Approach to Elevated Liver Tests

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Lecture Objectives

At the conclusion the audience should have a better understanding of

- What constitutes an abnormal aminotransferase
- How to make an initial evaluation of an abnormal test
- Understand disease specific serologic tests
- Understand laboratories which are prognostic in chronic liver disease

Lab Value Ranges

- Alanine aminotransferase (ALT):
  - Male: 29 to 33 units/L
  - Female: 19 to 25 units/L
- Aspartate aminotransferase (AST):
  - Male: 10 to 40 units/L
  - Female: 9 to 32 units/L
- Alkaline phosphatase:
  - Male: 45 to 115 units/L
  - Female: 30 to 100 units/L
- Bilirubin, total: 0.0 to 1.0 mg/dL (0 to 17 micromol/L)
- Bilirubin, direct: 0.0 to 0.4 mg/dL (0 to 7 micromol/L)
- Gamma-glutamyl transpeptidase (GGT):
  - Male: 8 to 61 units/L
  - Female: 5 to 36 units/L
- Prothrombin time (PT): 11.0 to 13.7 seconds
- Albumin: 3.3 to 5.0 g/dL (33 to 50 g/L)

Normal versus Abnormal

- Most laboratories use > 2 SD to define abnormal
  - The differences in clinical laboratories abnormal is based on the health of the reference population

- Understand the difference between statistical significance and clinical significance
  - ALT = 35 (>2 SD but is it relevant? . .)
  - Blood glucose 101 (>2 SD but is it relevant? . . .)

A “normal” ALT lab value does not exclude liver disease or histologic damage

Who to test? Do we screen?

No recommendation to routinely test healthy, asymptomatic persons

- When Do We Screen for a Disease?
  - Medically important
    - Yes
  - Relatively high prevalence
    - Yes
  - Natural history of disease should be known
    - Is it serious?
    - Limited data (Lack of population based data)
  - Effective intervention should exist
    - Limited interventions for some diseases (NAFLD)
  - Cost Effective

LFTS: Worrisome?

20 yo male

- TB 1.8
- AP 180
- AST 2789
- ALT 6239
- Alb 3.0
- PT 20

29 yo female

- TB 22.0
- AP 99
- AST 560
- ALT 901
- Alb 2.1
- PT 66

LFTS: Worrisome?

20 yo male

- TB 1.8
- AP 180
- AST 2789
- ALT 3239
- Alb 3.0
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29 yo female

- TB 22.0
- AP 99
- AST 560
- ALT 901
- Alb 2.1
- PT 66

Interpretation of Liver Tests

True “liver function tests”

- What does the liver do?

Hepatocellular damage

Cholestasis

Are the abnormalities noted acute or chronic?

True Liver **Function** Tests

- Prothrombin time
  - High PT/INR: increased risk of bleeding
  - Vitamin K deficiency, consumptive coagulopathy
- Albumin
  - Low albumin: edema, anasarca
  - Nephrotic syndrome, malnutrition, protein losing enteropathy
- Bilirubin
  - Jaundice (total bilirubin > 2-3 mg/dL)
- Cholesterol

Markers of Hepatocyte Damage

- ALT (alanine aminotransferase--SGPT)
  - Cytosol of hepatocytes
  - More hepatocyte specific
- AST (aspartate aminotransferase--SGOT)
  - Cytosol and mitochondria
  - Muscle, intestine, brain, kidney, pancreas, red blood cells
  - Mitochondrial induction/damage by alcohol explains higher AST levels in persons consuming excessive ETOH, vitamin deficiency leads to lower ALT
- Lactate dehydrogenase (LDH)
  - Can be markedly elevated in shock liver

Markedly Elevated Aminotransferase Levels (> 1,000 U/L)

Drug/toxin induced injury

- Acetaminophen
- NOT alcohol alone

Acute viral hepatitis

Shock liver / Ischemic Injury

Veno-occlusive disease/Budd-Chiari syndrome

Autoimmune hepatitis

Common bile duct stone

Acute liver failure

1: alt/ast >10 times the upper limit of normal

2: hepatic encephalopathy

3: prolonged prothrombin time

ALT/AST ratios

- In most liver diseases ALT > AST

- Exceptions:
  - Alcoholic liver disease
  - >2:1 ratio Wilson's disease
  - Accompanying hemolytic anemia
  - Advanced fibrosis

Markers of Cholestasis

- Alkaline phosphatase
  - Localized in microvilli of bile canaliculus
  - Hepatic synthesis ⇑ in cholestasis
  - Fractionation can help
  - Bone, intestine, placenta
- Gamma glutamyl transferase (GGT)
  - Induced by alcohol, medications
- 5'-Nucleotidase
  - Specific to liver
- Bilirubin
  - Mild cholestasis or partial biliary obstruction do not necessarily increase bilirubin.
  - Bilirubin level represents balance between production, conjugation, and excretion into bile.

Cholestasis

Unconjugated hyperbilirubinemia	Conjugated hyperbilirubinemia	Elevated Alkaline phosphatase
Gilbert's syndrome Crigler-Najjer syndrome Hemolysis Hematoma resorption	Bile duct obstruction Severe hepatitis Cirrhosis Medication/Toxin PBC PSC Sepsis TPN Benign recurrent cholestasis Vanishing bile duct syndrome Dubin-Johnson syndrome Rotor syndrome	Hepatobiliary Bile duct obstruction PBC PSC Medications Hepatic metastasis Severe hepatitis Cirrhosis Vanishing bile duct syndrome Benign recurrent cholestasis Infiltrating diseases Sarcoid TB Fungal Amyloidosis Heme malignancy

Bilirubin Metabolism

- Bilirubin is a normal heme degredation product
  - Predominant excretion is in bile
  - Unconjugated (indirect) is taken up by hepatocytes
  - Conjugated (direct) by the endoplasmic reticulum using enzyme bilirubin UDP-glucuronyltransferase
  - Water soluble bilirubin glucuronides secreted across canicular membrane into bile
- Clinical correlate**: Gilbert's syndrome**
  - Diminshed expression of bilirubin UDP-glucuronyltransferase
  - Up to 4-9% of population
  - Benign, unconjugated hyperbilirubinemia
  - Can be worsened by stress, fasting

First Approach

- Repeat abnormal tests(?????)
  - Many will normalize without intervention, **ONLY** consider if no risk factors are present
  - Discontinue alcohol, potential hepatotoxins
  - Would not wait however if there are signs of synthetic dysfunction
    - Elevated bilirubin, PT prolongation
- Continued Elevation
  - Work up is based on pattern of abnormalities
    - Hepatocellular injury versus cholestatic
    - Acute versus Chronic

Clinical scenario

A 55 year old man is admitted overnight, he is new to LUMC and presents with melena

On US he has a nodular appearing liver with possible fatty infiltration

Relevant labs ALT 55, AST 77, TB 0.9, AP 88, PLT 55, HGB 8.9

He undergoes endoscopy finding recently bleeding varices which were banded

Continued

Which of the following labs sent over night are unnecessary?

Acute hepatitis panel (hep A IgM, HB S AG, Anti-HBV core AB total, Anti-HCV)

ANA, ASMA, AMA

Ceruloplasmin

Alpha-1 antitrypsin

Ferritin, iron, TIBC

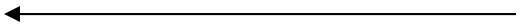
Tylenol level

Serum alcohol

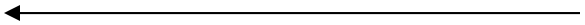
The “shotgun” approach

Liver ~~consult~~

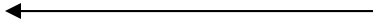
- HAV IgM
- HBV s Ag, core IgM
- Anti-HCV
- AMA
- ANA, ASMA
- Ceruloplasmin
- Alpha-1 antitrypsin
- Iron, TIBC, ferritin
- Tox screen
- RUQ US
- Consider Biopsy



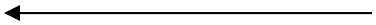
Chronic hepatitis?



Is there cholestasis?

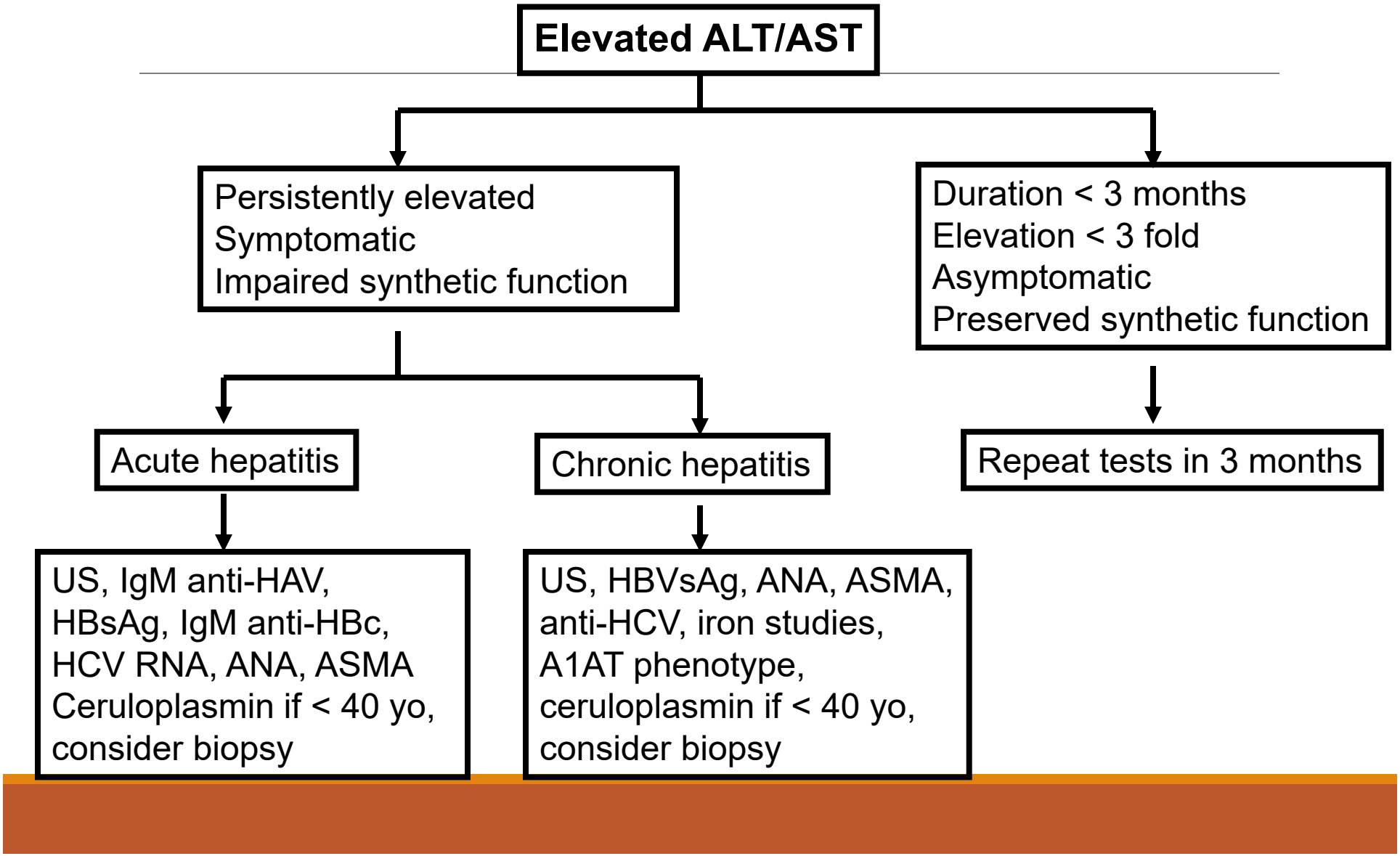


Patient age?

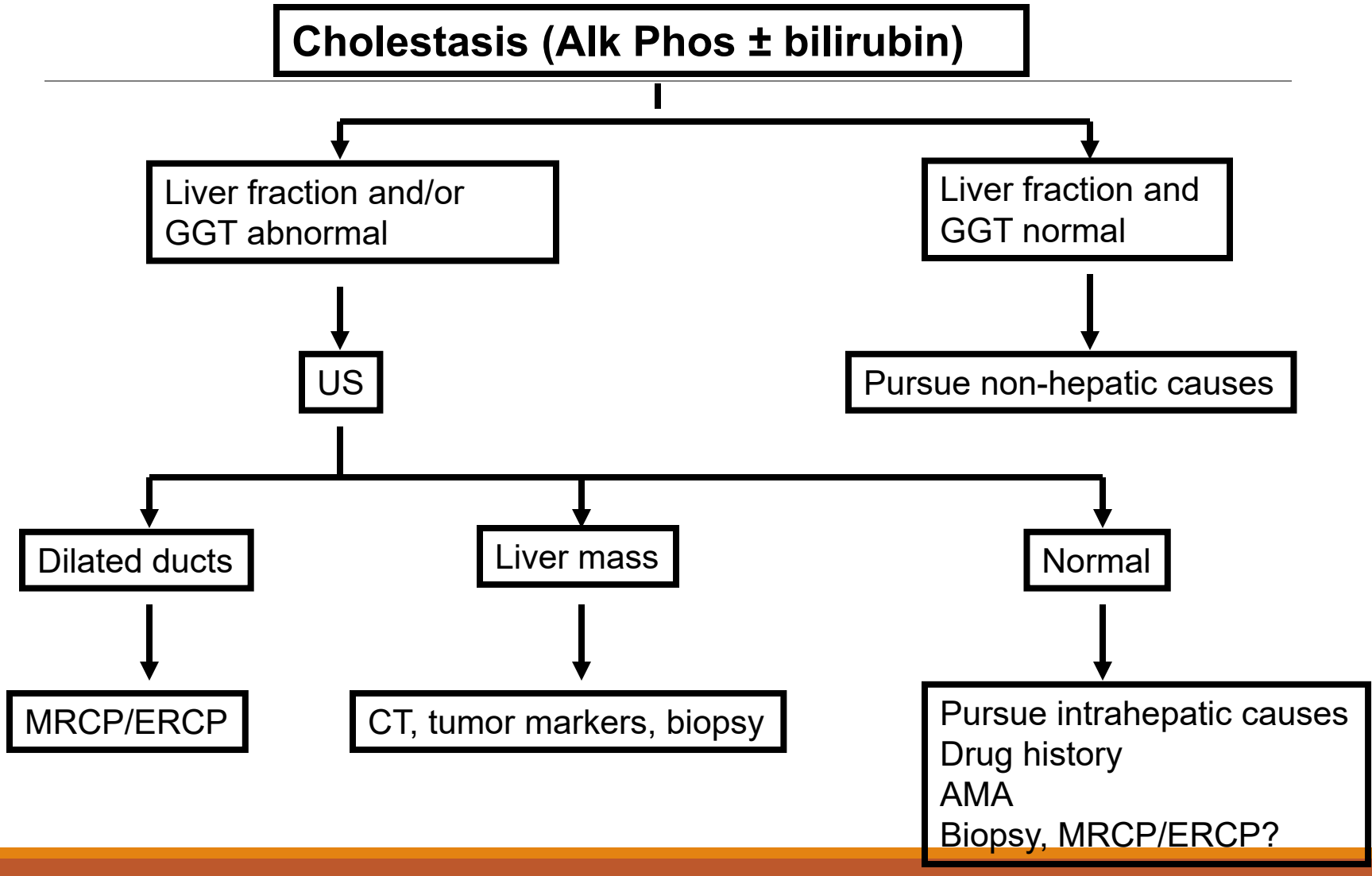


Acute ingestion?

General Approach to Abnormal LFTs



General Approach to Abnormal LFTs



Historical Clues

History Component	Disease Correlation
Remote history of jaundice	Viral hepatitis
Medical history of autoimmune diseases	AIH
Hypothyroidism	AIH, PBC
History of liver disease as a newborn	Alpha-1 antitrypsin deficiency
Family history of liver disease	HBV, hemochromatosis
History of alcohol abuse, DUI	Alcohol
History of IVDA, blood transfusion prior to 1990	HCV
Diabetes	Hemochromatosis, NAFLD
Components of Metabolic Syndrome	NAFLD
Medications, CAM therapy	Drug induced liver injury
Pruritis	PBC
Ulcerative Colitis	PSC
Arthritis	Hemochromatosis, HCV

Physical Clues

Physical Exam Findings	Disease Correlates
Spider angiomas	Cirrhosis
Palmar erythema	Cirrhosis
Splenomegaly	Portal hypertension
Jaundice	Cirrhosis, Biliary obstruction, hemolysis, Gilbert's
Hyperpigmentation	Hemochromatosis
Kayser-Fleisher rings	Wilsons disease
Emphysema/Lung disease	Alpha-1 antitrypsin deficiency
Ascites	Portal hypertenson, cirrhosis
Asterixis	Portal hypertension
Xanthelasma	PBC

Patient Characteristics

- Sex:
  - Female (AIH, PBC)
  - Male (PSC)
- Age:
  - Neonatal (A1AT)
  - < 40 (Wilson's, AIH)
  - > 40 (viral, HFE)
- Medications:
  - Antiepileptics
  - HAART
  - INH
- Risk factors HCV:
  - IVDA (viral, EtOH)
  - Blood transfusions
  - Tattoos
- Comorbidities:
  - DM/obesity: NASH
  - CHF: HFE
- Family Hx
  - A1AT deficiency
  - Hemachromatosis
- Country of Birth
  - HBV

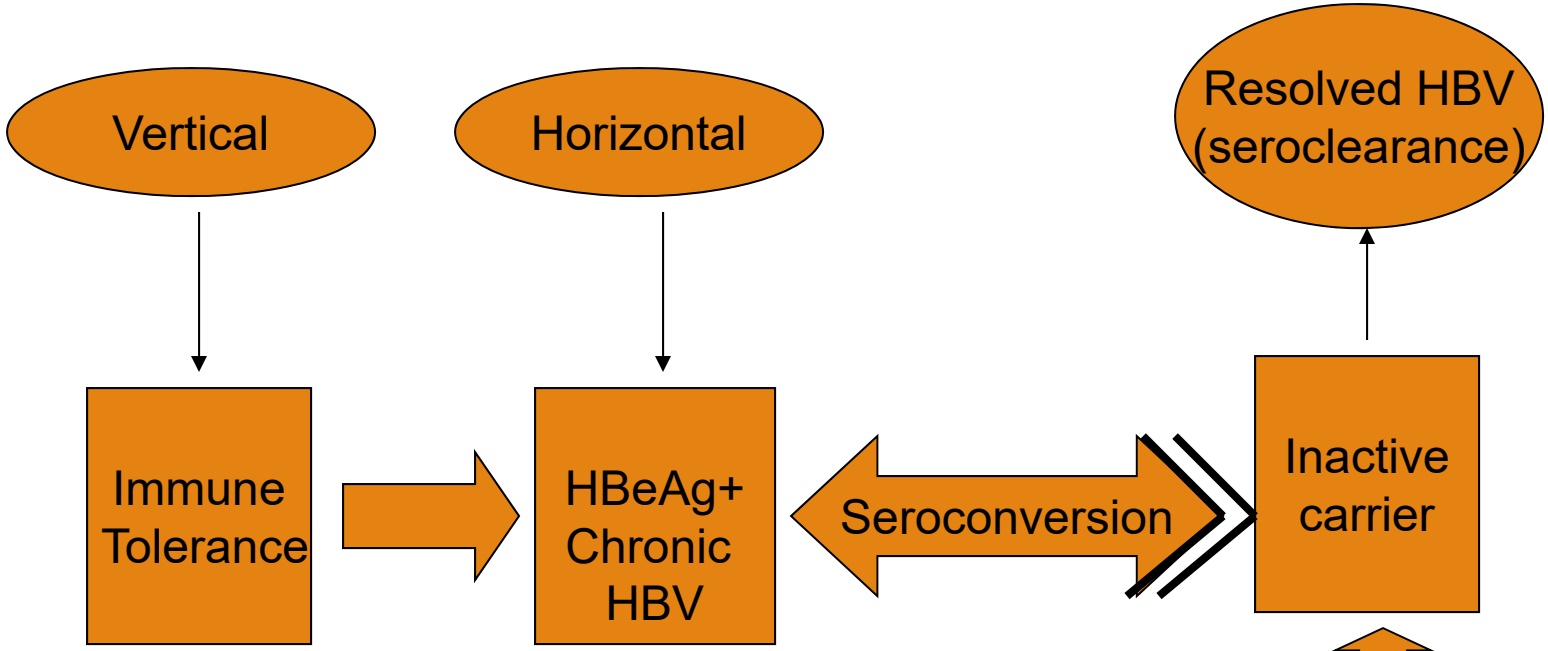
Liver Disease

A clinician is better able to understand the evaluation of liver disease with a basic understanding of each individual disease

The next section will focus on serology of chronic liver diseases

Hepatocellular causes

Disorder	Acute	Chronic
Hepatitis A	+	
Hepatitis B	+	+
Hepatitis C	+	+
Hepatitis E	+ (liver failure w/pregnancy)	(rare)
Autoimmune hepatitis	+	+
Wilson Disease	+	+
Hemochromatosis		+
Alpha-1 AT deficiency	(neonatal)	+
NAFLD		+
Alcohol	+	+
Medication/Toxin	+	+



Immune Tolerance:
Normal ALT
DNA > 20,000,000 IU/ml
Low grade on biopsy

Chronic HBV:
Elevated ALT
E Antigen Positive
DNA > 20,000 IU/ml
E Antigen Negative
DNA > 2,000 IU/ml

Inactive Carrier:
HbeAg-/Anti-HBe+
Normal ALT
HBV DNA < 2,000

Diagnosis of HBV

	HBsAg	HBc	HBe	HBsAb	HBV DNA
Acute	HBsAg	HBcIgM			+
Chronic (immune tolerant or active)	HBsAg	HBcIgG	HBeAg+ or eAg-		$>10^4$-10^5
Inactive Carrier	HBsAg	HBcIgG	eAb+		$<10^4$
Immune		HBcIgG		HBsAb	
Vaccinated				HBsAb	

HCV lab tests

HCV test	Comment
Anti-HCV	Seropositive in past and current infection
HCV RIBA	Seldom used Can distinguish false positive AB from past infection
HCV RNA	Viremia indicates current infection Viral load does not correlate with severity of liver disease
HCV genotype	Measure if considering interferon based therapy Genotype 1 predominates in US

Hemochromatosis

- **LABS: iron/TIBC, ferritin, genotype**
- Clinical suspicion
  - Fatigue, arthralgia, diabetes mellitus, hyperpigmentation, impotence
- Transferrin saturation and ferritin
  - TS > 45%
    - Sensitivity >97%
    - Specificity 45%
  - Ferritin > 1000 mg/ml marker of significant disease
- Genotype
  - C282Y (prevalence 5/1000 if Northern European descent)
    - Accounts for 80-85% of typical hemochromatosis
    - Only 10% of C282Y homozygotes will have end organ damage
  - Other mutations: ie H63D, S65C controversial

Autoimmune Hepatitis

- **LABS: ANA, ASMA, anti-LKM (kids), immunoglobulins**
- Type 1 AIH
  - Women (4:1), peak 20's to 40's
    - All ages and ethnic groups susceptible
  - ANA (67%), SMA (87%)
    - ANA found in PBC, PSC, viral hepatitis, drug related hepatitis, NASH, ETOH
    - pANCA common
  - Hyperglobulinemia (high IgG)
- Type 2 AIH (young women)
  - Anti-LKM1
  - Less hyperglobulinemia
  - Tends to be more severe at onset and more likely to progress to cirrhosis

Wilson's

LABS: ceruloplasmin, 24 urine copper, serum copper, genetic testing

Test	WD	Comments
Ceruloplasmin	<20 mg/dl	95% homozygotes 20% heterozygotes
Slit-lamp	KF rings	Absent early F(+) cholestatic disease
24 hour urine	>100 ug	F(-) early F(+) cholestatic disease
Hepatic copper	>250 ug/g	F(+) cholestatic disease F (-) sampling error

Genetic testing by whole-gene sequencing exists, but can be difficult as most persons with WD are compound heterozygotes and there are roughly 300 mutations

Alpha-1 Antitrypsin Deficiency

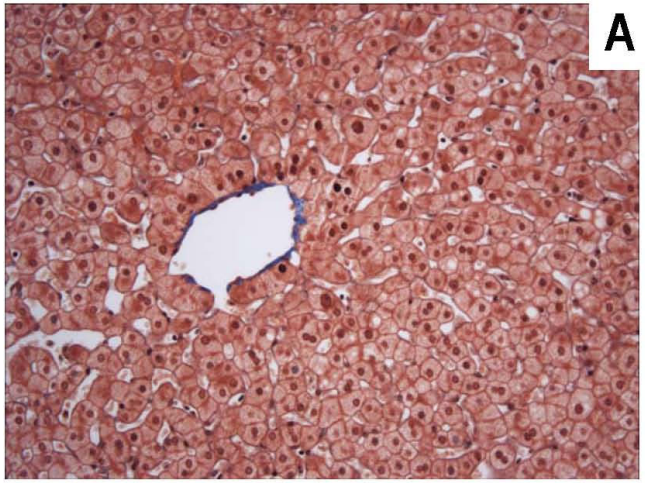
- **LABS: alpha1-antitrypsin level, phenotype**
- Serine protease inhibitor for which liver disease results from failure to export
- History
  - 10% develop neonatal hepatitis or obstructive jaundice
- Serum levels
  - Low
- Phenotyping
  - PiZZ most severe (10-15% of normal levels)
- Liver histology
  - A1AT globules in ER of periportal hepatocytes

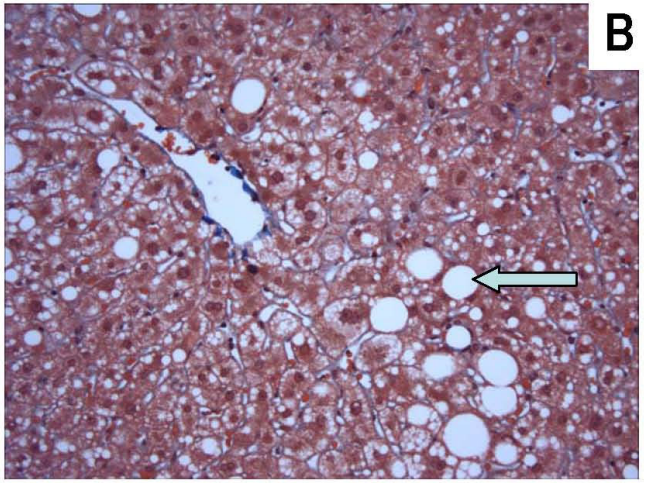
NAFLD

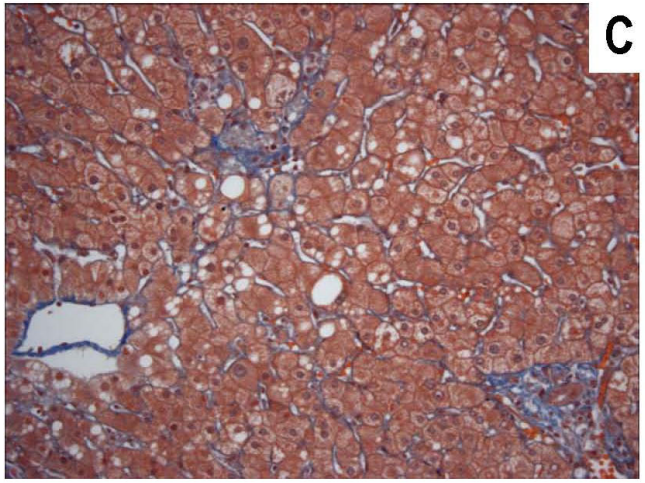
- NAFLD
  - 20-30% in US
- NASH
  - 3% of general population
  - 20% of obese individuals
- Disease associations
  - Metabolic syndrome
    - Visceral obesity, insulin resistance, dyslipidemia (HDL, TG), elevated blood pressure
- Asymptomatic transaminase elevation
    - ALT > AST
  - GGT may be increased
  - Alk phos usually < 2x ULN
  - Elevated ferritin—60% (marker for IR)

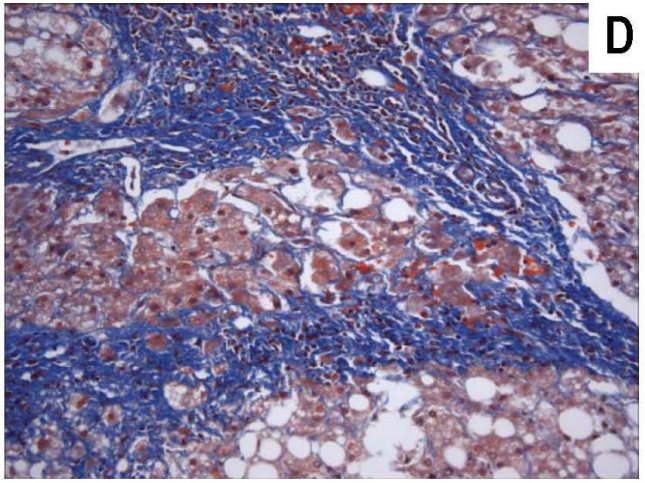
normal

steatohepatitis









steatohepatitis w/
mild fibrosis

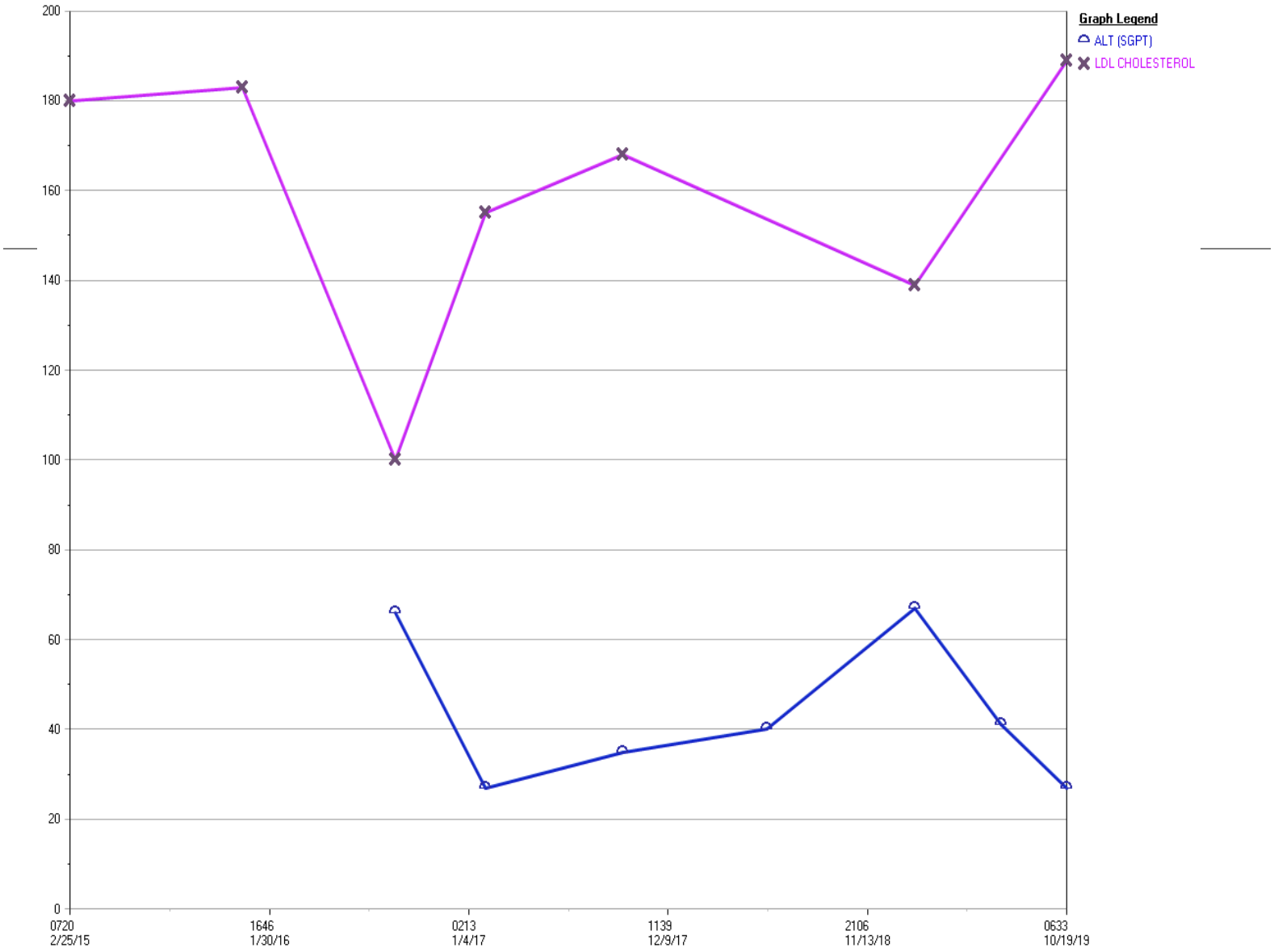
steatohepatitis w/
established cirrhosis

Alcoholic Hepatitis

- Diagnosis-History
  - Ask about DUI
  - AST>>ALT (both typically < 300 U/L)
  - Elevated bilirubin and prolonged PT
  - Alkaline phosphatase often normal
- Calculate discriminant function
  - Serum bilirubin + 4.6*(patient PT- control PT)
- DF > 32 is important
  - Designates poor prognosis, high mortality
  - Marker for therapy consideration
    - Prednisolone, pentoxifylline

Hepatotoxic Medications

- Commonly prescribed Medication
  - Augmentin
  - Anti-Epileptics
  - Azole (antifungal)
  - Isoniazid
  - Anesthetics
    - Halothane
  - Nicotinic acid
  - Nitrofurantion
  - Propylthiouricil
  - Oral hypoglycemics
    - Glyburide
    - TZDs
  - HMG CoA reductase inhibitors
  - Protease inhibitors
- OTC, CAM, illicit
  - Acetaminophen
  - NSAIDs
  - Ephedra
  - Kava
  - Chaparral
  - Black Cohosh
  - Ecstasy
  - Hydrofluorocarbons
  - Chloroform
  - Toluene


Graph Legend
ALT (SGPT)
LDL CHOLESTEROL
200
180
160
140
120
100
80
60
40
20
0
0720
2/25/15
1646
1/30/16
0213
1/4/17
1139
12/9/17
2106
11/13/18
0633
10/19/19

LFT's and Statins

- Chronic aminotransferase elevation and histological injury has never been convincingly proven
- Significant hepatotoxicity attributable to statins is very rare
- Use of lower doses and highly lipophilic (cerivastatin, lovastatin, simvastatin) may reduce hepatotoxicity

Agent	RR	CI
Highly Lipophilic	1.58	0.81, 3.05
Mildly Lipophilic	3.54	1.72, 5.58

Argo et al Hepatology 2008;48:662

Cholestatic Liver Disease

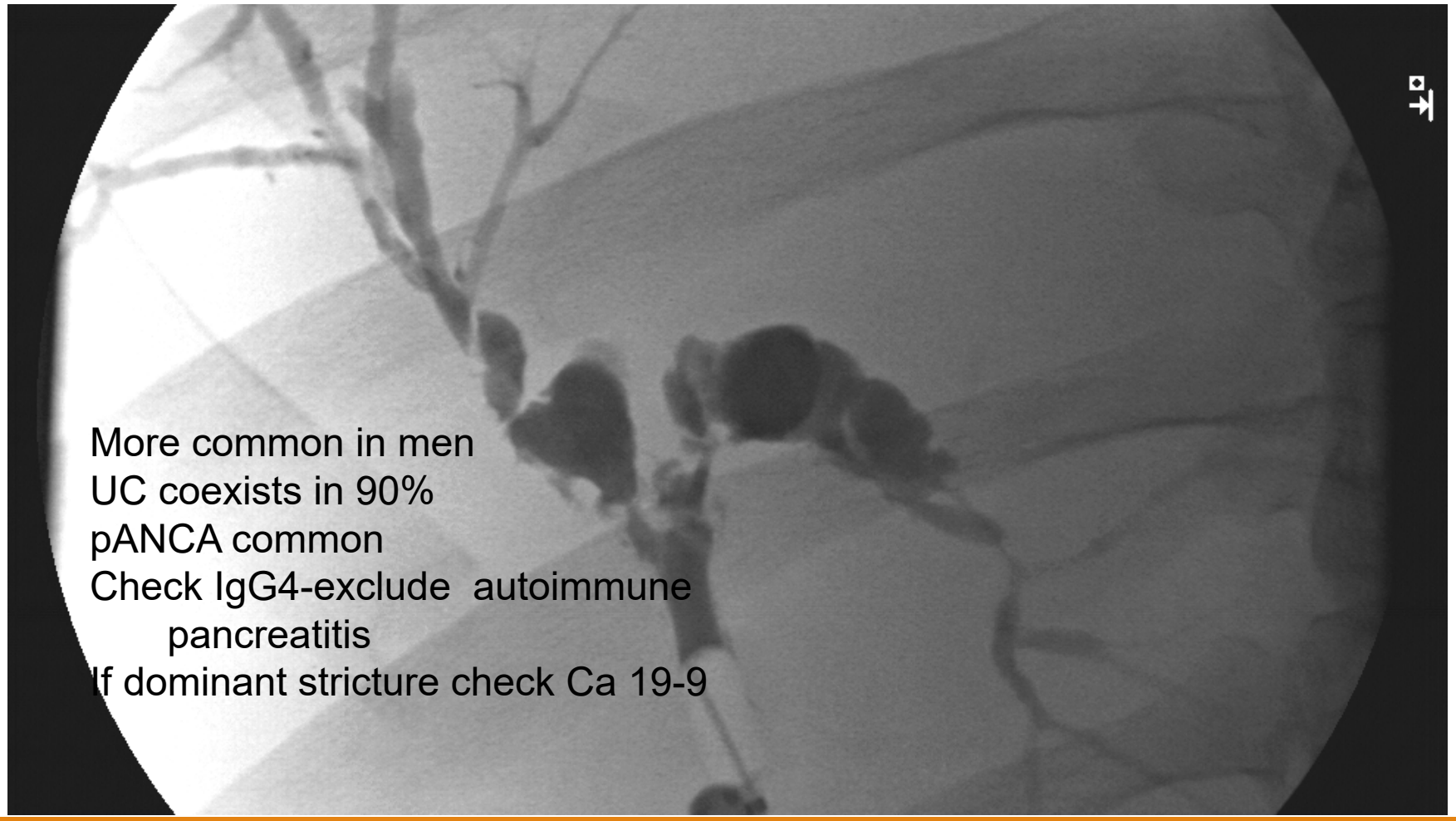
Disorder	Acute	Chronic
PBC		+
PSC		+
Obstructive Jaundice	+(pain)	+
Medications/Toxins	+	+

Primary Biliary Cholangitis

LABS: AMA, immunoglobulins

- Serologic
  - Anti-mitochondrial antibody (AMA)
    - 95% positive in PBC
    - 1% general population
    - 5% PBC patients AMA negative
    - Targets mitochondrial specific complexes
  - High levels of IgM
  - Alkaline phosphatase elevation > aminotransferases
  - Increased bilirubin associated with worsened disease severity
  - High cholesterol (especially HDL)

Primary Sclerosing Cholangitis



More common in men
UC coexists in 90%
pANCA common
Check IgG4-exclude autoimmune pancreatitis
If dominant stricture check Ca 19-9

Medicines that Cause Cholestasis

- Anabolic steroids
- Allopurinol
- Amoxicillin-clavulanic acid
- Atazanavir
- Diltiazem
- Erythromycin
- Estrogens
- Indinavir
- Nevirapine
- Methyltestosterone
- Quinidine
- Total parenteral nutrition
- Trimethoprim-sulfamethoxazole

Surveillance for HCC

AASLD recommends US (and AFP*) every 6-12 months for surveillence

- Hepatitis B carriers
  - Asian males ≥ 40
  - Asian females ≥ 50
  - Cirrhosis at any age
  - Positive family history
  - Africans ≥ 20
- *For those not listed above HCC risk varies; consider HBV viral load and grade of inflammation*

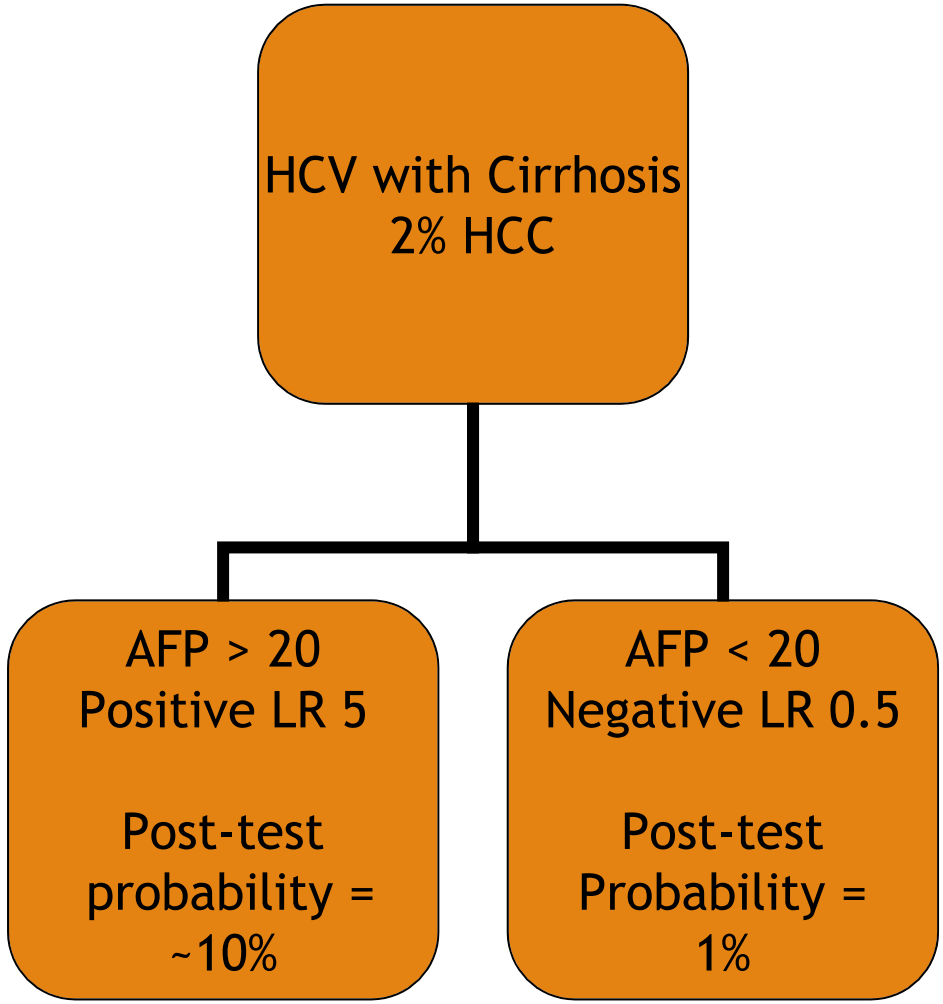
Non-hepatitis B Cirrhosis

- Hepatitis C
- Alcohol
- Hemochromatosis
- PBC
- Alpha-1 antitrypsin
- NASH
- Autoimmune hepatitis

Bruix Hepatology 2010 (AASLD position paper)
*AFP was dropped from 2010 guidelines

Alpha-Fetoprotein

- AFP is a marker of liver regeneration
  - It is often elevated in viral hepatitis
- AFP can be used for surveillance and diagnosis
- AFP > 20 ug/dl
  - Sensitivity 41-65%
  - Specificity 80-94%
  - Positive LR 3.1-6.8
  - Negative LR 0.4-0.6
    - Gupta Ann Intern Med 2003



Clinical scenario

A 45 year old woman sees you in follow up.

She has HCV and alcohol cirrhosis, but stopped drinking 2 years ago

Her labs include CR 0.8, TB 0.9 and INR 1.1, AST 66, ALT 48

She recently saw hepatology and was told she did not need transplant

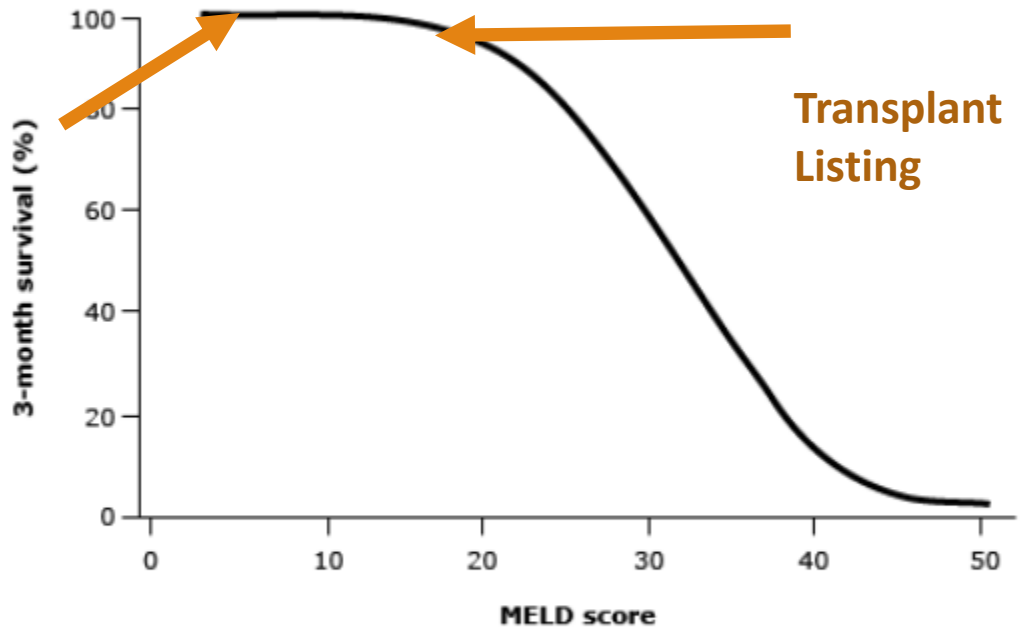
As her primary care doctor she asks if you agree

Severity of Liver Disease

- Child-Turcotte-Pugh System (CTP)
  - Not formally validated as prognostic tool
  - Useful means to rapidly assess prognosis
  - Also useful for pre-operative risk assessment
  - Semi-Subjective
- Model for End stage Liver Disease (MELD)
  - Currently used for transplant listing
  - Based on creatinine, INR, total bilirubin (Cr and INR more heavily weighted)
  - Objective values comprise score
  - Validated to predict survival
    - 3 month survival for a MELD of
      - 6 >90%
      - 40 < 7%
        - Malinchoc Hepatology 2003

Estimated 3-month survival as a function of the MELD score in patients with cirrhosis

OUR Scenario: MELD Score of 5



MELD: Model for End-Stage Liver Disease.

Adapted from: Wiesner, R, Edwards, E, Freeman, R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003; 124:91.

Graphic 77732 Version 4.0

MELD Score

- $3.8*\log_e(\text{serum bilirubin}) + 11.2*\log_e(\text{INR}) + 9.6*\log_e(\text{serum creatinine}) + 6.4$

- MELD – Na
  - Increase in mortality by 5 % per mmol decrease in serum Na between 125 - 140
  - If initial MELD score >11, the score is then re-calculated as the MELD-Na score
  - MELD-Na = MELD + 1.32 * (137-Na) - [0.033*MELD * (137-Na)]
  - For example, a patient with a MELD score of 12, but a serum sodium level of 125 mmol/L, will have a MELD-Na score of 23
    - elevates the transplant priority for about 12 % of listed patients
    - may be vulnerable to alterations by diuretic use and IVF

OUR Scenario: MELD Score of 5

CTP score

	1 point	2 points	3 points
Grade encephalopathy	None	1-2	3-4
Ascites	Absent	Slight	Moderate or more
Bilirubin	1-2	2-3	>3
Bilirubin (for PBC patients)	1-4	4-10	>10
Albumin	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Score ≤6 Class A, 7-9 Class B, ≥10 Class C

Important Disease Assocations

- Emphysema and Liver disease
- Cirrhosis, DM, arthritis, AFIB
- IBD and elevated alkaline phosphatase
- Viral hepatitis associated with liver failure in pregnancy
- Liver disease, with anemia and psychosis
- ALT greater than 5000 in someone with alcoholism
- Elevated alkaline phosphatase with itching and fatigue seen in a 50 year old woman

Case 1

A 25 year old presents 3 days after a significant acetaminophen ingestion

There is AMS and they are intubated early in the course- NAC is started

Lab	Day 1	Day 2	Day 3
TB	3.2	4.1	4.8
AST	12000	13000	9000
ALT	9000	10000	8500
INR	3.0	4.1	5.3

By Day 3 is the course better, worse or stable?

Case 2

A person is referred for initial elevation in ALT (52)- synthetic function is normal and there are no prior available liver tests

Ultrasound one year prior suggested a fatty liver

Clinical history includes a blood transfusion in 1988 for a trauma, DM, BMI 29 and a family history of cancer in the liver but might have been metastatic

Medications include metformin, losartan and atorvastatin

Conclusions

When evaluating suspected liver disease

- Realize that aminotransferases are imperfect markers of disease state
- Following synthetic function is of vital importance
- Remember medications and complementary medicines
- Approach patients based on risk factors and pattern of liver injury (hepatocellular or cholestatic)
- Use models to assess severity of liver injury