A Rational Approach to

Abnormal LFTs

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Abnormal LFTs

- Magnitude of the problem
- Goals of evaluation
- Differential diagnosis
- Diagnostic work-up
- Role of liver biopsy

Abnormal LFTs

How big is the issue?

Third National

Health and Nutrition Survey

- cross-sectional study of US adults: representative sample of 20K people in 89 locations in US between 1988-1994
- 7.9% of population had elevated LFTs
  - 9.3 % of men, 6.6% of women

Abnormal LFTs

Why Do We Care?

- Liver disease is the 10th leading cause of death in the United States.
- Evaluation of abnormal LFTs provides an opportunity to discover subclinical liver disease at an early, treatable stage that might allow us to prevent the important outcomes of cirrhosis, liver cancer, and death.

6,493 Liver Transplants in 2007: Percentage by Diagnosis

• Hepatitis C	27%
• Alcoholic Liver Disease	14%
• Cirrhosis of unknown etiology	6%
• NonAlcoholic Steatohepatitis	5%
• Primary Sclerosing Cholangitis	5%
• Primary Biliary Cirrhosis	3%
• Hepatitis B	3%
• Autoimmune Hepatitis	2%
• Metabolic Liver Disease	2%
• Hepatocellular Carcinoma	15%

Abnormal LFTs

- Hepatocellular (transaminases: AST, ALT)
  - Hepatocyte injury
  - Skeletal muscle
  - Myocardium
  - RBC (hemolysis)
- Cholestatic (alkaline phosphatase, GGT)
  - Bile duct injury
  - Infiltrative process
  - Bone
  - Placenta

TABLE 1. CAUSES OF CHRONICALLY ELEVATED AMINOTRANSFERASE LEVELS.

Hepatic causes
Alcohol abuse
Medication
Chronic hepatitis B and C
Steatosis and nonalcoholic steatohepatitis
Autoimmune hepatitis
Hemochromatosis
Wilson's disease (in patients ≤40 years old)
$Alpha_1$-antitrypsin deficiency
Nonhepatic causes
Celiac sprue
Inherited disorders of muscle metabolism
Acquired muscle diseases
Strenuous exercise

Pratt DS. N Engl J Med 2000;342:1266-1271

Acute Hepatitis

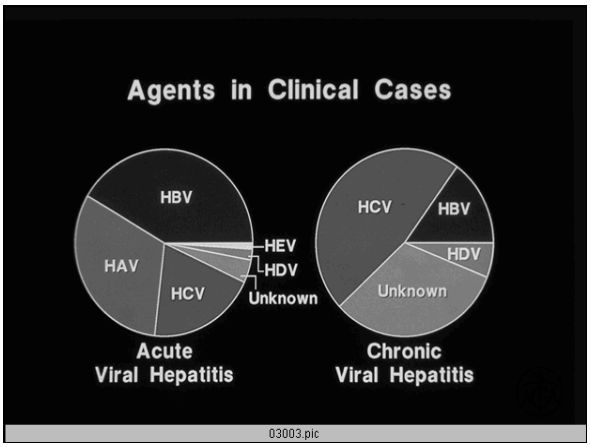
- ALT>AST and levels > 500
- Differential diagnosis
  - Viral
  - Toxic
  - Ischemic
- Lab Evaluation
  - HAV IgM, HBSAg, HBcAb IgM, HCV RNA
  - Acetaminophen level

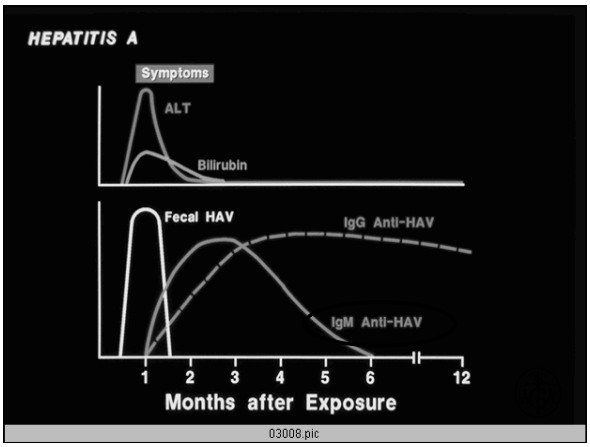
Alcoholic Liver Disease

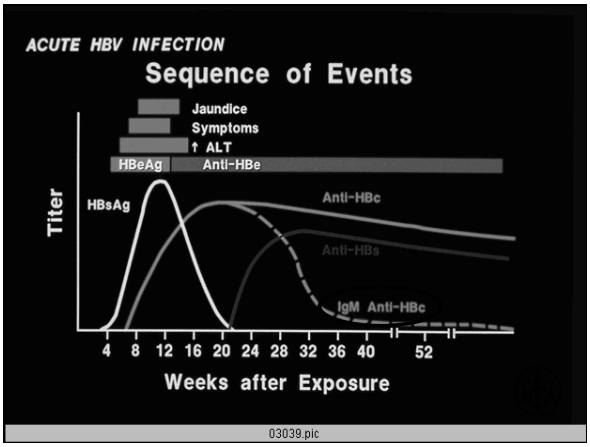
- The history is the key
- Lab clues: AST/ALT > 2, MCV > 94
- Alcoholic hepatitis:
  - Anorexia, fever, jaundice, hepatomegaly
  - Treatment:
    - Abstinence
    - Nutrition
    - Prednisolone 40 mg/d x 28 days

Non-Alcoholic Steatohepatitis (NASH)

- More common in women (75%)
- Associated conditions:
  -
  -
  -
- Diagnosis
  -
- Treatment
  -
  -



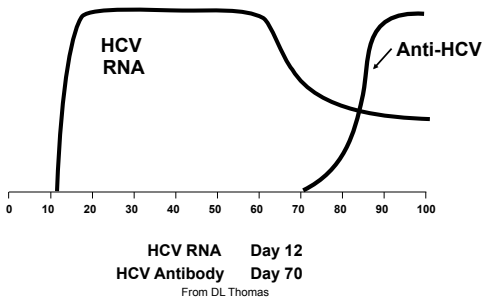




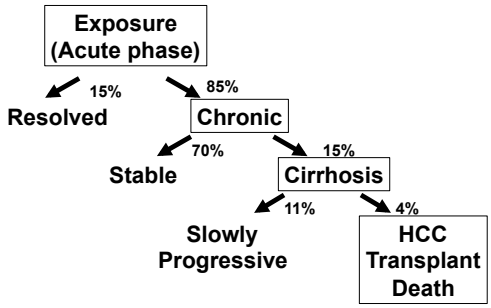
HBV Serology

	HBSAg	HBcAb IgM	HBcAb IgG	HBSAb
Acute HBV	+	+	-	-
Resolved HBV	-	-	+	+
Chronic HBV	+	-	+	-
HBV vaccinated	-	-	-	+

Acute Hepatitis C



Natural History of Hepatitis C



Hemochromatosis

- Autosomal recessive mutation of HFE gene
- Frequency 5:1000 (heterozygotes 1:10)
- Clinical manifestations:
  - –
  - –

    hyperpigmentation, cardiomyopathy
- Diagnosis: transferrin saturation > 50%

  ferritin > 200

  genetic testing C282Y/C282Y
- Treatment: phlebotomy to ferritin < 50

Drug-induced Liver Disease

- Hepatocellular
  - – acetaminophen, INH, methyldopa, MTX
- Cholestatic
  - – chlorpromazine, estradiol, antibiotics
- Chronic Hepatitis
  - – methyldopa, phenytoin, macrodantin, PTU
- Hypersensitivity Reaction
  - – Phenytoin, Augmentin, allopurinol
- Microvesicular Steatosis
  - – amiodarone, IV tetracycline, AZT, ddI, stavudine

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

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Autoimmune Hepatitis

- Widely variable clinical presentations
  - Asymptomatic LFT abnormality (ALT and AST)
  - Severe hepatitis with jaundice
  - Cirrhosis and complications of portal HTN
- Often associated with other autoimmune dz
- Diagnosis:
  - Compatible clinical presentation
  - ANA or ASMA with titer 1:80 or greater
  - IgG > 1.5 upper limits of normal
  - Liver biopsy: portal lymphocytes + plasma cells

Diagnosis of Immune-Mediated Liver Disease

	LFT	Serology	Quantitative Immunoglobulins	Biopsy
AIH	↑ALT	ANA ASMA	↑IgG	Portal inflammation Plasmacytes Piecemeal necrosis
PBC	↑ALP	AMA	↑IgM	Bile duct destruction granulomas
PSC	↑ALP	none	normal	Periductal concentric fibrosis

Wilson's Disease

- Autosomal recessive – copper metabolism
- Chronic hepatitis or fulminant hepatitis
- Associated clinical features:
  - Neuropsychiatric disease
  - Hemolytic anemia
- Physical exam: Kayser-Fleischer rings
- Diagnosis: ↓ceruloplasmin, ↑urinary Cu
- Treatment: d-penicillamine

Alpha-1 Antitrypsin Deficiency

- Lung disease
  - Inadequate protease inhibitor activity
- Liver disease
  - Accumulation of variant A1AT in hepatocytes
- Normal phenotype: MM pathogenic: ZZ
- Presentations:
  - Neonatal hepatitis, ↑LFTs, hepatitis, cirrhosis
- Treatment: Liver transplantation

Abnormal ALP

- Cholelithiasis
- Tumor
- Medication-induced Cholestasis
- Primary Biliary Cirrhosis
- Primary Sclerosing Cholangitis
- Chronic pancreatitis
- Benign Cholestasis of Pregnancy
- TPN or Sepsis
- Infiltrative process

Primary Biliary Cirrhosis

- Cholestatic liver disease (ALP)
  - Most common symptoms: pruritus and fatigue
  - Many patients asx, and dx by abnormal LFT
- Female:male ratio 9:1
- Diagnosis:
  - Compatible clinical presentation
  - AMA titer 1:80 or greater (95% sens/spec)
  - IgM > 1.5 upper limits of normal
  - Liver biopsy: bile duct destruction
- Treatment: Ursodeoxycholic acid 15 mg/kg

Primary Sclerosing Cholangitis

- Cholestatic liver disease (ALP)
- Inflammation of large bile ducts
- 90% associated with IBD
  - but < 10% of IBD patients get PSC
- Diagnosis: ERCP (now MRCP)
  - No autoantibodies, no elevated globulins
  - Biopsy: concentric fibrosis around bile ducts
- Cholangiocarcinoma: 10-15% lifetime risk
- Treatment: Liver Transplantation

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Maternal Liver Disease

- Intrahepatic cholestasis of pregnancy (ICP)
  - Intense pruritus, variable LFT, intact liver function
  - Treat with UDCA, cholestyramine, hydroxyzine
- Acute Fatty Liver of Pregnancy (AFLP)
  - Presents in 3rd trimester with HA, N/V, abd pain
  - Often associated with pre-eclampsia/eclampsia
  - LFTs show ↑ALT, ↑bili, ↑PT
  - Treatment: glucose, correct PT, delivery
- HELLP (hemolysis, ↑LFTs, ↓platelets)
  - Dx: schistocytes, plt<100, LDH>600, AST>70

Evaluation of Abnormal LFTs HISTORY

- Pain
- Edema, increased abdominal girth, confusion, GI bleeding
- PMH: DM, hyperlipidemia, autoimmune
- Medications
- Alcohol
- Sex, drugs, rock and roll; blood tx<1990
- Family history of liver disease

Evaluation of Abnormal LFTs PHYSICAL EXAM

- Skin: spider angiomata, gynecomastia
- Liver size
- Splenomegaly
- Ascites
- Edema
- Mental status, asterixis
- Obesity
- Hyperpigmentation, Kayser-Fleischer rings

Evaluation of Elevated AST

- Check ALT to confirm hepatic origin
- Review alcohol
- Review medications
- Review risk factors for NASH
- CBC, INR, albumin
- HBSAg, HCV Ab
- Transferrin saturation +/- ferritin
- ANA, ASMA, quantitative immunoglobulins
- Ceruloplasmin

Evaluation of Elevated ALP

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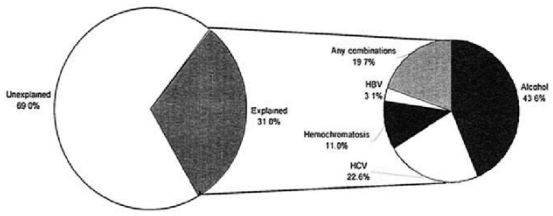

Clark JM. Am J Gastroenterol 2003;98:960-967

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Table 5. Distribution of the Different Etiological Factors of Altered Liver Tests, by Sex: Cittanova (Southern Italy), 2002-2003

Etiological Factor	Males n (%)	Females n (%)	Total n (%)
Alcohol alone*	85 (55.9)	8 (15.4)	93 (45.6)
HCV alone	16 (10.5)	22 (42.3)	38 (18.6)
HBV alone	2 (1.3)	–	2 (1.0)
Any virus plus alcohol*	14 (9.2)	4 (7.7)	18 (8.8)
Other†	3 (2.0)	1 (1.9)	4 (2.0)
Unexplained	32 (21.1)	17 (32.7)	49 (24.0)
Total	152 (100)	52 (100)	204 (100)

NOTE. Altered liver tests are for ALT >50 IU/L and/or AST >45 IU/L and/or GGT >60 IU/L and/or platelet counts <130,000/mmc.
*Alcohol intake ≥ 28 g/d.
†Three drug-induced and one coeliac disease.

Pendino GM. Hepatology 2005;41:1151-1159

Table 2. Histology Results*

	Asymptomatic	Symptomatic
Normal	6 (10%)	2 (9.5%)
Steatosis	29 (48%)	12 (57%)
Steatohepatitis	21 (35%)	5 (24%)
Fibrosis	3 (5%)	1 (5%)
Cirrhosis	1 (1.5%)	1 (1.5)

* Liver biopsy findings for patients with marker-negative abnormal liver function tests. Definitions of findings appear in text. There are no significant differences ($p > 0.05$) for the proportion of asymptomatic *vs* symptomatic patients with each histological finding.

Daniel S. Am J Gastroenterol 1999;94:3010-3014

Abnormal LFTs
A Rational Approach

- History
  - alcohol, risk factors for viral hepatitis
  - risk factors for NASH
  - medications
- Physical Exam – signs of cirrhosis?
- Laboratory evaluation
- Consider RUQ ultrasound
- Consider liver biopsy
- Clinical follow-up

Unknown Case #1

HPI: 62 year old male with no symptoms

Routine lab for life insurance revealed ↑ LFTs

No history of jaundiced illness or transfusion

No foreign travel except Southeast Asia

"partied a lot" in school +sex -IVDA

PMH: none **PSH:** none **meds:** none **FH:** -liver dz

SH: banker, married x 25 yrs, 2 drinks/d, - smoke

PE: VSS normal exam no stigmata CLD - HSM

lab: AST 62 ALT 95 bili 0.4 alb 4.2 INR 1.2

Unknown Case #2

- 54 year old female baker
  - Totally asymptomatic, for annual exam
  - No history of alcohol use
  - PMH: DM, HTN, osteoarthritis, obesity
  - Meds: glipizide, HCTZ, prn ibuprofen
- VSS afebrile, anicteric, no stigmata CLD
  - A/O, no asterixis no edema, no ascites
  - liver span 8 cm, no palpable spleen
- AST 42, ALT 56, ALP 115, bili 0.8
  alb 3.9 INR 1.1 TP 6.4 plt 224

Unknown Case #3

- 38 year old female manager of Mi Pueblo
  - 3 days of episodic severe RUQ pain
  - 2 days of fever/chills/rigors
  - Daughter noticed yellow eyes today
  - PMH: DM, HTN
  - Meds: glipizide, HCTZ
- BP 110/64 HR 112, temp 101.8
  - Jaundice, no stigmata of cirrhosis
  - RUQ tender to palp, no spleen, no ascites
- AST 112, ALT 154, ALP 256, bili 5.2

Unknown Case #4

- 19 year old female college student
  - 1 week history of anorexia, fatigue, fever
  - 1 day history of jaundice
  - mission trip to Guatemala 1 month ago
  - PMH: none PSH: none meds: none
- VSS T 100.3 F, jaundice, no stigmata cirrhosis
  - sl RUQ tender, liver span 14 cm, no palp spleen
- AST 2346, ALT 3572, ALP 85, bili 4.2
  alb 3.8 INR 0.9 TP 7.4 plt 356

Unknown Case #5

- 63 year old female accountant
  - 1 month anorexia, 10 lb weight loss; no pain
  - 1 week dark urine, 3 days of yellow eyes
  - 1 glass of wine/week, no IVDA
  - PMH: osteoarthritis, allergic rhinitis
  - Meds: ibuprofen, Nasocort
- VSS afebrile, jaundice, no stigmata CLD
  - A/O, no asterixis no edema, no ascites
  - No abd tenderness, no palp mass, no HSM
- AST 28, ALT 42, ALP 462, bili 6.4
  alb 4.3 INR 1.4 TP 7.4 plt 212

Unknown Case #6

- 24 year old female bartender
  - 1 month history of fatigue, anorexia, arthralgias
  - 1 week history of jaundice
  - No abdominal pain, no fever, 5 lb wt. loss
  - Denies EtOH "I never liked the stuff"
  - PMH: none PSH: none meds: rare Motrin
- VSS afebrile, anicteric, no stigmata CLD
  - No abdominal tenderness or mass, no HSM
- AST 256, ALT 302, ALP 162, bili 8.6
  alb 3.2 INR 1.3 TP 8.4 plt 256

Unknown Case #7

- 72 year old male lawyer
  - Nausea, vomiting, lethargy, chronic back pain
  - Drinks 3-4 scotch and water/day
  - PMH: HTN, hypercholesterolemia
  - Meds: Prinivil, Lipitor, Vicodin
- VSS afebrile, jaundice, no stigmata cirrhosis
  - A/O, no asterixis no edema, no ascites
  - sl RUQ tender, liver span 18 cm, no palp spleen
- AST 3246, ALT 4620, ALP 105, bili 5.2

Unknown Case #8

- 28 year old male teacher
  - Totally asymptomatic, found to have abnormal LFTs when applying for insurance
  - 3-4 beers/day, no IVDA
  - PMH: ACL repair 1996
  - Meds: prn naproxen
- VSS afebrile, anicteric, no stigmata CLD
  - A/O, no asterixis no edema, no ascites
  - liver span 10 cm, no palp spleen
- AST 17, ALT 28, ALP 85, bili 4.2
  alb 4.2 INR 0.9 TP 7.2 plt 285