

Clinical Approach of Liver Diseases

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The Skeleton

- **When should you look for liver disease?**
- **How can you diagnose the cause?**
- **What kind of liver disease did you find?**

When should you look for liver diseases?

Symptoms
Risk Factors
Physical Examination
Abnormal LCTs
Abnormal Abdominal Imaging

Symptoms

- **Jaundice or dark yellow urine: Highly specific**
- **Pruritus**
- **Significant fatigue**
- **Abdominal or leg swelling**
- **Altered cognitive function**
- **GI bleeding**
- **B symptoms**
- **Abdominal pain**

Risk factors for Liver Disease

- Alcoholic Liver Disease (ALD)
- HCV infection
- HBV infection
- NAFLD
- Autoimmune liver diseases
- Hereditary liver diseases
- Certain Medications

Risk Factors of ALD

- ALD is not a universal event
- Several risk factors are involved:
 - The amount
 - The type
 - The pattern
 - The gender
 - The racial and ethnic heritage
 - The presence and extent of protein calorie malnutrition
 - Genetic Factors
 - Associated viral hepatitis

The amount

- The most important risk factor
- Not a clear linear relationship
- Increased risk for cirrhosis with:
 - More than 60-80 gm/day for ≥ 10 years in men
 - More than 20 gm/day for ≥ 10 years in women
- Yet, even with these levels, only 6-41% develop cirrhosis
- In an Italian population-based study of 7000 subjects, among heavy drinkers (more than 120 gm/day), only 13.5% developed ALD

The type and the pattern

- In a survey of over 30,000 persons in Denmark, drinking beer or spirits was more likely to be associated with ALD than drinking wine
- Drinking outside of meal times \rightarrow \uparrow risk of ALD by 2.7 fold compared to drinking at mealtimes
- A subsequent French study revealed no difference
- Binge drinking has been shown to increase the risk of alcoholic liver disease*

*Wechsler H, Austin SB. Binge drinking: the five/four measure. J Stud Alcohol 1998 Jan;59(1):122-24.

Gender and Ethnicity

- Women are more susceptible
- Higher blood levels in women with same amount
- Low gastric ADH level
- The “safe” limit of ETOH intake has been estimated to be 21 units/week, but in women it is 7-14 units/week.
- The rate of alcoholic cirrhosis is higher in Hispanic and AA males compared to CMs
- ETOH mortality is higher in Hispanic males
- Not related to the amount

The presence and extent of protein calorie malnutrition

- From VA data, 666 patients with ALD*:
 - The degree of malnutrition correlated closely with the development of all the serious complications of the liver disease (ascites, encephalopathy, and HRS) as well as the overall mortality
 - ALD-related mortality was about 80% in patients with severe malnutrition

*Mendenhall C et al. Relationship of protein caloric malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. Alcohol Clin Exp Res 1995 Jun;19(3):635-641.

Over weight is associated with increased risk of ALD*

- 1604 patients with ALD (steatosis, AH, or cirrhosis)
- Over weight meant BMI $\geq 25/27$ in females/males
- In the multivariate analysis, a patient who was overweight over the preceding 10 years was:
 - Two and half times more likely to have steatosis
 - Three times more likely to have acute AH
 - Two times more likely to have cirrhosis

* Naveau S et al. [Liver weight risk factor for alcoholic liver disease](#) Hepatology. 1997 Jan;25(1):108-11

Genetics and ALD

- Children of alcoholics raised in adopted families had a significantly higher rate of alcohol dependence than adopted children of non-alcoholics (18% vs. 5%)
- In population-based studies:
 - Monozygotic twins (MT) were twice as likely to drink as dizygotic twins (DT)
 - Among those who drank, MT were more likely to have a similar frequency and quantity of alcohol consumption
 - Moreover, MT have a significantly higher prevalence of alcoholic cirrhosis than DT

Genetics and ALD

- Polymorphisms of genes involved in ETOH metabolism have been associated with ALD
- To date, specific genetic abnormalities for susceptibility to alcohol abuse and the development of ALD have not yet been firmly established

HCV and ETOH

- A clear synergistic relationship
- Disease onset at younger age, more severe histological features, and decreased survival
- In a large cohort of Post transfusion HCV patients:
 - Patients with HCV were 7.8 times more likely to develop cirrhosis than controls
 - Patients with HCV and heavy ETOH intake (Abuse or > 80gm/d), were 31.1 times more likely to develop cirrhosis than controls
- The safe ETOH amount in HCV patients: None UPO

• Harris DR, et al. The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse. Ann Intern Med 2001 Jan 16;134(2):120-124

HCV Risk factors: Screen regardless LCT

- IVDU: In the recent or remote past even once
- Hemophiliacs who received clotting factor concentrates before 1987
- Blood transfusion/ organ transplant before July 1992
- Patients on HD
- HIV patients
- Children born to HCV-infected mothers
- Sexual partners of HCV-infected patients
- Elevated liver enzymes
- Others: Occupational exposure, ?Tattoo, Snorting cocaine

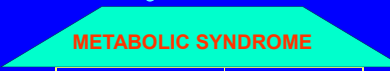
HBV Risk Factors: Screen regardless LCT

- Immigrants and adopted children
- Households of HBs Ag positive patients
- Sexual contacts of HBs Ag positive patients
- Persons who have ever injected drug
- Persons with multiple sexual partners or Hx of STD
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT or AST
- Individuals infected with HCV or HIV
- Patients undergoing renal dialysis
- All pregnant women

Risk factors for NAFLD

- A common disease
- Linked to Metabolic Syndrome & IR
- Could show up with manifestations of decompensated cirrhosis
- In diabetics, NAFLD is present in 63%
- In morbidly obese patients undergoing bariatric surgery, NAFLD is present in 96%
- In patients with otherwise unexplained elevated liver enzymes, NASH prevalence ranges from 34%-40%

The features of the MS are commonly seen in subjects with NAFLD



Feature	Prevalence
Obesity	50-90%
Diabetes	20-50%
Hypertension	25-70%
Dyslipidemia	35-75%

Still, Patients without any component of MS but with Insulin Resistance can have NAFLD

Risk Factors for Autoimmune Liver Disease

- Other Autoimmune Diseases:
 - About 35%-60% of patients with AIH
 - RA, SLE, HT, DM-2, ...
- IBD:
 - Among IBD patients (UC>CD), 4% have PSC
 - Among PSC patients, 2/3 have IBD
- Family history of PBC

Hereditary Liver Disease

- All are AR
- Hereditary Hemochromatosis
- Wilson Disease
- Alpha one Antitrypsin deficiency
- If you have an index case → Screen first degree relatives

Medications

- Almost any drug could cause liver injury
- Acute Liver Failure:
 - Dose Dependant: acetaminophen and Niacin
 - Dose independent: Abx, NSAIDs, seizure meds,...
- Steatosis and Steatohepatitis:
 - amiodarone, Tamoxifen, MTX
- Cholestatic Liver Disease:
 - Bactrim, Augmentin, ACEIs, Androgen, OCP
- Granulomatous hepatitis
 - Allopurinol, Tegretol, Hydralazine
- Liver tumors:
 - OCP and anabolic Steroid

Physical Examination

- Jaundice
- Hepatomegaly
- Splenomegaly
- Ascites
- Leg edema
- Asterixis
- Spider nevi
- Palmer erythema
- Testicular atrophy

Abnormal LCTs

- More accurate than LFT
- Platelet count counts
- First step to interpret abnormal LCT is to determine the pattern:
 - Hepatitic: AST and ALT >> Alk phosphatase
 - Cholestatic: Alk Phosphatase >> ALT and AST
 - Infiltrative: Mixed
 - Total Bilirubin is not helpful
- Need a clinical scenario

ALT & AST

	ALT	AST
Main Location	Liver	Heart
Other locations	Kidney, heart, Skeletal Ms.	Liver, kidney, Skeletal Ms., brain, pancreas, lungs, RBCs & WBCs

AST: ALT ratio

- **< 1.0** in viral & NAFLD without cirrhosis
- **If > 1.0:** High specificity (97%) but low sensitivity (60%) for cirrhosis
- **If > 2.0,** think of ETOH related liver disease because:
 - Vitamin B6 def → ↓ ALT
 - ETOH ++ mitochondrial AST release to plasma

Causes of AST and ALT elevation “Acute hepatitic hepatitis”

- **Alcoholic hepatitis** BUT not more than 400 U/L
- **Acute ischemic hepatitis:** Rapid ↑ then rapid ↓
- **Viral Hepatitis:** Hepatotropic and Non-Hepatotropic
- **Wilson disease**
- **Drug-induced:** Acetaminophen and others

Causes of AST and ALT elevation “Acute hepatitic hepatitis”

- **Autoimmune hepatitis flare**
- **Budd-chiari syndrome**
- **With acute CBD obstruction,** AST & ALT will be elevated sometimes > 1000s within 24-48 hours with rapid decline even with persistent obstruction.
- **veno-occlusive disease, HELLP syndrome, acute fatty liver of pregnancy,...**

AST & ALT alteration in non-hepatic diseases

- **With AMI,** AST increases and it is mainly mitochondrial
- **With muscle diseases,** AST & ALT increase but < 300, except with rhabdomyolysis in which AST may be > 1000 → Remember it in alcoholics
- **With uremia,** Subnormal AST and ALT

AST& ALT elevation: The prognostic value

- The extent of liver cell necrosis correlates poorly with the magnitude of AST& ALT
- The absolute elevation in AST& ALT is of little prognostic value
- **BUT**, a rapid ↓ in plasma AST and ALT levels, together with ↑ bilirubin and prolongation of PT → poor prognosis in patients with acute hepatitis.

Alkaline phosphatase (AP)

- Liver, Bone, Placenta, Small bowel
- With isolated AP ↑ → think of all of them
- If so:
 - Iso-enzyme
 - GGT
 - 5-Nucleotidase
 - Leucine aminopeptidase
- If of hepatic origin, think of bile ducts “Cholestatic hepatitis” Either IHBD or EHBD pathology → U/S helps

Moderate elevation of AP (<4 ULN)

- Non-specific: Hepatic or extra-hepatic
- Viral hepatitis
- Chronic hepatitis
- Infiltrative diseases of the liver
- CHF
- TPN
- Certain medications as Phentoin

Marked elevation of AP (>4 times ULN)

- 1-Obstructive jaundice due to cancer
- 2-Common duct stones
- 3-Sclerosing cholangitis
- 4-Bile duct stricture
- 5-Drug and toxins associated with cholestasis
- 6-Primary biliary cirrhosis
- 7-Liver allograft rejection
- 8-Infectious hepatobiliary diseases seen in patients with AIDS
- 9-Infiltrative liver disease (Sarcoid, TB, Cancer)
- 10-Alcohol-induced steatonecrosis (rarely)

Subnormal AP

- Fulminant WD due to replacement of zinc, which is important for AP activity, by copper → AP (IU/L) : TB (mg/dL) < 2
- Hypothyroidism
- Pernicious anemia
- Vitamin D intoxication
- Celiac disease
- Fibrate therapy

Albumin

- The average adult has 300-500 gram
- The daily rate of synthesis is 200mg/kg/day
- The rate of degradation is 4% daily, but the location is unknown
- The half life is 19-21 days

Causes of hypoalbuminemia

- Chronic liver disease
- Protein losing enteropathy
- Malnutrition
- Burn
- Chronic infection, TB, Fungal, AIDS,...
- Nephrotic syndrome

Types of hyperbilirubinemia

- Direct hyperbilirubinemia → if direct bilirubin is >50% of the total bilirubin
- Indirect hyperbilirubinemia → if indirect bilirubin is >85% of the total bilirubin
- Mixed hyperbilirubinemia → others

Direct hyperbilirubinemia

- **Hepatic:** Hepatic dysfunction as with:
 - Viral hepatitis
 - Alcoholic hepatitis
 - WD, CAAIH
 - Toxic hepatitis
 - ESLD
- **Cholestatic:**
 - IHBD (Intrahepatic Cholestasis): Drugs, TPN, Sepsis, post-surgery
 - EHBD (Obstruction)
- **Infiltrative:** Sarcoidosis, TB, Malignancy,...

Indirect hyperbilirubinemia

- Hemolysis (with T. bilirubin < 5 mg/dl)
- Gilbert syndrome
- Medications

PT/INR

- Liver synthesizes 11 clotting factors including I, II, V, VII, IX, X, XII, and XIII
- Vitamin K dependant ones are II, VII, IX, and X
- Therefore, factor V is not Vitamin K dependant, so with elevated INR and normal factor V, vitamin K deficiency rather than CLD is the most likely cause.

Causes of elevated PT/INR

- Hepatocellular diseases either acute or chronic (unlike albumin)
- Coumadin
- Consumptive coagulopathy like DIC
- Severe GI bleeding
- Vitamin K deficiency which occurs with
 - Obstructive jaundice → Normal factor V & good response to IV Vitamin K
 - Steatorrhea as in patients with chronic pancreatitis
 - Abx intake
 - Dietary deficiency
- High hematocrit which causes false elevation in PT.

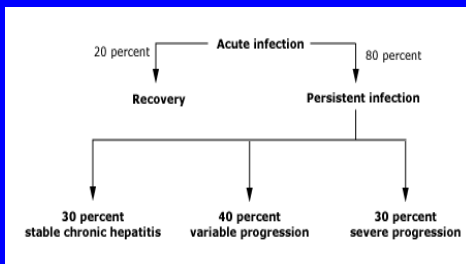
Abnormal Abdominal Imaging

- **Hepatomegaly:** Any cause but do not forget cardiac dysfunction or BCS
- **Splenomegaly:** Portal HTN but do not forget MPD
- **Fatty liver (coarse echogenicity):** ALD& NAFLD
- **Lobulated liver margin, shrunken Liver, or nodular Liver:** Cirrhosis
- **Liver mass**
- **Varices**
- **Ascites**

How can you diagnose the cause?

HCV

- **RNA virus**
- **About 4 million Americans are infected**
- **The Natural History:**



HCV Serology

	EIA-1 (1990)	EIA-2 (1992)	EIA-3(1996)
Sensitivity	75%	95%	98%
PPV	80%	92%	Slightly higher
Window phase	16 weeks	10 weeks	8 weeks

HCV serology

- Not for acute HCV infection
- May give false negative results in patients with AIDS or in hemodialysis
- Very rarely, False positive results in those with AIH
- Always confirm positive ones with qualitative PCR testing

Recombinant Immunoblot Assay (RIBA)

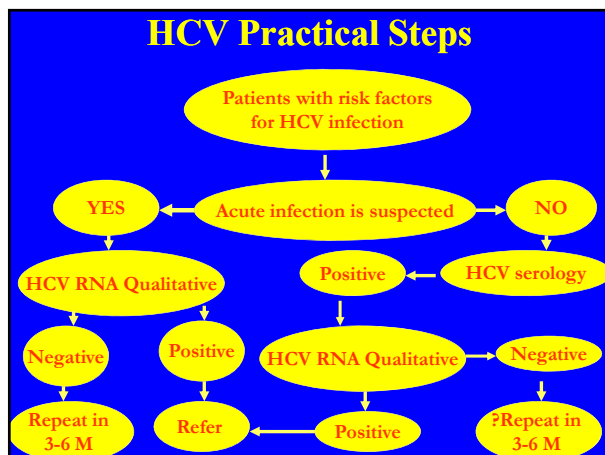
- RIBA-2 has the same antigens as EIA-2 → not more sensitive
- 2/3 or 3/3 → positive test
- RIBA is more technically demanding than EIA

HCV RNA by PCR

- Two weeks after infection
- The lower limit for Qualitative one is 50 IU/mL
- For Quantitative one:
 - 75-200 IU/mL → detected below the limit of Quantitation
 - > 200 IU/mL → Will give the number

HCV Genotypes

- Genotype 1:
 - The most common in the US (75%)
 - The least responsive to therapy (48 weeks) (about 45-50%)
- Genotype 2 & 3:
 - About 20%
 - More responsive to therapy (24 weeks)
- Genotype 4:
- Genotype 5:
- Genotype 6:



- ### HBV: What test should you order
- Hepatitis B surface antigen (HBs Ag)
 - Anti Hepatitis B surface (HBs Ab)
 - Anti hepatitis B core IgM (HBc-IgM)
 - Anti hepatitis B core total (Hbc-total)
- ↓
- If HBs Ag is positive → Refer
 - If negative but with HBc IgM positive → Refer
 - If HBc Total is positive → OK EXCEPT with planned immunosuppressive therapy
 - If at risk with negative HBs Ab → Vaccinate

HBs Ag	HBe Ag	IgM anti-HBc	Total anti-HBc	Anti-HBs	Anti-HBe	HBV DNA	Interpretation
+	+	+	-	-	-	+++	Acute HBV, early phase
-	-	+	-	-	+	+	Acute HBV, window phase
+	+	-	+	-	-	+++	HBeAg+ chronic hepatitis
+	-	-	+	-	+	++	HBeAg- Chronic hepatitis
+	-	-	+	-	+	±	Inactive carrier state
-	-	-	+	±	-/+	-	Resolved hepatitis B

- ### Hereditary Hemochromatosis (HH)
- The overall prevalence in whites is 1:300
 - HH is classified broadly into 2 groups:
 - 1-HFE-related HH (about 90%):
 - C282Y/C282Y → 85-90 %
 - C282Y/H63D (compound heterozygote) → 5%
 - Others → including mis-sense mutations as S65C
 - 2-Non -HFE-related HH (about 10%):
 - Hemojuvelin mutations (AR)
 - Hepcidin mutations (AR)

Stages of HH

Name	Age	Parenchymal iron	Organ damage
Insignificant iron accumulation	0-20	0-5 gram	No
Iron overload with no organ damage	20-40	10-20	No
Iron overload with organ damage	> 40	> 20	Yes

Diagnosis of HH 1-Iron studies

- Get the three: iron, TIBC, and ferritin (Not necessarily fasting)

TS %	Sensitivity for HH	Specificity for HH
50% for Female 60 % for Male	92%	93%
45%	99%	44%, the other 56% are with NASH, ETOH, CHC, or C282Y/normal

Diagnosis of HH 2-HFE gene testing

- All patients with abnormal iron studies (TS \geq 45%)
- First degree relatives (at age of 20 years or more) of patients with C282Y/H63D mutations
- The result could be:
 - 1-wt/wt (normal)
 - 2-H63D/wt
 - 3-H63D/H63D
 - 4-C282Y/wt
 - 5-C282Y/H63D
 - 6-C282Y/C282Y

Other Diseases-1

- AIH:
 - Total IgG (very helpful)
 - ANA and/or SMA or LKM (young female)
- PBC:
 - AMA (positive in 90%-95%)
 - ANA, SMA in AMA-negative cases
- PSC:
 - MRCP or ERCP (If to intervene): accuracy is 88% versus 91% respectively
 - pANCA

Other Diseases-2

- **WD:**
 - Young patient (< 55 YO)
 - Ceruloplasmin: Not highly specific nor sensitive
 - 24 hour urine of Copper
- **A1ATD:**
 - Phenotype (ZZ and may be MZ)
 - Smoking
- **NAFLD:** No marker exists

Liver Mass

- **Benign:** Hemangioma, Adenoma, FNH,...
- **Malignant:**
 - Primary (HCC or Cholangiocarcinoma)
 - Secondary (More common)
- **Dynamic imaging** (Triphasic CT or MRI w/wo)
- **Tumor markers** (AFP, CA19-9, and CEA)
- **Look for extrahepatic primary source**
- **Screen patients with cirrhosis OR CHB for HCC with AFP + U/S every 6 months**
- **Biopsy:**
 - Not always needed (HCC)
 - Not always safe (Adenoma)
 - Sometimes, it is contraindicated (Hemangioma)

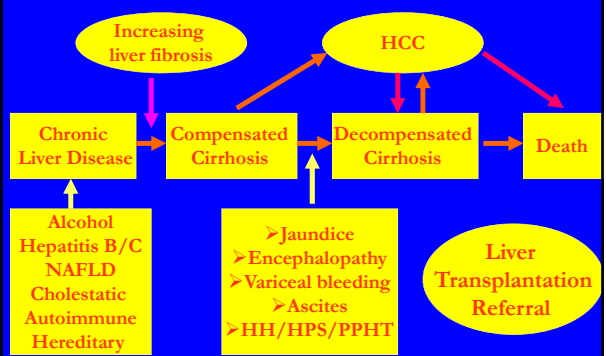
What kind of liver disease did you find?

- **Acute Liver Disease:**
 - Acute Hepatitis
 - Acute Liver Failure
- **Chronic Liver Disease:**
 - Chronic hepatitis without cirrhosis
 - Cirrhosis: Compensated or decompensated
 - Liver Tumor:
- **Acute on top of Chronic liver disease**
 - CLD with a new acute insult
 - CLD with flare of the underlying cause:
 - Alcoholic hepatitis
 - AIH
 - HBV
 - WD

Acute Liver Disease

- **Acute Hepatitis:**
 - Acute new rise in LFTs
 - Hepatic: Viral, Ischemic, Medications, AIH, WD
 - Cholestatic:
 - Extrahepatic: CBD pathology
 - Intrahepatic: Medications, TPN, infections
 - U/S is a good start
- **Acute Liver Failure:**
 - Triad of Encephalopathy, Coagulopathy, and Jaundice
 - Transfer to a Liver Transplant Center

Natural History of Chronic Liver Disease



Orthotopic Liver Transplantation

- The same anatomic place
- The 1-year survival is now about 90% form 30 % Forty years ago
- Refer patients with:
 - Child score > B7
 - MELD > 10,
 - Significant complication of Cirrhosis
 - HCC
- Extensive evaluation
- MELD score
- Demand is >>> the available livers → Living Donor Liver Transplantation

Thank you