Introduction to Clinical Liver Disease

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Objectives

- Recognize common presentations of liver disease and patterns of liver injury
- Differentiate acute from chronic hepatitis
- Recognize clues in history, physical exam, and basic laboratory tests.
- Basic knowledge of common liver diseases (alcoholic, NASH, hepatitis B and C)
Presentations of Liver Disease

- Jaundice
- Hepatomegaly +/- splenomegaly
- Abnormal Liver Chemistries (ALT, AST, Alkaline phosphatase, Bilirubin)
- Portal hypertension (ascites, bleeding from esophageal varices, encephalopathy, thrombocytopenia)
- Viral markers for hepatitis B or C.
- Right Upper Quadrant pain
Jaundice

- Yellow skin and sclera (bilirubin $> 2.8$ mg/dl)
- Differential Dx:
  - Parenchymal (hepatocellular and/or canalicular)
  - Biliary obstruction-choledocholithiasis, carcinoma of the pancreas
  - Brisk hemolysis (unconjugated bilirubin)
Types of Liver Injury

- **Hepatocellular**: injury mostly to hepatocytes; dominant aminotransferase elevation (ALT usually > AST); “Hepatitis”

- **Intrahepatic cholestasis**: damage mostly to very small biliary canaliculi; dominant elevation of alkaline phosphatase and GGT +/- bilirubin.
Types of Liver Injury

- **Extrahepatic cholestasis:**
  damage/obstruction of large bile ducts;
  dominant elevation of alk. phosphatase
  and bilirubin. Radiologic studies show
dilation or stricture of bile ducts.

- **Mixed**

- **Micro and macrovascular:** portal
  hypertension with normal liver enzymes
Classification of Hepatitis

- **Acute**: elevation of ALT / AST for days or weeks.
- **Fulminant**: acute hepatitis with hepatic encephalopathy within 8 weeks of onset.
- **Subacute or subfulminant**: development of encephalopathy 8 to 24 weeks from onset of acute hepatitis.
- **Chronic**: elevations of ALT / AST for more than 6 months or due to etiology that is always chronic (Wilson’s disease, Autoimmune hepatitis)
Liver Disease: History

- Anorexia - related to change in taste/smell
- Weight loss - >10 lbs. (Malignancy?)
- Fatigue, mild fever, myalgia – viral hepatitis
- Chills, fever, RUQ pain – biliary tract disease
- Pruritus – cholestatic liver disease
Liver Disease: History

- Exposures – blood transfusions, IVDA, sexual exposure, history of sexually transmitted disease, organic solvents
- Medications or “natural products” – FARE – fever, arthralgia, rash, eosinophilia
- Alcohol use/abuse
Physical Examination

- Scleral icterus – if bilirubin >2.8 mg/dl
- Muscle wasting: cirrhosis, malignancy
- Needle tracks: viral hepatitis, HIV
- Excoriations: cholestasis
- Spider angiomas >12: portal hypertension
- Dupuytren’s contracture, gynecomastia, and parotid enlargement: alcohol abuse
Physical Examination ( Likely Cirrhosis )

- Ascites
- Hepatic encephalopathy (confusion often with asterixis / flapping)
- Fetor hepaticus (sweet apple smell)
- Collateral circulation (caput medusae)
- Clubbing of fingers
Laboratory Testing

- Hepatocellular – AST/ALT
- Alkaline phosphatase – obstructive or infiltrative disease (confirm with GGTP)
- Biosynthesis – albumin, PT
- Transport – bilirubin, bile acids
Almost all from liver cytosol; injury causes rise

- Alcohol injury: usually $< 200 \text{ IU/L} + \frac{\text{AST}}{\text{ALT}} \geq 2$
- Hepatocellular injury: usually $> 300 \text{ IU/L}$
- Obstruction: usually $< 400 \text{ IU/L}$
- Acute bile duct obstruction or liver ischemia
  
  $> 300 \text{ IU/L} \times < 48 \text{ h}$
Patterns of Aminotransferase Elevation

- **Rapid and high (> 300 IU/L) up and down:**
  acute biliary obstruction or liver ischemia
- **Sustained and high (> 300 IU/L x > 1 week):**
  viral or toxic hepatitis
- **Prolonged (months) with peaks and troughs:**
  HCV
- **Prolonged (months) mild/ moderate elevation:**
  chronic viral hepatitis, metabolic, immune or toxic liver disease
Alkaline Phosphatase

- Found in liver, bone, kidney, intestine, placenta
- ‘Inducible’ enzyme
- Elevated in cholestatic, obstructive, and infiltrative liver disease (infiltrative = sarcoidosis, tuberculosis, liver abscess, metastatic malignancy)
Alkaline Phosphatase

- Elevation $\geq$ 4-fold suggests intra- or extra-hepatic cholestasis
- Elevation < 3-fold is less specific
- “Isolated” elevation (normal bilirubin): partial bile duct obstruction, infiltration or focal liver mass
- Elevated hepatic alkaline phosphatase without liver involvement:
  - Hodgkin’s, myeloid metaplasia, congestive heart failure, renal cell carcinoma, intra-abdominal infections
**Synthetic Function**

- **Albumin**: 12-15 gm/d normally synthesized, synthesis inhibited by malnutrition, alcohol, and inflammation. Low albumin suggest advanced liver disease.

- **Prothrombin time (PT)**: Coagulation factors – I, II, V, **VI**, IX, X, XII, XIII produced in liver, II, VII, IX, X- vitamin K dependent; Lack of response of PT to vitamin K injection suggest severe liver disease.
Bilirubin

- Bilirubin $\geq 10$ mg/dl in absence of biliary tree dilatation supports non-obstructive jaundice
- Degree of bilirubin elevation do not correlate well with severity of acute disease
- Bilirubin in urine usually indicates hepatobiliary disease (direct bili)
- Urobilinogen (in urine) is decreased in biliary obstruction (but also with antibiotics)
Hepatitis B
Hepatitis B

- 42 nm, partially double-stranded circular DNA virus.
- 350 million carriers world-wide; causes 250000 deaths a year.
- 1.25 million carriers in USA.(0.5 %); > 8% in Alaskan Eskimos.
- **Transmission**: In USA predominantly sexual and percutaneous during adult age. In Alaska predominantly perinatal.
Hepatitis B Transmission

- **Sexual**: heterosexual in 41% of acute cases. Men having sex with men have 10% risk.
- **Percutaneous** (mostly illicit drug use): 15% of acute HBV cases
- **Perinatal**: 10% of acute cases (mother-child)
- **Transfussion**: 1/63000 transfusions.
- **Other**: organ transplant, tattoo, piercing, acupuncture, ...
Hepatitis B
High-Risk Groups

- Born in high prevalence area
- Active homosexual men
- Promiscuous heterosexuals
- Healthcare & Public Safety workers
- Attendant/family of institutionalized mentally handicapped
- Intravenous drug abuser
- Person requiring frequent transfusions
- Inmate in long-term correctional facility
- Hemodialysis patient
- Traveler > 6 months to endemic area
- Sexual partner of HBsAg(+) person
Hepatitis B Vaccination

- All children and adolescents
- If not previously vaccinated: All high-risk groups
- Post-Vaccination testing:
  - Healthcare & Public-Safety workers
  - Infants from HBsAg(+) mother
  - Hemodialysis patients
  - Sexual partner of HBsAg(+) persons
Acute Hepatitis B

- **Incubation**: 1-4 months
- **Prodrome**: arthralgia, arthritis, skin rash
- **Symptoms**: malaise, anorexia, jaundice, nausea, fatigue, low-grade fever, myalgia, change in taste and smell. Tender hepatomegaly in most patients; splenomegaly in 5-15%.

- Infrequently: confusion, edema, coagulopathy, coma (Fulminant Failure in 0.5%)
Acute Hepatitis B

- **Diagnosis**: anti-HBc IgM antibody; frequently HBsAg in early phase and anti-HBs in late phase.

- **Evolution to Chronicity**:
  - a) Infants: 90%,
  - b) Children 1-5: 25-50%,
  - c) Adults & older children: 5%

- **Treatment**: Supportive
Chronic Hepatitis B

- In low prevalence areas (USA) 30-50% history of acute hepatitis (rare in high prevalence)

**Symptoms**: frequently asymptomatic; sometimes RUQ or epigastric pain or acute-like hepatitis episodes.

**Extrahepatic**: serum-sickness, polyarteritis nodosa, membrano- or membranoproliferative-glomerulonephritis, mixed cryoglobulinemia, IgA nephropathy, papular acrodermatitis.
Chronic Hepatitis B

- **Diagnosis**: HBsAg (+) & HBV-DNA (+) for > 6 months, with anti-HBc IgM (-) but anti-HBc total (+) [excludes incubation]

- **States of Disease**
  - Inactive Carrier
  - Immunotolerant
  - Immunooactive
  - Occult Hepatitis B
Chronic Hepatitis B states

- **Inactive Carrier state**
- Normal ALT (male < 30 U/L, female < 19 U/L) and
  - HBe(+) or Wild-HBe(-): HBV-DNA < 20000 IU/mL,
  - Mutant-HBe(-): HBV-DNA < 2000 IU/mL,

*(in HBe(-): if HBV-DNA > 2000 IU/mL but < 20000 IU/mL, needs testing for PreCore or Core-promoter mutation to classify, but management will not change)*
Chronic Hepatitis B states

- **Immunotolerant state**
  - Normal ALT (*male* < 30 U/L, *female* < 19 U/L) and
    - HBe(+) or Wild-HBe(-): HBV-DNA > 20000 IU/mL,
  - Mutant-HBe(-): HBV-DNA > 2000 IU/mL

- **NOTE:** Consider Liver Bx in older than 40 years & HBV-DNA > 2000 IU/mL (10^4 copies/mL), (May be immunoactive)
Chronic Hepatitis B states

- **Immunoactive state**
  - *Elevated ALT (> ULN)*
    - HBe(+) or Wild-HBe(-):
      - HBV-DNA > 20000 IU/ mL
    - Mutant-HBe(-):
      - HBV-DNA > 2000 IU/ mL
  - **Treat**
Occult Hepatitis B

- **Highest risk groups:** Natives from highly HBV-endemic areas, chronic HCV infected, HIV infected, hemodialysis patients, hemophiliacs, former/current IV drug abusers

- **Clinical Relevance:**
  - a) Transmission of infection by blood transfusion in Taiwan and India,
  - b) Reactivation due to immunosuppression: Rituximab, Alemtuzumab, Infliximab, liver transplant, hematological malignancies, HIV infection, stem cell transplantation, chemotherapy, kidney or heart transplantation,
  - c) Acceleration of liver damage in chronic HCV and cryptogenic liver disease,
  - d) Increased risk of HCC

- **Management:**
  - a) Test donated blood for HBV-DNA in highly endemic areas.
  - b) Test for HBsAg & anti HBc before immunosuppression; if HBsAg(+), investigate and treat accordingly; if only HBc(+), pre-treat with Lamivudine.
Chronic Hepatitis B Treatment Candidates

- HBsAg(+) and HBV-DNA > 20000 IU/mL for wild virus, or > 2000 IU/mL for mutant virus.
  - With elevated ALT, or
  - With moderate or severe activity in liver biopsy

- **Interferon or Peg-Interferon**: if non-cirrhotic

- **Entecavir, or Tenofovir**: cirrhotic or non-cirrhotic. Other drugs that are active, but avoided due to rapid drug resistance are: Lamivudine, Adefovir, and Telbivudine.
Hepatitis C
Hepatitis C

- 50 nm enveloped, positive-sense, single-stranded RNA hepacivirus. Six genotypes and > 100 subtypes.
- 170 million infected worldwide; 4 million in USA (1.8%); 38,000 new infections/year.
## Prevalence of HCV

<table>
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<th>GROUP</th>
<th>%</th>
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<tr>
<td>Infant of RNA(+) mother</td>
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<tr>
<td>Homosexual men</td>
<td>4</td>
</tr>
<tr>
<td>Monogamous partner</td>
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<tr>
<td>General population</td>
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<tr>
<td>Volunt. blood donor</td>
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<table>
<thead>
<tr>
<th>GROUP</th>
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<tbody>
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<td>Hemophilia &lt;’87</td>
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<td>IVDA</td>
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<tr>
<td>Hemodialysis</td>
<td>10</td>
</tr>
<tr>
<td>Transfusion &lt; ’90</td>
<td>7</td>
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<tr>
<td>Person w STD</td>
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</table>
Risk of HCV in IVDU (% infected)

- Year 1: 78%
- Year 5: 83%
- Year 10: 94%
Acute HCV

- **Incubation**: 2-26 weeks (usually 7-8)
- **Symptoms** in < 30%, mild & < 1 month: anorexia, arthralgia, myalgia, fatigue; rarely jaundice, fever or skin rash. Very rare FHF.
- **DX**: HCV-RNA (+) days to weeks after acquisition; anti-HCV (+) in 6 weeks.
- **Spontaneous HCV clearance**:
  - Children < 2 y.o. & young women = 45%
  - Others = 23%
Acute HCV Treatment

- If HCV-RNA(+) 3 months after inoculation, spontaneous clearance is rare.
- Best regimen is unknown: starting 3 months after inoculation, IFN 5 MU QD x 4 wks + 3 MU TIW x 20 wks gave 98% clearance; the mildest & shortest effective therapy is unknown.
- Patients should be abstinent from alcohol and drugs (anti-HCV is not protective).
Chronic HCV

- Most are asymptomatic; 6% symptomatic before diagnosis.

- **Symptoms**: fatigue, RUQ discomfort, anorexia, nausea, itching, arthralgia, myalgia.

- **Extrahepatic**: mixed cryoglobulinemia, purpura, mononeuritis multiplex, PCT, membrano-proliferative glomerulonephritis, xerostomy, low-grade B-cell lymphoma, corneal ulcers and idiopathic pulmonary fibrosis, lichen planus.
Pattern of ALT Elevation in Chronic HCV

Pattern of ALT Elevation

- Normal ALT: 31
- ALT < 2X-ULN: 15
- ALT 2-3X-ULN: 12
- ALT > 3X-ULN: 42
Degree of Fibrosis in Chronic HCV

- None: 16
- Stage 1: 22
- Stage 2: 19
- Bridging: 19
- Cirrhosis: 24

Degree of Fibrosis
Outcome of HCV
25-30 year Follow-up

- Resolves @ acute hepatitis
- Chronic / No-cirrhosis
- Compensated Cirrhosis
- Decompensated Cirrhosis
- Death/ Decompensated
- Death/ HCC
HCV Cirrhosis
Survival

SURVIVAL IN CIRRHOSIS

YEARS

% 0 20 40 60 80 100

0 2 4 6 8 10

COMPENSATED
DECOMPENSATED
HCV Cirrhosis
Decompensation & Hepatocellular CA

![Graph showing the percentage of decompenation and hepatocellular carcinoma over years.](image)
Chronic Hepatitis C

Treatment
PEG-Interferon + Ribavirin 1-1200

Genotype & Viral Load on SVR

![Bar chart showing SVR rates for different genotypes and viral loads. The chart compares Rebetron and PEG-Ifn+R treatments.](chart.png)
Alcohol Liver Disease

- Most prevalent liver disease in the USA
- Correlation between per capita consumption of alcohol and the frequency of cirrhosis
- 1 oz “spirit” = 4 oz wine = 12 oz beer = 11.5 gm alcohol.
- Males 40-80 gm/ day (3.5-7 beer); females 20-40 gm/ day for more than 5 years (10 years)
- Lab - AST/ ALT ratio 2/ 1, total usually less than 300, other labs variable (WBC, bilirubin, PT)
- Spectrum - fatty liver - alcohol induced hepatitis - cirrhosis
Non-Alcoholic Steatohepatitis

- Histologically similar to alcohol induced liver disease; fatty liver & Mallory bodies or fibrosis

- Risk factors
  - Central obesity, hypertension, insulin resistance, diabetes, hypertriglyceridemia
  - Total Parenteral Nutrition
  - Protein calorie malnutrition
  - Jejuno-Ileal bypass
  - Drugs
NASH - Obesity

- 300,000 yearly deaths in US due to complications of obesity
- Prevalence of obesity is increasing – Kentucky – 22.3% year 2000
- Obesity and physical inactivity account for 9.4% of US healthcare expenditures
Natural history
- Slow progression, often silent
  ALT > AST
- Cirrhosis
- Portal hypertension
- Liver failure
Cirrhosis

- Final Stage of chronic liver injury.
- Can be reversible if cause of injury is eliminated.
- Diagnosis is by liver biopsy; in absence of biopsy, evidence of chronic liver disease + portal hypertension (ascites, gastro-esophageal varices, hepatic encephalopathy, thrombocytopenia) support the diagnosis.
Cirrhosis

- Decompensated cirrhosis: associated with ascites, or variceal bleed, or hepatic encephalopathy. Has a 50% mortality at 1 year.

- Risks associated with cirrhosis:
  - Hepatic encephalopathy with sedatives & narcotics
  - Bleeding with procedures and NSAIDS.
  - Ascites with Sodium intake.
  - Ascites and renal failure with NSAIDS.
Medications and Cirrhosis

- Careful titration of sedatives and narcotics.
- Avoid NSAIDS
- Acetaminophen is good choice if patient is eating and not drinking alcohol; try not to exceed 2 gm a day.
QUESTIONS ?
HCV Infection: Risk Factors

Known risk:
- Injection – drug use (shared paraphenalia)
- Receipt of clotting factor before 1987
- Immigration from areas without universal precautions

Unproven/low risk:
- Perinatal transmission
- Transfusion after 1992
- Body piercing/scarification
- Long-term hemodialysis
- Occupational exposure (healthcare worker)
- Intranasal cocaine use
- Sex with multiple partners

Risk Factors for Fibrosis/ Cirrhosis

- Alcohol consumption
- Advanced age at infection
- Longer duration of infection
- Male sex
- Overweight
- Genotype or viral load *not* associated with progression

Spectrum of Hepatitis C

- Frequently asymptomatic; many have fatigue.
- Slow progression over 20-30 years unless aggravated by alcohol, obesity, HIV co-infection, etc.
- Treatment can be curative in 45% infected with genotype 1, and 80% infected with genotype 2 or 3.
Acute Liver Failure: Etiology

- Viral hepatitis – A, B +/- D and E
- Epstein-Barr virus, adenovirus, herpes viruses
- Drug induced – acetaminophen
- Toxin – carbon tetrachloride, trichloroethylene, mushrooms – *Amanita* and *Galerina* species
ALF: Complications

- Encephalopathy – grade 3/4 poor prognosis
- Cerebral edema – cerebral perfusion pressure <50mm/Hg (CPP=MAP-ICP)
- Renal failure
- Metabolic disorders – hypoglycemia, acidosis, alkalosis
- Coagulopathy
- Sepsis – common due to invasive procedures
QUESTIONS ?
Bilirubin

- Direct bilirubin – ‘conjugated’ with glucuronic acid
- Delta bilirubin – bound to albumin
- Indirect bilirubin – unconjugated, most common in serum
- Urobilinogen – product of deconjugation in the gut by bacteria, small amount may be excreted in urine (due to enterohepatic circulation)
Aminotransferases

- Markers of Hepatocellular Necrosis
  - **ALT** – alanine aminotransferase or SGPT
  - **AST** – aspartate aminotransferase, or SGOT
AST

- **Higher in:** liver, heart, skeletal muscle, kidney, brain, pancreas, lungs, WBC and RBC; injury causes rise
- **In liver:** 80% mitochondrial/20% cytosol
- **In serum:** mostly from cytosol
- **Alcohol injury:** usually < 300 IU/L and AST/ALT ≥ 2
- **Hepatocellular injury:** usually > 300 IU/L
- **Obstruction:** usually < 400 IU/L
GGT (γ-Glutamyl Transpeptidase)

- Not in bone
- Normal range in children > 4 y.o. and during pregnancy
- Elevation: alcohol, Dilantin, COPD, diabetes, renal failure
- Elevated alkaline phosphatase with:
  - Elevated GGT suggest liver origin
  - Normal GGT, unlikely liver origin