Liver

Summary
- Organization
- Patterns of injury
- Labs
- Clinical syndromes
- Infectious and inflammatory disorders
- Alcohol and drug induced disease
- Metabolic and inherited Liver disease
- Disease of the biliary tract
- Circulatory disorders

Liver reincarnation
- Metabolic homeostasis
  - Process: dietary elements
  - Carbs metabolism (Gluconeogenesis)
  - Amino acid metabolism
  - Lipids (cholesterol/ lipoprotein/ PO4 lipid)
  - Vitamins metabolism
- Storage
  - Vitamin B, D, E, K, glycogen, iron, copper
- Synthesis: serum proteins
  - Albumin, coagulation factors (fibrinogen, prothrombin, 5,7,9,10,11; protein C/S)
- Detoxification of noxious products
- Excretion into bile
- Enormous reserve/regeneration
  - 2/3 of liver removed = minimal hepatic impairment
  - Regeneration in 4 - 6 weeks

Normal Liver
Stellate cells (Ito cells) = myofibroblast, APC, vitamin A storage
- Space of Disse: Like Bowman’s space in glomerulus

Patterns of injury

Prototypical Microscopic Features

Hepatic injury
Summary
- Organization
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Liver Injuries
- Acute liver injury with massive hepatic necrosis
  - Drugs/toxins, viral hepatitis, eclampsia
  - Eg. Acetaminophen
  - 2 to 3 weeks
  - Life-threatening condition (liver transplant)
- Chronic liver injury
  - Hepatocytic, biliary, or vascular
  - Drugs/toxins and viral hepatitis included here too
  - Most common route to hepatic failure
  - Often → cirrhosis
- Hepatic dysfunction without necrosis
  - Mitochondrial injury (Reye syndrome), acute fatty liver of pregnancy, and some drug/toxin injuries
  - Dysfunctional hepatocytes

Hepatic Enzymes

Labs
- Serum liver function tests
  - AST, ALT, ALP, GGT, UB
- Urine
  - Bilirubin, conjugated bilirubin, urobilinogen

Infectious and inflammatory disorders
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    - Dysfunctional hepatocytes
Complications: Hepatic Failure

Characteristics of Severe Hepatic Dysfunction

- Portal Hypertension
- Assoc. with Cirrhosis

Other complications of Hepatic Failure/Cirrhosis

- Jaundice
- Hepatic encephalopathy (Asterixis and altered CNS)
- Hypoalbuminemia
- Hypoglycemia
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Coagulopathy
- Splenomegaly
- Portopulmonary hypertension
- Fetor hepaticus (breath of the dead)
- Hemorrhoids
- Caput medusae
- Hyperammonemia
- Gynecomastia, Spider angiomas, Palmar erythema

*80-90% of hepatic function must be eroded before severe hepatic dysfunction (failure) present

Cirrhosis

- "Diffuse process characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules."
- κίρρος [kírhós] meaning yellowish
- Major causes
  - Alcoholic steatohepatitis (#1 cause)
  - Nonalcoholic steatohepatitis (NASH)
  - Chronic viral infection
  - Autoimmune hepatic/biliary disease
  - Iron overload, Copper overload (Wilson’s)
  - Genetic deficiency diseases (eg. Alpha-1 antitrypsin disease)

Cirrhosis

- Irreversible and progressive
- Chronic inflammation
- Destroyed framework
- Botched regeneration
- VASCULAR REORGANIZATION (shunting)

Cirrhosis/Fibrosis

- Fibrosis is irreversible!!
Bleeding Tendency

- Ascites
- Hypoalbuminemia
- Oncotic pressure decreased
- Risk for spontaneous bacterial peritonitis
- Caput Medusa

Hyperestrogenism - Gynecomastia

Hyperestrogenism - Spider angioma

Hepatic encephalopathy

- Reversible
- Defective urea cycle
- Factors precipitating
  - Consume increased protein
  - Portosystemic shunts - ammonia gets around liver
- Neurotransmitter abnormalities
  - GABA/glutamine disengagement
  - False neurotransmitters
- Clinical
  - Altered mental status including coma
  - Asterios (flapping tremor)
- Treatment: reduce ammonia diet/gut

Portal hypertension

- Reduced hepatic flow
- Intra- and Extra-hepatic shunting
- Prehepatic:
  - Obstructive thrombosis
  - Massive splenomegaly
- Intrahepatic:
  - Cirrhosis (most cases)
- Post-hepatic:
  - Right-sided CHF
  - Hepatic vein outflow obstruction
Esophageal varices
Boy do they bleed!

Portal hypertension

Splenomegaly

Jaundice

Types of Jaundice
- Unconjugated (indirect) bilirubinemia
- RBC breakdown
- Reduced uptake/excretion (drug)
- Impaired conjugation (newborn)
- Genetics (Crigler-Najjar, Gilberts)
- Conjugated (direct) bilirubinemia
  - Elevated cholesterol etc
  - Obstruction (stones, biliary dz, mass)
  - Genetics (Dubin-J, Rotor)

Bile function

Bile Formation

UDP–glucuronyltransferase

Enterohepatic circulation

Bile detergent effect
- Lipid emulsification
- Cholesterol & Lipophilic compound elimination

Jaundice of The Neonate
**Neonatal jaundice**

Kernicterus - Unconjugated bilirubin in brain (BG)

1. UDP-glucuronyl transferase (UGT) decreased function
2. No UGT function
3. Defective canalicular transport system

**Hereditary hyperbilirubinemia**

Hereditary hyperbilirubinemia: DJ syndrome

**Jaundice/Cholestasis**

- Lack of bile flow
- Labs: Conjugated (direct) bilirubinemia, +/elevated alk phos, GGT
- Obstructive
  - Gallstone
  - Mass
  - Cystic fibrosis
  - Bilary disorders
  - Primary Biliary Cirrhosis
  - Primary Sclerosing Cholangitis
  - Genetic/Drug related

**Cholestasis Morphology**

1. Cholestatic hepatocytes
2. Dilated canalicular spaces
3. Apoptotic cells
4. Kupffer cells
5. Bile ductular proliferation
6. Bile plugs
7. Degenerating hepatocytes
Jaundice/ Cholestasis

Jaundice

- Elevated serum bilirubin levels
- >2 mg/dL
- >30 mg/dL with severe disease

Prehepatic: Hemolysis/ Bad erythropoiesis
- Unconjugated hyperbilirubinemia

Intrahepatic: Hepatic Disease
- Unconjugated hyperbilirubinemia
  - Include CrigNj and Gilbert syndrome

Posthepatic: Obstructive/Stone
- Conjugated hyperbilirubinemia
  - Include D-J, Rotor Syndrome

Labs of Jaundice

Summary

- Organization
- Tumors/nodules
- Patterns of injury
- Labs
- Clinical syndromes
- Infectious and inflammatory disorders
- Alcohol and drug induced disease
- Metabolic and inherited Liver disease
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Liver

The Hepatitis Viruses, ALT-AST

Virus | Incubation | Transmission | Frequency of chronic hepatitis | Clinical | Other |
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<tr>
<td>A</td>
<td>28 days</td>
<td>Fecal-oral</td>
<td>Never</td>
<td>Fever, nausea/vomiting, abdominal pain. Majority recover; no carrier state; no chronic hepatitis</td>
<td>#1 hepatitis producing jaundice #2 cause acute hepatitis in U.S. Most preventable infection in travelers (immunization)</td>
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<tr>
<td>B</td>
<td>6-26 weeks</td>
<td>Parenteral</td>
<td>10%</td>
<td>Fever, malaise, painful hepatomegaly, Other associations: Serum sickness, Immunocomplex disease, Vasculitis, polyarthritis, Membranous glomerulopathy</td>
<td>#1 cause HBV in health care via accidental needlestick #1 Acute hepatitis in the U.S. #2 Fulminant hepatitis.</td>
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<tr>
<td>C</td>
<td>6-26 weeks</td>
<td>Parenteral</td>
<td>~80%</td>
<td>Mild symptoms Jaundice uncommon 20% develop cirrhosis Hepatocellular carcinoma (~2% risk per year) Other associations: Glomerulopathy, cryoglobulinemia</td>
<td>#1 chronic blood-borne #1 infection indication for liver transplantation (end-stage) Posttransfusion hepatitis is rare.</td>
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<td>D</td>
<td>28 days</td>
<td>Parenteral</td>
<td>1%</td>
<td>No symptom, only virus in developing countries</td>
<td>In the hepatitis only virus in developing countries</td>
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Acute Viral Hepatitis

ALT>AST

Acute Viral Hepatitis

ALT>AST
Acute Viral Hepatitis

- Hepatic injury with massive necrosis
- Entire liver or random areas
- Shrunken, muddy red, mushy
- Hepatocyte destruction, collapsed reticulin framework and preserved portal tracts
- Usually acute process: Toxins (e.g., Acetaminophen, CCl₄), eclampsia, viral hepatitis etc.

Chronic Viral Hepatitis

- Entire liver or random areas
- Shrunken, muddy red, mushy
- Hepatocyte destruction, collapsed reticulin framework and preserved portal tracts
- Usually acute process: Toxins (e.g., Acetaminophen, CCl₄), eclampsia, viral hepatitis etc.

Chronic Hepatitis

- Fulminant hepatitis
- Liver inflammation later to cirrhosis
- Liver failure
- Jaundice
- Hemosiderosis (brown looks)
- Portal hypertension
Hepatitis A Virus

Route of infection: Oral ingestion

Hepatitis B Virus

Envelope – HBsAg
Core – HbcAg
DNA polymerase/reverse transcriptase
HbeAg

Hepatitis B Virus - Serology

<table>
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<tr>
<th>HBsAg</th>
<th>DNA</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>Anti-HBe</th>
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Hepatitis C Virus

Route of infection: Intravenous drug abuse > Sexual

Detection(Screen): anti-HCV IgG (does not confer immunity)
Confirmation: HCV RNA detection (usually RTPCR however RIBA recombinant immunoblot is used)
Transfusion related infection rare (now)
Hepatitis C Virus

- 2% risk/year

Hepatitis C Virus

"Councilman bodies" = acidophil body

Hepatitis C Virus

Delta Agent

Hepatitis D Virus
Fulminant Hepatitis

Hepatitis E

**Geographic Distribution of Hepatitis E**
Outbreaks or Confirmed Infection in >20% of Sporadic Non ABD Hepatits

Liver Abscess

**Liver Abscess**
Bacterial or parasitic

Other Infectious etiologies

- **Other viruses**
  - “Yellow fever” – flavivirus
  - CMV (Immunocompromised)
  - EBV (mononucleosis)
- **Other bacterial/parasites**
  - Leptospira
  - Liver flukes (Clonorchis, Shistosomia)
  - Worms (Ascaris)
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Liver

Alcoholic Liver Disease

AST>ALT

ROS = reactive O₂ species cause lipid peroxidation/damage

Mallory's Hyaline/Body

Ballooning degeneration
Microvesicular fatty change
Macroversicular fatty change
Pericellular fibrosis

Alcoholic Liver Disease

Steatosis is reversible
Fibrosis is IRREVERSIBLE

= REVERSIBLE STEATOSIS
#1 chronic liver disease in the US
10-20% → cirrhosis
Features are similar to alcoholic steatohepatitis

NonAlcoholic Steatohepatitis (NASH)

Pathogenesis
Mitochondrial damage
Urea cycle disruption
Defective Beta-oxidation of fatty acids (steatosis)

Levy’s Syndrome
Aspirin + viral infxn (chickenpox/flu)
Postinfectious triad:
Encephalopathy
Microvesicular steatotic change
Increased transaminases

Reye’s Syndrome
Hapatotoxin causes massive necrosis and fulminant liver failure
#1 cause of acute liver failure necessitating transplant in US
Toxic metabolites via cytochrome P<sub>450</sub> in zone 3 (Pericentral) hepatocytes
P<sub>450</sub> upregulated by alcohol

Autoimmune Hepatitis
Women
Plasma cell rich
Antibodies
Anti-nuclear (ANA)
Anti-smooth muscle (SMA)
Anti-liver and kidney microsomal (LKM)
Presents @ advanced stage
Progresses to cirrhosis
Respond to steroids
HLA [B8/Dw3]
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Liver
- Tumors/nodules

Iron Overload
- Primary vs Secondary
- AR North European Male
  - Homozygous 1:220
  - Heterozygous 1:9
- HFE protein- Chromosome 6
  - Missense mutations (C282Y and H63D)
  - Others
- "Bronze diabetes", HCC
- Treatment?

Wilson's Disease
- AR, Late childhood presentation
- HLA-A3
- Defective incorporation into ceruloplasmin
- Inadequate biliary excretion of copper
- Liver, spleen, kidney, brain damage from copper
- Penicillamine chelates Copper

α1-Antitrypsin Deficiency
- Autosomal codominant
- PiMM normal
- Decreased aAT
- S and Z allele
- Assoc with cirrhosis and emphysema, HCC
- #1 cause cirrhosis in kids
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Liver

Obstructive Conditions

Intrahepatic Biliary Disease

Primary Biliary Cirrhosis
- Women 40-50
- Assoc with autoimmune dz
- ANA, Antimitochondrial Ab
- Hepatosplenomegaly, xanthelasma, arthropathy, Retained copper

Hepatomegaly, Bile stained liver
Primary Biliary Cirrhosis
- Granulomatous reaction,
- Bile duct lesion
- Bile duct destruction
- Leads to Cirrhosis and HCC

Primary sclerosing cholangitis
- Males 30y
- Bile duct obliterative fibrosis "onionskin"
- ANCA associated
- HLADR52 & HLACw7
- Assoc with IBD (esp Ulcerative colitis)
- Cirrhosis and Cholangiocarcinoma

Primary sclerosing cholangitis
- Inheritance:
  - Autosomal Dominant

- Associated with PCD, PKD, and other malformations

Cirrhotic transformation
- Associated with IBD (esp Ulcerative colitis)

Circulatory Disorders

Vascular lesions
- Portal Hypertension
- Esophageal varices
- Hemorrhage
- Ascites
- portal hypertension
- Budd-Chiari syndrome
- Hepatic vein thrombosis
- Portal vein thrombosis
- Splenic vein thrombosis

- Elevated portal venous pressure
- Variceal bleeding
- Ascites
- Esophageal varices
- Hepatic encephalopathy
- Fulminant hepatic failure

- Portal hypertension
- Hepatic failure
- Cirrhosis

- High-dose chemotherapy, bone marrow transplantation
- Ascites
- Variceal bleeding
Hepatic artery infarct

Centrilobular hemorrhagic necrosis

Most often from right sided heart failure secondary to left sided heart failure

Hepatic vein thrombosis

- High mortality (75%)
- Causes
  - Polycythemia (sludgy blood)
  - Hypercoag state
  - Oral contraceptives
  - Deficiencies
  - Tumor (e.g., HCC)
- Labs: ↑ ALT, AST, ↑ Prothrombin time
- Dx: Ultrasound, MRI

Budd-Chiari Syndrome

- Budd-Chiari
- Liver Disease of Pregnancy
  - Preeclampsia
    - 3rd trimester HTN, proteinuria, edema, burning liver pain
    - Periportal hepatocyte necrosis with fibrin deposition → hematoma
    - Eclampsia
    - Hypertension/convulsions
    - HELLP (DIC)
    - Hemolytic anemia
    - Elevated AST/ALT
    - Low platelets

Periportal Edema

Fatty Liver of pregnancy
- Rare
- Fetal fatty acid metabolites washed into maternal circulation and cause hepatic toxicity
- Can be fatal to mother
Hematoma

Focal Nodular Hyperplasia (FNH)
- Benign tumor-like
- Women > men
- Central stellate scar
- CT: DDX includes HCC, hemangioma

Hepatic Adenoma
- Benign tumor
- Women > men
- Vascular can rupture
- Anabolic hormones or contraceptives
- Regress without hormones

Hepatocellular Carcinoma
- Males > females, 50-60y
- #1 primary tumor of liver
- 30-50% 5 year survival
- Increased αFP, AlkPhos, GGT
- Ectopic hormone production
  - Epo (Erythropoetin), Insulin-like GF, PTH-related

Hepatocellular Carcinoma
- Metastases
- Lung > GI > Breast > Kidney
- #1 cancer involving liver
Fibrolamellar Hepatocellular Carcinoma

Other cancers
- Angiosarcoma - Malignant vascular tumor
  - Exposure to vinyl chloride (PVC), arsenic, thorotrast (thorium contrast)
- Intrahepatic cholangiocarcinoma - thorotrast, see later lecture
- Hepatoblastoma - malignant tumor of children

Biliary Tract
- Congenital cyst of extrahepatic bile ducts
- Risk for cholelithiasis, choledocholithiasis, cholangiocarcinoma, cirrhosis
- **Ectatic Ducts with portal fibrosis**
- **Complications**
  - Cholangitis, sepsis, choledocholithiasis, and cholangiocarcinoma
  - Association with polycystic kidney disease

**Caroli’s Disease**

**Cholangiocarcinoma**

- Carcinoma of biliary origin
- 90% extrahepatic
- 60% Perihilar (Klatskin tumors)
- Cause early jaundice or ↑ transaminases

**Causes:** PSC, Flukes, Thorotrast, PVC, Choledochal cyst, Caroli’s

**Clinical:** Palpable Gallbladder, Jaundice, Big Liver

**Gallbladder**

- Function store/concentrate bile
- Express in response to hormones

**Gallstones**

- Mixed stones: Bile salts, Leucine, Cholesterol
- Pure calcareous:
  - Calcium carbonate
  - Calcium oxalate
- Pure mucous:
  - Mucus, Hypocitraturia
  - Gallbladder hyperplasia
- Pure protein:
  - Protein A or B

**Bile acids**

- CHOLATES
- PHOSPHOLIPIDS
- CHOLESTEROL (LPH)
- BILE ACIDS (LTA)
- UMBRELABOXYLATES
- LITHOCHOLATES
Biliary Obstructive Disease

- Cholesterol stones
  - Most common stone (80%), radiolucent
  - Fat, Fertile, Female, Forty
- Black pigment stones
  - Produced via hemolysis
  - Radiopaque – calcium bilirubinate

Clinical presentation:
- Fever
- Vomiting
- Murphy’s sign (pain on palpation)
- Colicky midgastic pain switches to RUQ/scapula pain

Acute cholecystitis
- 90% by obstruction of cystic duct

Cholecystitis

Charcot triad: Fever, Jaundice, RUQ pain
Duct obstruction/infection
E coli usually
Cause abscess
Life threatening
Gallbladder Carcinoma
- Women, 70 y
- Cholelithiasis (95%)
- Porcelain Gallbladder (calcified)
- 50% risk of carcinoma progression

Pancreatic Disease
Etiologies:

**METABOLIC**
- Alcoholism
- Hyperlipoproteinemia
- Hypercalcemia
- Drugs (e.g., azathioprine)

**GENETIC**
- Mutations in the cationic trypsinogen (**PRSS1**) and trypsin inhibitor (**SPINK1**) genes

**MECHANICAL**
- Gallstones
- Trauma
- Iatrogenic injury
- Operative injury
- Endoscopic procedures with dye injection

**VASCULAR**
- Shock
- Atheroembolism
- Vasculitis

**INFECTIOUS**
- Mumps (also CMV)

Especially Trypsin
Chronic Pancreatitis

the most common cause of chronic pancreatitis is long-term alcohol abuse
Multiloculated Pseudocyst

Serous cystadenoma

- Benign Neoplasm
- Women > Men
- 25% of Cystic Neoplasms
- Most benign
- 95% Women
- Risk for Pancreatic Carcinoma
- Mucinous epithelium with “Ovarian stroma”

Mucinous cystadenoma

- Men > women
- Risk for pancreatic cancer higher than mucinous cystadenoma

IPMN (intraductal papillary mucinous neoplasm)

- Men > women, 60-80 y
- Risk factors: TOBACCO and Alcohol
- Very poor prognosis, 20% 5yr survival – one of the worst cancers
- 65% in Pancreatic head
- Jaundice etc
- Tail and body tumors present at later stage

Pancreatic Cancer
Pancreatic Cancer

- Marantic Endocarditis
- Migratory thrombophlebitis
- Trousseau sign
- Cancer associated hypercoagulability

Endocrine Pancreas

Small Vessel Disease

Diabetes mellitus
Islet Cell tumors (neuroendocrine tumors)

- Seen in MEN-I syndrome
  - 3 P's
  - #1 = insulinoma
  - Whipple's triad:
    - Hypoglycemia
    - CNS problems
    - Reversal of CNS problems with glucose

- Gastrinoma
  - Associated with ZES (Zollinger-Ellison Syndrome)
  - HCl Hypersecretion, Several ulcers in strange places (duodenum, hypergastrinemia)

- Glucagonoma = Necrolytic migratory erythema