Approach to Elevated Liver Tests

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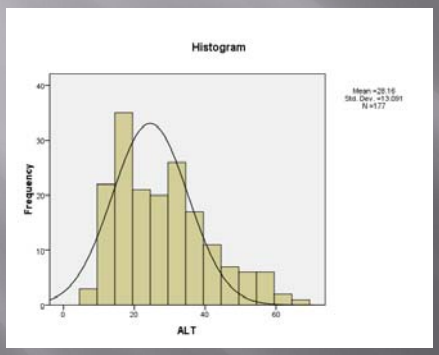
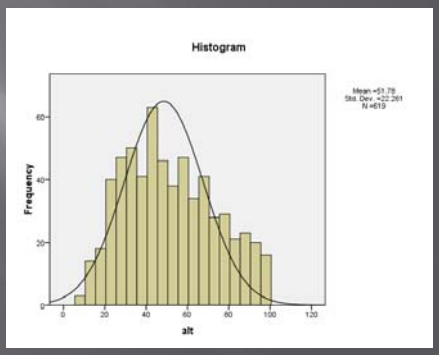
Lecture Objectives

- 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

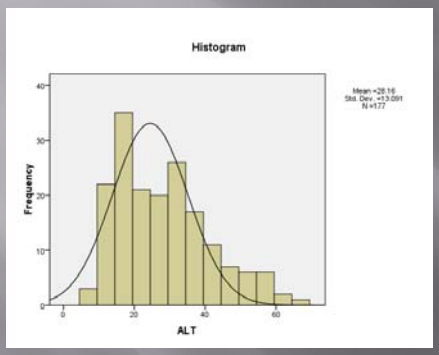
Defining Normal

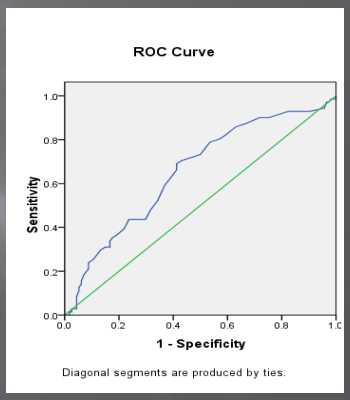




The left depicts 177 overweight patients undergoing routine surgery
The right depicts 629 patients undergoing evaluation for HCV

Defining Normal





For obese persons undergoing bariatric surgery 2 SD above the mean was an ALT of 60 IU/mL
The right is the ability of ALT to discriminate the presence of fatty liver disease in patients undergoing bariatric surgery (AUC = 0.653)

Refining Normal

- Population of persons donating blood
  - Selected those at lowest risk for liver disease (normal BMI, normal lipids and glucose, no medications)
  - Median ALT was 11 U/L
  - Value at the 95th percentile for
    - Women was 19 U/L
    - Men was 30 U/L
- Applied this to a population with HCV RNA
  - Reference of lab "abnormal" was 55% sensitive and 97% specific
  - The above criteria was 76% sensitive and 89% specific

Prati Ann Intern Med 2002;137:1-9

Significant disease can occur at "normal"

- Data from Italy-patients at risk for NAFLD
- 63/458 patients had a liver biopsy with an ALT < 40 U/L (long standing steatosis)
- Mean ALT was 28 ± 7 U/L
- Fibrosis ≥ 2 (moderate) was seen in 22% with "normal" ALT and 34% with increased ALT (p=ns)
- 5/63 (8%) persons had cirrhosis
- Of 37% of persons with NASH and a normal ALT, 27% met more stringent criteria for normal
  - Fracanzani Hepatology 2008 ;48:792-798

Conclusions

- Most laboratories use > 2 SD to define abnormal
  - The differences in clinical laboratories abnormal is based on the health of the reference population
- There is difficulty defining "normal" so your clinical suspicion for disease should must supersede labs
- A "normal" ALT does not exclude liver disease or histologic damage

Who to test?

- No recommendation to routinely test healthy, asymptomatic persons
- Screened disease
  - Medically important
    - Yes
  - Relatively high prevalence
    - Yes
  - Natural history of disease should be known
    - Limited data (Lack of population based data)
  - Effective intervention should exist
    - Limited interventions for some diseases (NAFLD)

Prevalence of abnormal aminotransferases

- NHANES III data
- Used ALT > 40 for men and > 31 for women as abnormal
- Prevalence of abnormal aminotransferases was 7.9%
- Men 9.3%, women 6.6%
- Hispanic 14.9%, African American 8.1% and non-Hispanic white 7.1%
- Only 31% of cases had an etiology for abnormal aminotransferases (viral hepatitis, alcohol, iron overload)
- If more stringent criteria for abnormal ALT used 26% had an elevated ALT, of which 21.2% had no explanation

Clark Am J Gastroenterol 2003

Interpretation of Liver Tests

- True "liver function tests"
- Hepatocellular damage
- Cholestasis

True Liver Function Tests

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

Prolonged PT

- Machines are calibrated to activated thromboplastins for patients on warfarin
  - There is significant variation in INR from lab to lab in cirrhotic patients
- Common clinical dilemma- vitamin K deficiency, consumptive coagulopathy or cirrhosis

Factor	Cirrhosis	Vit K def	Consumption
Abnormal V	Yes	No	Yes
Abnormal VII	Yes	Yes	Yes
Abnormal VIII	No	No	Yes

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
- **Lactate dehydrogenase (LDH)**
  - **Can be markedly elevated in shock liver**

ALT/AST ratios

- In most liver diseases ALT > AST
- Exceptions:
  - Alcoholic liver disease
  - >2:1 ratio Wilson's disease
  - Accompanying hemolytic anemia
  - Advanced fibrosis
    - AST/ALT ratio >1 had a sensitivity of 41%, a specificity of 78% to identify advanced fibrosis
      - Unpublished data

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

- Drug/toxin induced injury
  - Acetaminophen
  - NOT alcohol alone
- Acute viral hepatitis
- Shock liver

- **Autoimmune hepatitis**
- **Common bile duct stone**

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

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 5% of population
  - Benign, unconjugated hyperbilirubinemia
  - Can be worsened by stress, fasting

First Approach

- Repeat abnormal tests
  - Many will normalize without intervention
  - 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
    - Cholestasis
    - Mixed

Worrisome?

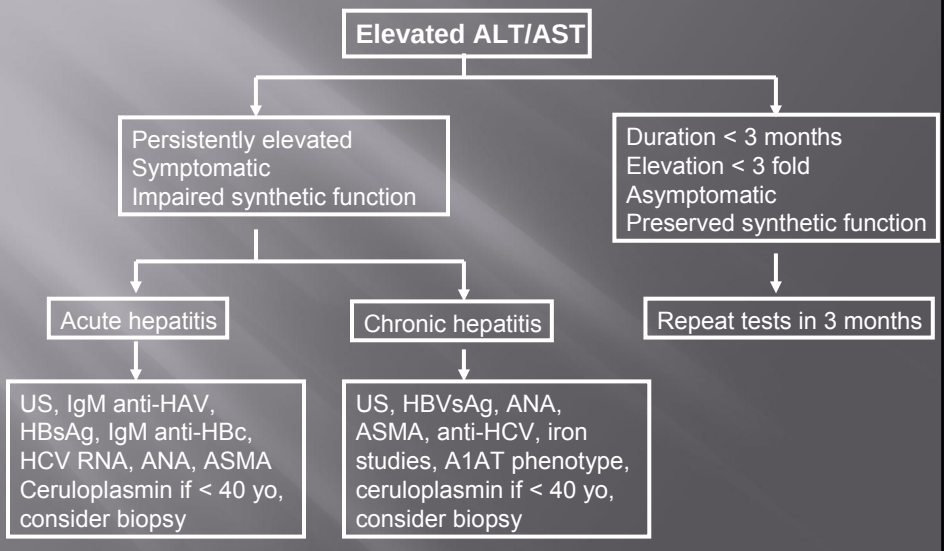
- 20 yo male
  - TB 1.8
  - AP 180
  - AST 2789
  - ALT 6239
  - Alb 3.0
  - PT 20
- 29 yo female
  - TB 22.0
  - AP 99
  - AST 560
  - ALT 901
  - Alb 2.1
  - PT 66

Listing for fulminant hepatic failure requires onset of encephalopathy within 8 weeks of onset of liver disease symptoms and one of the following: 1) ventilator dependence, 2) requiring renal replacement therapy or 3) INR > 2.0

The "shotgun" approach

- Liver consult
  - HAV IgM ← Chronic hepatitis?
  - HBV s Ag, core IgM
  - Anti-HCV
  - AMA ← Is there cholestasis?
  - ANA, ASMA
  - Ceruloplasmin ← Patient age?
  - Alpha-1 antitrypsin
  - Iron, TIBC, ferritin
  - Tox screen
  - RUQ US
  - Consider Biopsy

General Approach to Abnormal LFTs



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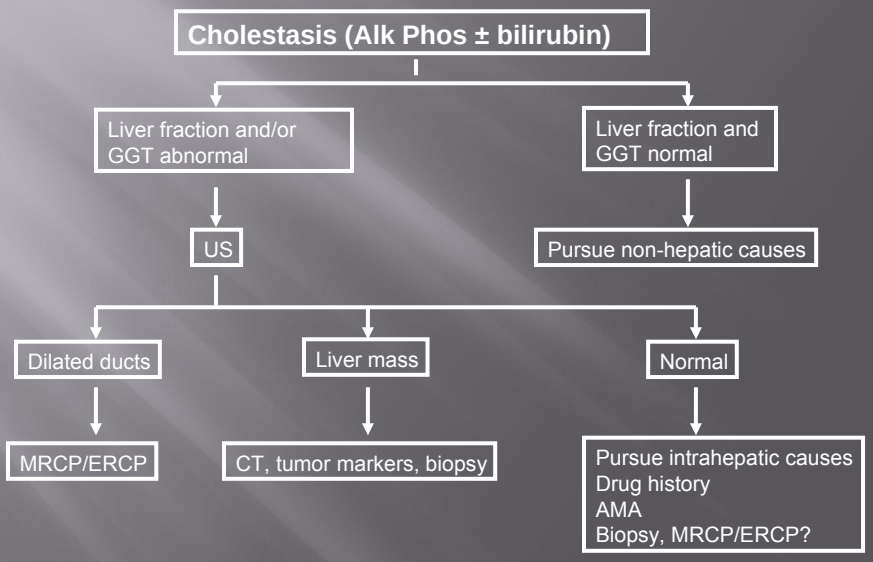


Patient Characteristics

- 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

Historical Clues

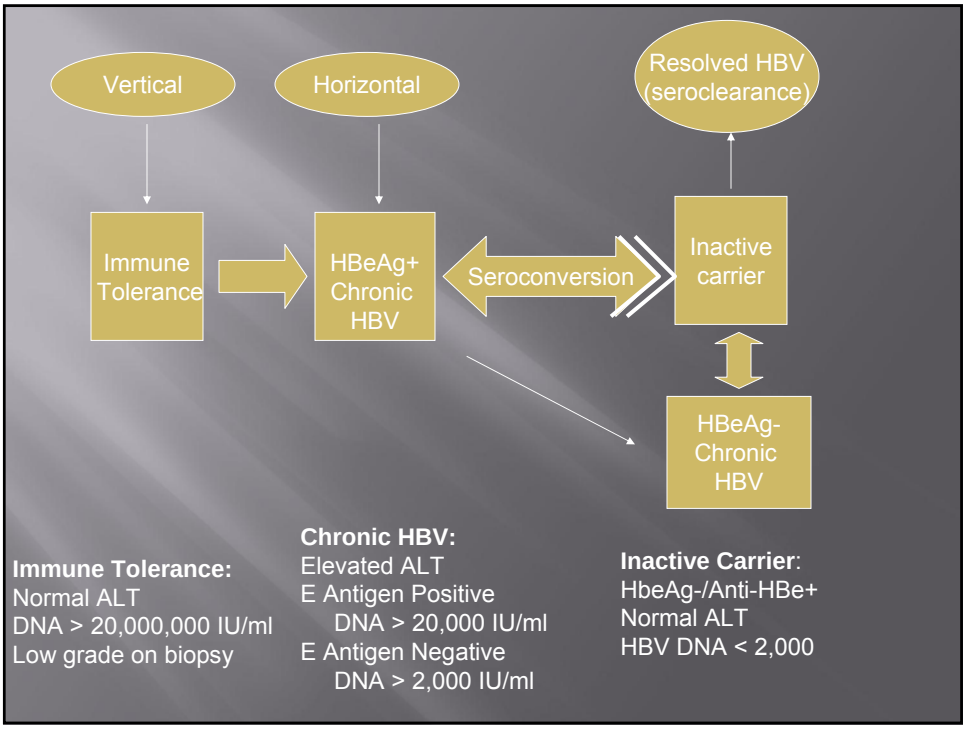
History Component	Disease Correlation
Remote history of jaundice	Viral hepatitis
Medical history of autoimmune diseases	AIH
Hypothyroidism	AIH, PBC
History of liver disease as a newborn	Alpha-1 antitrypsin deficiency
Family history of liver disease	HBV, hemochromatosis
History of alcohol abuse, DUI	Alcohol
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
Xanthalasma	PBC

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



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

IL-28 in HCV genotype 1

Prevalence genotype (%)				SVR rate (%)		
CC	CT	TT	Ethnicity	CC	CT	TT
37	51	12	Caucasian	69	33	27
14	49	37	African American	48	15	13
29	48	22	Hispanic	56	38	27

Thompson et al Gastroenterology 2010

Hemochromatosis

- 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
- Liver biopsy (HII >1.9 μmol/g dry weight)

Hemochromatosis

- Other mutations can lead to hemochromatosis
- Childhood
  - Hemojuvelin (Autosomal Recessive)
  - Hepcidin (Autosomal Recessive)
- Adult
  - Transferrin receptor 2 (Autosomal Recessive)
- Secondary iron overload and ferroportin-related (autosomal dominant)
  - Reticuloendothelial iron deposition, lower incidence of organ damage
- Remember not all iron overload is HFE

Autoimmune Hepatitis

- 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

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

- 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
- Liver histology
  - A1AT globules in ER of periportal hepatocytes
  - PAS positive, diastase-resistant

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)

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

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

Incidence of Aminotransferase Elevation with Statin Use for Cardiovascular Disease

Table 1. Incidence of Aminotransferase Elevation with Statin Use for Cardiovascular Disease

Study	Year	Agent	Multiple Assessments of AST or ALT	Statin (%)	Placebo (%)	Total (%)
EXCEL	1991	Lovastatin	Yes	45/6,582 (0.6)	2/1,663 (0.1)	47/8,245 (0.6)
4S	1994	Simvastatin	No	49/2,221 (2.2)	33/2,223 (1.5)	82/4,444 (1.8)
ACAPS	1994	Lovastatin	No	6/460 (1.3)	6/459 (1.3)	12/919 (1.3)
CRISP	1994	Lovastatin	Yes	0/289 (0)	0/142 (0)	0/431 (0)
Oxford	1994	Simvastatin	No	0/414 (0)	2/207 (1.0)	2/621 (0.3)
WOSCOPS	1995	Pravastatin	No	16/3,302 (0.5)	12/3,293 (0.4)	28/6,595 (0.4)
KAPS	1995	Pravastatin	No	4/224 (1.8)	3/223 (1.3)	7/447 (1.6)
CARE	1996	Pravastatin	No	66/2,081 (3.2)	73/2,078 (3.5)	139/4,159 (3.3)
LCAS	1997	Fluvastatin	Yes	2/214 (0.9)	0/215 (0)	2/419 (0.5)
AFCAPS-TEXCAPS	1998	Lovastatin	Yes	18/3,242 (0.5)	11/3,248 (0.3)	29/6,490 (0.4)
LIPID	1998	Pravastatin	No	95/4,512 (2.1)	85/4,502 (1.9)	180/9,014 (2.0)
LIPS	2002	Fluvastatin	Yes	10/844 (1.2)	3/833 (0.4)	15/1,677 (0.9)
PROSPER	2002	Pravastatin	No	1/2,891 (0)	1/2,913 (0)	2/5,804 (0)
Total				312/27,276 (1.1)	231/21,999 (1.1)	543/49,275 (1.1)
Odds ratio				1.26 (NS)	1.00	

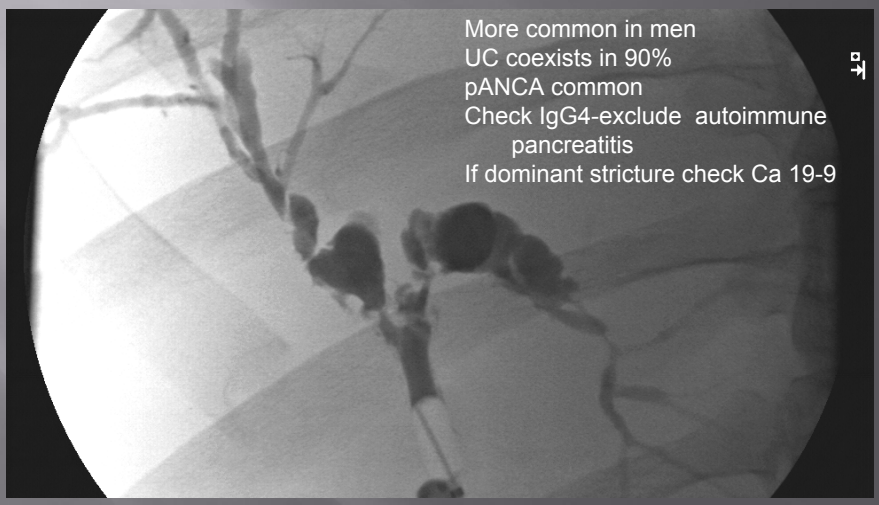
This table was adapted from de Denus et al.[7]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NS, not significant.

PBC

- 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)

PSC



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

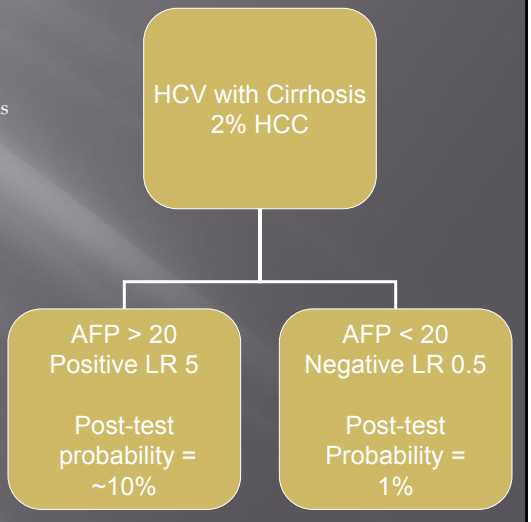
AASLD recommends US (and AFP*) every 6-12 months for surveillence

- 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 rejeneration
  - 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



Ultrasound and AFP

Six month AFP and US (58% adherent)

- Tumor < 5 cm 45%
- Resection 47%
- Conservative therapy 21%
- Survival 1 year 66%
- Survival 5 year 46%
- HCC mortality rate 83.2/100,000

No Screening

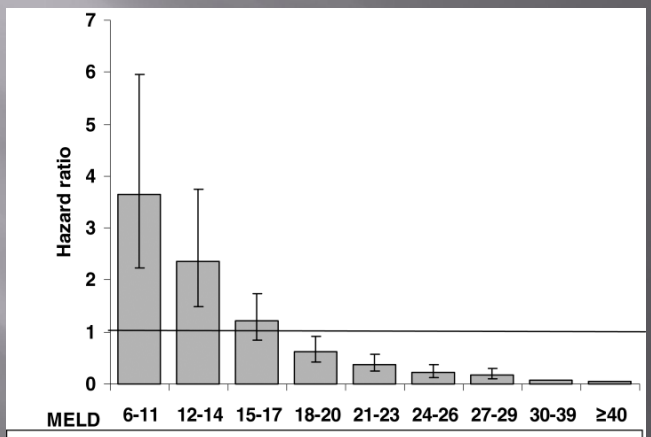
- Tumor < 5 cm 0%
- Resection 8%
- Conservative therapy 51%
- Survival 1 year 31%
- Survival 5 year 0%
- HCC mortality rate 131.5/100,000

Zhang J Cancer Res Clin Oncol 2004. 18,816 persons enrolled in prospective study

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

Cirrhosis ≠ Transplant



MELD	6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-39	≥40
Hazard Ratio	3.64	2.35	1.21	0.62	0.38	0.22	0.18	0.07	0.04
p-values	<0.001	<0.001	0.41	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001

Merion Am J Transplant 2005

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

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