increasing incidence due to increase in obesity
- Risk factors: obesity esp. truncal obesity, hypertriglyceridemia, HTN, insulin resistance, family history
- Treatment: weight loss, treat risk factors
- Statins are ok to use!!!

**Table 2. Lifestyle Management for Patients with NAFLD**

<i>Intervention</i>	<i>Comments</i>
Weight loss: aim to lose 7% to 10% body weight	For patients who are overweight or obese
General nutrition: low-fat to moderate-fat, low-carbohydrate, or Mediterranean diet	All have been shown to be effective in improving NAFLD, but it is unclear which dietary component is superior
Fructose intake: avoid fructose-containing beverages and foods	High fructose intake is associated with NAFLD
Physical activity: 150 to 200 minutes per week of moderate to vigorous exercise*	Vigorous activity may improve nonalcoholic steatohepatitis and fibrosis over moderate activity
Alcohol intake: daily intake less than 30 g for men and less than 20 g for women†	Limiting alcohol intake may lower the risk of NAFLD
Coffee drinking: no liver-related limitations	Coffee drinking may lower the risk of NAFLD

*NAFLD = nonalcoholic fatty liver disease.*

*\*—Moderate exercise: three to six metabolic equivalents of exercise (e.g., slow jogging, brisk walking, gardening); vigorous exercise: more than six metabolic equivalents of exercise (e.g., running, fast cycling, fast swimming).*

*†—14 g of alcohol is equivalent to one standard drink: 12 oz of beer (5% alcohol), 5 oz of wine (12% alcohol), or 1.5 oz of 80-proof spirits (40% alcohol).*

*Information from references 11 through 14.*



# Other liver diseases

- Alpha-1-antitrypsin
  - Abnormal excretion of alpha-1-antitrypsin protein out of hepatocytes: increased buildup in liver, low levels in lung causing emphysema
  - Check Phenotype: ZZ is abnormal
  - Results of a-1-antitrypsin level can change with various disease states, so less specific
- Wilson disease
  - Abnormal copper excretion
  - Low ceruloplasmin (copper binding protein)
  - High 24 hour urine copper
  - Generally young people

# So what does all this mean?

# How to evaluate a patient with abnormal LTs

- Full H&P
- Have patient completely quit ETOH
- Stop ALL unnecessary medications
  - Emphasize to patient to avoid herbal supplements/teas



# How to evaluate a patient with abnormal LTs

- If LT abnormalities are modest (1-2x ULN)
  - Recheck in 1-2 months
  - Rule out chronic viral hepatitis
    - HBsAg, anti-HBs, anti-HBc, anti-HCV
  - BMI, iron sat, repeat alc and medication hx
  - Monitor for 3-6 months
- If they remain elevated
  - Check ANA, AMA (if cholestatic), p-ANCA, quantitative immunoglobulins, Fe studies in Caucasian patients, alpha-1-antitrypsin phenotype, ceruloplasmin if patient <45, TSH, celiac panel (anti-endomysial Ab, anti-TTG), US liver.Ab

# How to evaluate a patient with abnormal LTs

- If LT abnormalities are markedly elevated  $\geq 3x$  ULN
  - Check acute viral serologies: HAV IgM, HBsAg, anti-HBs, anti-HBc (IgM), HCV Ab, HEV total and IgM
  - Then check serology for chronic VH: anti-HBc total
  - ANA, ASMA, pANCA
  - AMA if cholestatic (high AP/GGT > ALT)
  - Fe studies, iron Sat is best screening test
  - Alpha-1-antitrypsin level and phenotype
  - Ceruloplasmin if age <65
  - Quant Ig panel
  - TSH
  - Celiac Panel

# How to evaluate a patient with chronic abnormal LTs

- If LT abnormalities are elevated above ULN confirmed
- HBsAg (and full HBV panel)
- Anti-HCV
- Fe Sat
- Alc history, detailed
- BMI, Glc, Lipid, waist circumference
- History of: OTC medications, prescription meds, herbs, supplements, vitamins



# How to evaluate a patient with chronically abnormal LTs

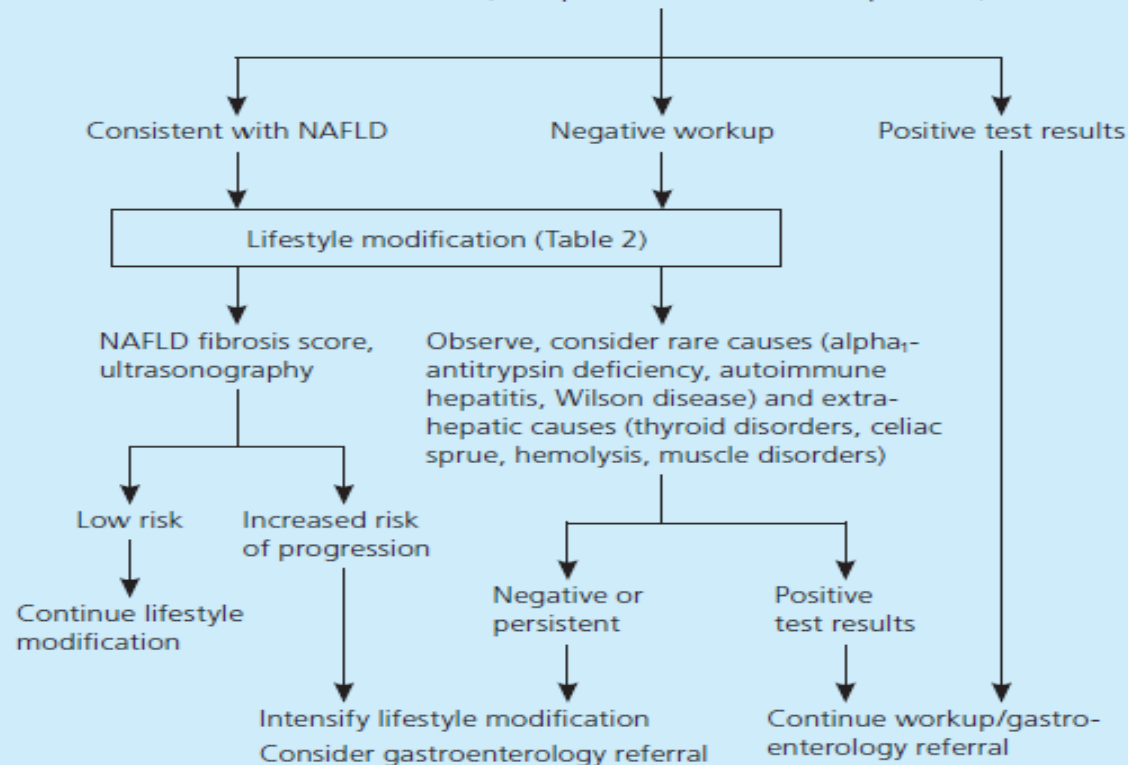
- Every patient needs an imaging study
  - Ultrasound with doppler flow of portal vein, hepatic veins, hepatic artery, spleen size, PV diameter
- If LTs significantly elevated, increasing or persistently elevated
  - Consider referral to Gastro/hepatology

## Management of Mildly Elevated Liver Transaminase Levels

Mild, asymptomatic elevations in ALT and AST (less than five times the upper limit of normal)

History and physical examination aimed at detecting common causes (NAFLD, alcoholic liver disease) and uncommon causes (drug-induced liver injury, viral hepatitis, hereditary hemochromatosis)

Laboratory testing (e.g., fasting lipid levels, blood glucose level [or A1C], hepatitis B surface antigen and hepatitis C virus antibody testing, serum iron level, total iron-binding capacity, ferritin level, serum albumin level, complete blood count with platelets)



**Figure 1.** Algorithm for the management of mildly elevated liver transaminase levels. (ALT = alanine transaminase; AST = aspartate transaminase; NAFLD = nonalcoholic fatty liver disease.)

# Q & A

For more information, visit the  
**American Liver Foundation** at:

[www.liverfoundation.org](http://www.liverfoundation.org)

or call

**800-GO-LIVER (800-465-4837)**



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