Diseases of the Liver

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Liver Physiology

3 Main Functions of the Liver
1.) Processing nutrients
2.) Synthetic function
3.) Protection and clearance
Processing Nutrients

3 main classes of nutrients

• Carbohydrates
• Proteins
• Lipids
Carbohydrates

1. Glycogenesis – storage
2. Gluconeogenesis – glucose – transport
3. Glycogenolysis – back to glucose
After a big meal, lots of glucose is available. Insulin stimulates glycogen synthesis, leading to increased glycogen levels.
Glycogen good for storage because insoluble
Glucose soluble – good for transport - hepatic dysfunction can cause Hypoglycemia
Liver not only organ which performs glycogenesis – brain, muscles, kidney & others
Proteins

GI tract breaks down proteins in food to amino acids and the liver puts them back together again as functional proteins pre hormones to be built up in other organs.
70% of protein in blood is albumin which helps maintain oncotic pressure
Coagulation factor produced by liver except Factor 8 and calcium
Transport and Binding Proteins

1. Apoferritin bound with Fe = Ferritin for Fe storage
2. Transferrin for transfer of Fe hematological
3. Immunoglobulins and complement – loss of liver function thus causes an immunosuppressed state
Bile salts Immulsiviers
Products of hepatocytes – calculi – bile ducts – s. intestine – chylomicrons – suspension of fat for absorption
Liver has an important role in lipid synthesis
All water soluble nutrients transported to liver by portal vein

Lipids packaged into chylomicrons – transported by lymphatics to thoracic duct – left subclavian vein to liver
Liver breaks down chylomicrons to triglycerides and cholesterol. Lipoproteins produced by liver transport triglycerides and cholesterol.

*Also storage of vitamins and minerals, i.e. – Vitamin A in Kupffer cells
3rd Function – Protection & Clearance

1. Portal vein – sinusoids – Kupffer cells
2. Clearance of toxins
   Metabolism of medications (poisons) and toxins
   i.e. – oxidation – cleans proteins in body & lose function
   Amino acids are toxins if built up
   Amino acids – urea – kidney breakdowns products excrete – NH$_3$ - urea cycle
Breakdown toxins – oxidation free radicals

Free radicals damage proteins and DNA

Liver must protect itself from oxidation major contributor glutathione if liver loses glutathione then oxidation stress damages tissues

Major cause of damage from acetaminophen overdose
Basic Structure of Liver Lobule

- Hepatocytes
- Hepatic Portal Vein
- Hepatic Artery
- Central Vein
- Bile Canaliculi
- Bile Ducts
- Venous Sinuses
Type of cells

Reticuloendothelial cells
1. Endothelial cells – liver sinusoids
2. Kupffer cells – macrophages liver sinusoids
3. Stellate cells – star shape, space of disse
4. Cholangiocytes – liver bile ducts intrahepatic
**liver acinus**

**Zone I:**
- gluconeogenesis
- oxidative energy metabolism
- urea synthesis

**Zone II:**
- display attributes of both zone I and III

**Zone III:**
- glycolysis
- lipogenesis

*CV* stands for central vein, and *PS* stands for portal space (or triad).
Portal triad

Bile duct
Portal vein – 75% of blood to liver – nutrients from GI tract – Deoxygenation
Hepatic artery – 25% oxygenation
Central vein
Space of disse
Between hepatocytes and endothelial cells
Bile calculi
Endothelial cell – liver sinusoids
Fenestrated (window)

Get image of endothelial cell
Cholangiocytes

motility of bile flow
formation of bile salts some and water and electrocytes

Cholestasis – increased bilirubin - Jaundice
Dysfunction of cholangiocytes or obstruction
Internal Anatomy of Liver

- Hepatic vein
- Aorta
- Central vein system
- Branch of hepatic artery
- Branch of bile duct
- Branch of portal vein (distributing vein)
- Right and left hepatic ducts (bile ducts)
- Right and left hepatic arteries
- Portal vein
- Portal triad of structures

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Physical Exam

1. Spider angiomas – chronic
2. Palmar erythema
3. Gynecomastia – ETOH or hemachromatosis
4. Testicular atrophy – normal 3 cm
5. Hair loss chest
6. Opaque nails – (loss of lunulae)

Feminizing signs – altered estrogen metabolism
Findings (physical exam with acute liver injury – Jaundice, coma, Ascites

Findings in chronic liver disease – ascites, muscle wasting, coma, Dupuytren’s contracture, parotid gland enlargement, hepatic encephalopathy, asterixis, fetor hepaticus – methyl - Mercaptan
Blood Chemistries

1. Bilirubin – breakdown of Hgb in reticuloendothelial cells tightly bound to albumin taken up by liver cells and conjugated by glucuronyl transferase
Lab measure direct or conjugate circulating Bilirubin unconjugated
Direct Bilirubin reacts with diazo agent
Add ETOH & blood in diazo agent – total Bilirubin
Elevated Indirect Bilirubin

Hemolysis
Gilberts Syndrome
Neonatal jaundice
Alkaline Phosphatase

Present in canalicular membrane of liver cells
• Cholestasis \( \uparrow \) alkaline phosphatase release in blood
• Can be extra and intra hepatic cause
• Infiltrative process
• Found in liver, bone & placenta
• To determine source can fractionate Alk. Phos., old test, measure GGTP or
• 5’-nucleotidase
• Elevated with bone growth in children
Transaminases

SGOT AST Aspartate Aminotransferase
SGPT ALT Alanine Aminotransferase
Soluble enzymes that escape into blood with hepatocyte injury
SGOT – RBC’s – heart - liver
SGPT – liver specific
Do not determine prognosis
3 Main Causes of High Transaminase Elevation

- Viral hepatitis
- Toxic hepatitis
- Ischemia
Liver Function Tests not really the Transaminases

Protime or INR – Cholestasis - Vit K – Absorption – Antibiotics

Albumin

21 day half life
chronic liver disease
renal loss
gut losses
malnutrition
acute illness – cytokines effect
Cholestasis – Failure or impairment of bile flow

Easiest to understand by dividing intra hepatic and extra hepatic causes

Elevation of Bilirubin cholesterol bile salts – Alk.Phos.

Clinical manifestations Jaundice

Xanthomas and pruitis
Extra Hepatic Cholestasis

Diagnose by x-ray - mechanical
Blockage of bile ducts – CT, US, ERCP
Extra Hepatic Causes

Cancer of bile ducts or pancreas
Strictures of bile ducts – surgery, pseudocysts
Gall stones
Sclerosing Cholangitis
Dilation of bile duct proximal to obstruction may be normal with early obstruction, i.e. - gall stones or sclerosing, cholangitis which causes fibrosis or entire ductal system
Intra Hepatic Cholestasis

Hepatitis – viral – ETOH – drugs – erythromycin chlorpromazine
1° biliary cirrhosis
Infiltrative disease – fat, tumor, granuloma, amyloid
Pericholangitis – ulcerative colitis
Sepsis
Circulating failure
Hemolytic crisis
Liver test

Aminotransferases – liver cell injury
Protime – severity of liver injury
Albumin – chronic liver injury
Globulins – chronic inflammation
Blood flows out of the liver through 3 hepatic veins into a big vein called the Inferior Vena Cava.

Bile flows out of the liver through the bile duct.

Oxygen-rich blood flows into the liver through the hepatic artery.

Nutrient-rich blood coming from the bowel flows into the liver through the portal vein.
Bile is chief exocrine secretion of the liver - & secreted by active transport at the canalicular membranes
Bile flow depends upon hepatic secretion and unobstructed ducts
Endocrine function includes metabolism of steroids and thyroid hormones
Liver Disease

Acute – 8 weeks or less
Subacute – 8 weeks to 6 mons.
Chronic - >6 mons.
Liver Failure

Decompensated
1.) Jaundice, encephalopathy & coagulopathy
2.) Can occur with acute, subacute & chronic liver disease
3.) Cirrhosis – histologic diagnosis
   fibrosis and regenerating nodules
4.) Not all cirrhotic patients are in liver failure (compensated)
Diagnosis of Liver Disease

1. Symptoms
2. Physical Exam
3. History
4. Test – Lab & X-Ray
5 Groups of Liver Test Patterns

1. Unconjugated bilirubinemia

2. Acute hepatocellular injury transaminases – bilirubin alk-phis >1000 U/dl toxic ischemia viral hepatitis

3. Chronic Hepatitis ↑ transaminases ↑ bilirubin ↑ protime or INR ↓ albumin ↑ globulins

4. Cholestasis Alk.Phos. more than transaminases, bilirubin ↑ protime may be abnormal due to Vit K absorption


infiltrative – fat, tumor granuloma, partial bile duct obstruction with tumor or abscess
Group 1 – R/O Hemolysis, LDH
Group 2 – Hepatitis  ETOH history  
   Hepatitis serology
Group 3 – Hemochromatosis, Wilsons Disease, chronic viral hepatitis, autoimmune hepatitis, liver biopsy often done
Group 4 & 5 – Imaging studies US & CT  
   ERCP, PTC, MRCP, EUS
Viral Hepatitis

A B C D E – most a silent disease
CMV, Epstein-Barr
Hepatitis A

Fecal oral route
Incubation 15-50 days
RNA virus
No capsule
10% Jaundice
Enterovirus
HAV Serology

Anti HAV IgM – early
Anti HAV IgG – mid & late
Human immunoglobulin – vaccine
Prodrome 2 – 14 days – flu like symptoms
Isteric phase <6 weeks symptoms improve
Recovery phase 2-6 weeks
No chronic disease – Fulminent Hepatitis 0.2%
HBV – Hepatitis B Virus

Double stranded DNA
Transmitted by body fluids
Sexual, shared needles
Medical personnel
Transfusion
Vertical transmission
Hepatitis B

- Structure
- Transmission
  - Hepadnavirus
- Pathogenesis
- Serology
- Diagnosis
- treatment
HBV Structure

- DNA
- Capsule
HBV Pathogenesis

Virus invades hepatocytes
Viral specific cytokines
T-Lymphocytes
Hepatocellular damage
Inflammation
SGOT – SGPT ↑
30% have symptoms
25% icteric
10% chronic
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HB vaccine

Made to capsule
Not active virus
Case 1

1) HBSAg+
   HBCAg+
   HBeAg+
Acute HBV infection

No IgG Anti SAb.
Case 2

HBSAg negative
IgG Anti BSAb
Case #3

HBSAg – negative
IgG Anti HBc
IgG HBSAb
Past infection
(Recovered)
HBV Chronic Infection
(>6 mons)

[Graph showing titer over time with markers for HBSAg, IgG HBc, and IGM]
Chronic Hepatitis B

3 phases

1. Replication phase – high transaminases – cell damage – HBCAg HBVDNA

2. Immunoreactive phase – spontaneous rise in pts. own cell mediated response to viral infection - ↑ inflammation – high transaminasines can mimic acute hepatitis

3. Integration phase – viral genome integrates host DNA – little inflammation – HbeAg & HBV DNA disappear – inactive carrier

Finally HbSAb + HbSAg -
HBV Treatment
Chronic Infection

- Alpha Interferon
- Adefovir
- Lamivudine
- Entecavir
- Tenofovir

Goal to covert from replication to integration phase
Post Exposure Prophylaxis

Hepatitis vaccine
Hepatitis B Immunoglobulin HBIG
Hepatic C Virus

Single stranded RNA
Flavivirus group
Transmission mostly parenteral
IV drug abusers
Transfusion in past
Sexual transmission rare
HCV Genotypes I - VI

Ia & Ib in USA 70%
85-90% chronic
Fulminant liver failure rare
Can take up to 16 weeks to develop
Ab in 50% of patients
Anti HCV – HCA RNA  PCR
No prophylaxis  - No vaccine
Chronic infection characterized by fluctuating transaminases

II & III 24 week Rx – High response rate
Harvoni
Ledipasvir/sofusbuvir
Rx for HCV Type I
12 weeks one pill except prior Rx with cirrhosis
>90% sustained viral response
HCV Type II – III – IV sufosbuvir & riboviron
Leipsasvir is an inhibitor of HCV NS5B RNA protein required for viral replication. The multi-functional NS5A protein required for viral replication and viroplasm assembly. A number of NS5A inhibitors have shown antiviral efficacy in HCV infected patients.
Sofosbuvir is an inhibitor of HCV NS5B-dependent RNA polymerase which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphophate (GS-461203) which can be incorporated into HCV RNA and acts as a chain terminator.
Delta Virus – Hepatitis D

Defective virus requires anti delta IgmHBV surface Ag for replication
Patients are sicker – more likely Fulminant
Require transplant sooner
Common in Mediterranean
In US – IV drug abusers & hemophiliacs should be checked
Delta Virus

15 million globally
60 – 70 thousand USA
>genomes
Enveloped virus embedded in HBV
Adult acquired 7% have Delta
Vertical transmission of HBV 25% cirrhosis & cirrhosis & CA risk doubles
HBV + Delta  5 x more likely to accelerate progression to cirrhosis & hepatocellular cancer
Curable in some cases 15% with Interferon
Hepatitis E Virus

Mostly in underdeveloped countries
Water
Fulminant in pregnant females
Hepatitis E virus seroprevalence and risk factors for individuals in working contact with animals

In industrial countries genotypes 3 & 4 of HEV are detected in swine, wild boar, deer and rabbits, and they are associated with autochthonous infections suggesting the existence of zoonotic HEV infections, compatible with the putative involvement of undercooked pork and big game products as a source of infection.

Occupational exposure to animals and consuming raw or undercooked pork liver sausage or pork liver play a significant role in HEV transmission.
Hepatitis E Virus

Hepatitis E virus is one of the most common causes of acute hepatitis worldwide. Physicians should be aware of Hepatitis E as a cause of both acute & chronic hepatitis in immunocompromised patients. The best treatment option for HEV infection remains to be defined, but both ribavirin & peg-interferon may have a role in therapy.
Cirrhosis

Fibrosis & nodular regeneration
Many causes but most common in the world
  Schistosomiasis
In USA – fatty liver Hepatitis C and alcohol
Diagnosis of Cirrhosis

Gold standard liver biopsy but history + ↑ Protime + thrombocytopenia

Indirect evidence
Physical Exam

1. Fetor Hepaticus
2. Spider angiomas – S.V.C. drainage only fills from center to periphery
3. Palmar Erythemia
4. Gynecomastica
5. Testicular atrophy
6. Loss of body hair
7. Opaque nails
Cirrhosis Complications

1. Bleeding esophageal varices
2. Ascities & edema
3. Encephalopathy
4. Hepatorenal Syndrome
Varices

Hepatic pressure >12
Size
Beta blockers
Band ligation
Octreotide
Ascites

Portal hypertension
Oozing from splanchnic capillaries
↑ Hepatic lymph
low protein  few WBC’s
Serum – ascities albumin
>1.1 - portal HTN  gradient
<1.1 – peritoneal inflammation
Spontaneous Bacterial Peritonitis

Fever abdominal pain
Worsening Hepatic Encephalopathy
Or no symptoms
Gram neg – E. Coli, pneumococcus
Not anaerobes
WBC > 500
PMN > 250
Mortality rate < 2 years
Treatment of Ascities

Salt restriction
Diuretics
Pericentesis + albumin
Hepatorenal Syndrome
Encephalopathy

Ammonia
Gaba receptors
Lactulose
Neomycin
Xifaxan
Causes of Cirrhosis

Alcohol, Hepatitis B & C, Alpha-1 antitrypsin deficiency, Wilsons Disease, hemochromatosis, sclerosing cholangitis, NASH, 1° biliary cirrhosis
Wilson’s Disease

Autosomal recessive syndrome
↑ Copper in tissues
↓ Ceruloplasmin
↑ Urinary copper
Movement disorders
Psycosis
Kayser Fleisher rings
Age 4 to 40
Hemolytic anemia
Hemochromatosis

Most common recessive genetic disorder
1:400 persons homozygous
↑ Iron absorption
Liver, pancreas, heart, testicles
Bronze, DM
↑ ferritin, transferrin sat.
TIBC ↓
Fe Index >2.0
Chromosome study
Primary Biliary Cirrhosis

Antimitochondrial antibody
Pruitis
Female
Liver biopsy for staging
Ursodeoxycholic acid
Inflammatory Bowel Disease

Sclerosing cholangitis
Pericholangitis
cholangiocarcinoma
Alpha 1 – Antitrypsin Deficiency

Liver + Lung
↓ Alpha 1 antitrypsin
Electrophoresis phenotype ZZ liver disease
Nonalcoholic Steatohepatitis NASH

Liver biopsy – fibrosis steatosis
PMN cells, mallory bodies & hepatocyte necrosis
NAFL  nonalcoholic fatty liver
US & CT – suggestive
DM, ↑ triglycerides and obesity
Vit. E
Weight reduction
Autoimmune Hepatitis

ANA + anti smooth muscle Ab + mostly middle aged females
Rx – steroids and Imuran
Can lead to cirrhosis & acute hepatitis & death
## Child – Pugh Classification of Cirrhosis

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<td>1.71-2.24</td>
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Tumors of the Liver

Metastatic – portal vein – GI tract
Needle biopsy  testicular,  lymphoma, lung CA
1° liver tumors
Hepatoma  Hepatitis B, C
Any cause cirrhosis
Cirrhosis – US – every 6 mons.
Liver transplant
Hemangiomas 5-7%  Diagnosis – dynamic CT – MRI
Adenomas – oral contraceptives
Focal nodular hyperplasia
Classic Presentation of Gall Bladder Pain

Biliary colic
N & V
Location RUQ
Confused with MI – PUD appendicitis
pneumonia, flu
Abscess of Liver

Bacterial, fungal, entamoeba histolytica
Alcoholic Liver - Disease
Very common in USA
Women more common than men
Alcohol metabolized in liver
2 pathways
  1. alcohol dehydrogenase
  2. cytochrome P 450
ADH pathway ETOH is oxidized generates NADH in amounts the liver can not reoxidize
Cytochrome P450 system plays greater role in abusers
Product of both pathways is acetaldehyde. Which is oxidized to acetate
Alcoholic Hepatitis

Symptoms highly variable
Liver biopsy infiltrated with PMN’s
Mononuclear cells, inflammation, cell necrosis & fatty infiltration – steatohepatitis, mallory bodies

Symptoms – fever, ↑WBC’s, abdominal pain

Prognosis – total bilirubin + 4.8 – protime – control
  >32 prognosis poor

AST < ALT

SGPT (SGOT)
Stages of liver damage

Fatty Liver
Deposits of fat causes liver enlargement.

Liver Fibrosis
Scar tissue forms.

Cirrhosis
Growth of connective tissue destroys liver cells.
Cirrhosis

Regenerating nodules = separated by fibrous bands

No ETOH for 6 mons. for liver transplant

30% of alcoholics develop liver disease
Drugs Causing Hepatic Injury

Any drug that its initiation coincides with abnormal liver tests should be withdrawn.

Hepatitis generally resolves after withdrawal of drug.
Medications that cause abnormal Aminotransferase Levels

Intentional medication overdose, acetaminophen
Some pain medication, ie – diclofenac, naproxen
Cholesterol-lowering medications, statins
Some antibiotics, ie – sulfonamides, nitrofurantoin
Some tuberculosis meds – isoniazid
Some anti-fungal meds – fluconazole, itraconazole
Some psychiatric medications – tricyclic antidepressants
Some seizure meds – phenytoin, carbamazepine, valproic acid
Idiosyncratic drug-induced liver injury

Idiosyncratic drug-induced liver injury (DILI) is rare, with an incidence of approx. 19 per 100,000 treated individuals. Cumulative drug exposure and HLA phenotypes play an important role in the pathogenesis of DILI. Patients who present with suspected DILI and jaundice should have biliary obstruction and acute viral hepatitis, including hepatitis E excluded. Immune-mediated DILI will respond to steroid therapy. Women have increased risk of hepatocellular DILI. Antibiotics, anticonvulsants and antidepressant therapy remain the commonest causes of DILI.
Case 1

30 yr old male – history of fever 2 weeks R sided pleural effusion, TB skin test neg.

Phys. – liver normal size

Lab – Hgb 12, WBC 14,000, Alk.Phos. 400, SGOT 60, Albumin 4, globulin 2.9
Case 2

60 year old - referred for eval of enlarged liver – DM II, obese
Vague discomfort, RUQ
No exposure to toxins or poisons
No history of jaundice, no IV drug abuse
Lab – CBC wnl, Exr normal, PT normal, SGOT 90, Alk.Phos. 140, Albumin & globulin normal
Physical exam normal
Case 3

40 year old female – jaundice
Flu like symptoms & fatigue
Dark urine
No signs of chronic liver disease
Epidemiological info. – travel, shell fish, tattoos, IV drug abuse, ETOH history
Lab – SGOT 1000, Alka-phos 140, Protime 12, INR 1.1, Bilirubin 8.7
Same patient 3 mons. later

Remains jaundice & tired – unable to work
Phys – spider angiomas pedal edema
Lab – SGOT 325, Bili 4, CBC wnl, Albumin 3.5, globulin 4, liver biopsy
Case 5

35 yr old female – diarrhea, jaundice, temp 101°F, ascites
Enlarge veins of abdomen
Opaque nails, muscle wasting, spleen enlarged
Lab – Hgb9.5, WBC 14,000, protime 20, bilirubin 11, SGOT 400, Alka-phns 168, albumin 2, globulin 3, ?? count 67,000
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