Liver Tests at a glance

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Liver Function Tests and Diagnostic Studies

**first clues**

*assess 1) severity 2) prognosis 3) effectiveness of therapy.*

Liver biopsy = gold standard

**Microanat:** Zone 1 (portal: arteriole, vein, bile duct)
- Zone 2 (in between)
- Zone 3 (central vein)

Hepatocytes: 2 cell thick, reticulin stain (healthy)

Kupffer Cells: PAS (mP of Liver)

**Bilirubin metabolism:**

- 85% senescent erythrocytes
- 15% hepatic heme or hemoproteins + red cell precursors (bone marrow)
- **Free = unconjugated bilirubin** = tightly bound to albumin
- Insoluble → not excreted in urine
- may be increased 1) severe hemolytic diseases 2) protein binding drugs
- Liver conjugates w/ UDP-glucuronyl transferase → diglucuronide (and monoglucuronide)

**Conjugated bilirubin** (Bilirubin+glucoronide)
- Water soluble, non toxic, → excreted in urine
- Bilirubin delta fraction = conj-bili covalently bound to albumin (no bilirubinuria)
- Liver excretes into bile → hydrolyzed by beta-glucoronidases to form unconjugated bilirubin, → gut bacteria → colorless urobilinogens.
- small amount urobilinogen → reabsorbed by the enterohepatic circulation → 1) mostly excreted in the bile 2) small urinary excretion

**Measurements of serum bilirubin:**

*total, direct and indirect bilirubin.*

Indirect = unconjugated bilirubin = total - direct (calculation)

**Hyperbilirubinemia**

*Unconjugated:* overproduction or defective uptake /storage

*Conjugated:* cholestasis, hereditary

**Bilirubinuria:** dark urine due to increase in conjugated (direct)

**Urinary urobilinogen:** hemolysis, GI hemorrhage, hepatocellular disease

**Congenital disorders of bilirubin metabolism**

**Gilbert syndrome** (Idiopathic unconjugated hyperbilirubinemia)
- 2-5% of the population
- increase after a 24 hour fast, decrease after phenobarbital

**Crigger-Najjar syndrome**

Fasting/stress → enzyme deficiency → high-unconjugated bilirubin levels

Type I → kernicterus (bilirubin deposition in brain) + fatal.

Type II → responds to phenobarbital treatment, increase enzyme production

**Dubin-Johnson syndrome and Rotor syndrome**

defective protein carrier in the bile canal → impaired conjugated excretion → Impaired bile excretion, black pigmentation of the liver + Elevated conjugated bilirubin levels.

**Serum enzyme levels**

enzymes not specific to liver

*Organs with high concentrations of “liver” enzymes:*

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<th>AST (SGOT)</th>
<th>ALT (SGPT)</th>
<th>ALKALINE PHOSPHATASE</th>
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<td>kidney</td>
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**Serum aminotransferases**

injured hepatocytes → hepatic inflammation or cell necrosis

early marker for 1)viral 2) autoimmune 3) drug-induced hepatitis.

**Aspartate (AST, SGOT [serum glutamic oxaloacetic transaminase])**

**Alanine** (ALT, SGPT [serum glutamic pyruvic transaminase])

(higher sensitive and specific, L is for Liver).

- Men: 30 U/L | women: 19 U/L
- **AST: ALT ratio > 2.1:** Alcohol-related liver injury *(MITO Injury)*
- Mostly **ALT:** viral, autoimmune, hemochromatosis, Wilson disease, highest in acute hepatitis *(normal and drug-induced)*

**Alkaline phosphatase**

intrahepatic or extrahepatic **biliary tract obstruction:**

Non-hepatic causes: bone metastasis, small bowel obstruction, and normal pregnancy.

**Simultaneous elevation of GGT → hepatic origin**

if elevated → undergo abdominal US [gallstones, focal lesions, etc.]

**Gamma glutamyl transferase (GGT)**

*Origin:* biliary canaliculi + microsomes (drug/toxin metabolizing region of hepatocytes).

Ergo: canalicular damage + exposure to drugs → inc GGT

**Evaluation of synthetic ability (plasma proteins)**

Factor VII → acute liver damage  short t1/2 6-8 hours.

Prothrombin → acute severity and Px

Albumin → chronic liver disease t1/2=20days

Abnormal protein levels → early cirrhosis.

**Use of hepatic imaging studies**

Ultrasound: initial radiologic study of choice

CT, MRI: known liver masses

Cholangiopancreatography (MRCP)

Endoscopic ultrasonography (EUS)

CT or US-guided biopsy of suspected malignancies

**Liver biopsy =** Definitive test

prognosis in chronic liver diseases.

transplant allograft dysfunction/ acute cellular rejection.
II. CLINICAL SYNDROMES ASSOCIATED WITH LIVER INJURY

HEPATIC FAILURE = most severe consequence
1) sudden massive hepatic destruction [acute]
2) end point of progressive chronic liver disease [chronic]
   e.g. repetitive exacerbations of hepatocyte damage
       insidious disease, decompensation (infection)
                   ↓
       lose 80-90% of the liver function
                   ↓
       mortality is 80-90% without liver transplantation.

**Signs and symptoms**
- hyperbilirubinemia → Jaundice and icterus
- Hypoalbuminemia → peripheral edema and ascites
- Hyperammonemia
- Feto Hepaticus
- Hyperestrogenemia → palmar erythema, spider angiomas of the skin,
  hypogonadism , gynecomastia
- Coagulopathy (bleeding)
- Sepsis
- Multiple organ system failure

**Hepatorenal syndrome:** renal failure in patients with severe liver disease w/o renal cause

**Hepatic encephalopathy** with asterixis (hand flapping tremor)

**Hepatopulmonary syndrome:** hypoxemia and intrapulmonary vascular dilatation due to enhanced NO production in lungs.

**Acute liver failure (ALF) (acetaminophen)**
Rapidly progressive hepatic dysfunction associated with high risk of mortality.

**Clinical:** hepatic encephalopathy, coagulopathy and jaundice in patients without prior liver disease, *Absence of stigmata of chronic liver disease is characteristic.*

**Lab:** elevation of transaminases, PT, PTT
US leading cause *acetaminophen toxicity (see massive necrosis)*
antimycobacterial, antidepressants, mushroom poisoning and halothane
(14%)
HepA (4%) HepB (8%), autoimmune (15%) Hep B>A>C

**Fulminant hepatic failure:** Rapid progression → hepatic encephalopathy in 2-3 weeks from onset

**Complications:**
- Jaundice and icterus
- Peripheral edema and ascites
- Spontaneous bacterial peritonitis
- Bleeding
- Hypoglycemia
- Hypotension
- Renal failure

**Liver transplantation has a major impact on survival.**

**Chronic liver disease (CLD)**
**Definition:** inflammation and hepatocyte destruction > 6 months
**Biopsy:** documented inflammation and fibrosis
**MC cause:** HCV (also HBV, HDV) (not HAV or HEV)
**Young Age** → high risk chronicity

**Signs/Symptoms:** non-specific, MC fatigue (Less common malaise, loss of appetite, bouts of mild jaundice)

**Stigmata of CLD:**
- Hyperestromism → spider telangiectasias, palmar erythema, hypogonad, gynecomastia
- hyperbilirubinemia, hypoalbumin, fetor hepaticus (NH4), bleeding, hematemesis (varices)

**Hepatomegaly** and hepatic tenderness, Mild splenomegaly
**Severity does not predict outcome**

**Histo:** Fibrosis all over (Masson Trichrome): pericellular, periductal, portal, periportal → *Portal extension leads to expansion → nodules of cirrhosis*
**Lab:** elevated transaminases, bilirubin (conjugated), prolonged PT hyperglobulinemia
Alkaline Phosphatase mildly elevated
Cryoglobulinemia in chronic HepC.
**Hallmark = progressive fibrosis portal -> periportal> septal -> bridging between portal to portal or portal to central veins**

**Mortality 80% w/o and 35% w/ transplantation.**

**Gross:** *necrosis (Red) + collapse → small + wrinkling of capsule*
Cut section shows a muddy red liver w/ mushy consistency.
entire liver or random

**Micro:** Extensive hepatocyte necrosis: single or multiple contiguous lobules
collapse of reticulin framework (elastin +, trichome - → no fibrosis yet)

**Preserved portal tracts**

**Acute Hepatitis A with significant hepatocyte necrosis**

**Case of Acetaminophen Toxicity with massive hepatic necrosis**
Cirrhosis (Final Common Pathway)

End stage liver disease = FINAL COMMON PATHWAY
characterized: diffuse bridging fibrosis encircling parenchymal nodules
and disruption of the normal architecture

Micronodular < 3 mm, uniform size. (alcohol, Wilson disease).
Macronodular > 3 mm, varying size. (post-infectious, drug-induced).

Pathogenesis:
- Decompensation of sinusoidal HTN and hypoalbuminemia; hepatic lymphatic congestion
- Portal hypertension and virtually all portal collateral vessels
- Hapatocellular carcinoma
- Development of nodules and eventual formation of nodules in cirrhotic liver
- Portal hypertension and virtually all portal collateral vessels
- Portal hypertension and virtually all portal collateral vessels

Ascites: peritoneal fluid > 500 ml of Serous fluid, <3gm/dL

Hepatic encephalopathy (ammonia)
elevated blood ammonia levels.

Jaundice (bilirubin)
Imbalance between bilirubin production and clearance → Elevated bilirubin → Yellow pigment of the skin (jaundice) and sclerae (icterus)

Major Causes:
- Alcohol-induced liver disease: 60-70%
- Viral hepatitis: 10-40%
- HBV (1%)
- HCV (20-25%)
- Cryptogenic (unknown causes): 10-15%
- Biliary diseases: 5-10%
- Primary hemochromatosis: (5%).

Jaundice Path: Net uptake of bilirubin (bilirubinises) and clearance

Symptoms:
- Stigmata of CLD: see above, important, I think
- Peripheral neuropathy
- Complications: spontaneous bacterial peritonitis, ascites, variceal hemorrhage, hepatic encephalopathy, hepatocellular carcinoma.

Portal Hypertension (varices)
Inc portal venous pressure (resistance to portal blood flow).

Prehepatic: Obstructive + narrowing, see splenomegaly
- Portal or splenic vein thrombosis
- Cavernous transformation of the portal vein

Posthepatic:
- Severe right-sided heart failure
- Constrictive pericarditis

Increased serum bilirubin
Rule out hemolysis

Conjugated Bilirubin
- Dubin-Johnson Syndrome
-Rotor

Unconjugated Bilirubin
- Gilbert, < 3 mg/dL
- Crigler-Najjar, type I, > 25 mg/dL
- Crigler-Najjar, type II, 5-20 mg/dL.
**CHOLESTASIS**
bile pigment in the hepatic parenchyma.

**Intrahepatic**
secretion or biliary tree

**Etiology:** Progressive Familial Intrahepatic Cholestasis (PFIC), cholestasis of pregnancy, drug and toxin-induced, post-operative (sepsis/hemolysis/shock)

**Pathology:** intracellular (within hepatocytes) and canalicular accumulation of bile pigment, feathery degeneration of hepatocytes: fine, foamy hepatocytes with accumulated bile droplets in cytoplasm.

no surgery

**Extra-hepatic**
Mech obstruction of duct@ outside of liver or porta hepatis
Amenable to Surgery

Etiology (in order of frequency): Stones in common bile duct, carcinoma
1) large bile ducts (Proliferation) 2) Ampulla of Vater 3) head of the pancreas, pancreatitis, strictures, biliary atresia

**BILE PLUGS**

**Clinical:** Jaundice, pruritus, skin xanthomas (focal accumulation of cholesterol), Intestinal malabsorption (fat soluble vitamin deficiency).

**Labs:** Elevated serum ALP + GGT, hepatocytes and cholangiocytes apical membranes enzymes
III) PATHOLOGY OF LIVER DISEASES:

**Acute viral hepatitis (MC liver disease worldwide)**

EBV in infectious mononucleosis; CMV in neonates or Immunocompromised; Yellow fever virus

**Acute asymptomatic infection with recovery:**
incidentally: transaminases or positive serology.

**Acute symptomatic Hepatitis with recovery**
All viruses, all histology is similar

**Phases**
1. Incubation 2) pre-icteric 3) Symptomatic icteric 4) Convalescence

**Peak infectivity:** between Phases 2 and 3

**Major causes of death:** failure, encephalopathy, esophageal varices, hepatocellular carcinoma (HBV or HCV).

**Signs/symptoms**
Nonspecific; subside as jaundice appears (icteric phase)

**Histopathology**
Diffuse liver cell injury (Balloon/feathery)
Isolated apoptotic hepatocytes (acidophilic or Councilman bodies)

**Portal inflammation:** cells extend to parenchyma (=interface hepatitis) → necrosis of perportal hepatocytes (piecemeal necrosis) → (if severe) bridging necrosis

**Chronic viral hepatitis**

HBV and HCV

**Extrahepatic**
HBV: polyarteritis nodosa, glomerulonephritis, cryoglobulinemia.

Histopath → Fibrosis distinguishes acute and chronic
Autoimmune hepatitis (use antibodies to distinguish from viral implications on treatment)
hypergammaglobulinemia + liver autoantibodies.
Female (78%), young, perimenopausal
clusters of plasma cells in the interface of portal tracts and hepatic lobules are characteristic.
Distinction from PBC+PSC difficult due to bile duct damage
Overlap syndrome: clinical + histologic : autoimmune, PBC, PSC.
high mortality rate (40% in 6 months) untreated
Responsive to prednisone and/or azathioprine

Recurrence in 22-42% of transplanted
Type 1- anti-smooth muscle (SMA), Tx = Steroids
US, associated with HLA-DR3.
40% Acute, 25% cirrhosis, rare fulminant
Concurrent: celiac disease, SLE, RA, thyroiditis, Sjogren, ulcerative colitis
Type 2- anti-liver kidney microsome-1 (ALKM-1) and anti-liver cytosol-1 (ACL-1).
children
Acute / fulminant presentations.
Concurrent: vitiligo, diabetes, thyroiditis.
**IV) HEPATOCELLULAR NEOPLASMS**

**Benign tumors or tumor-like lesions**

**Cavernous Hemangioma:** MC benign liver

discrete soft/spongy bluish subcapsular nodule up to 2 cm

Histo: vascular channels in a bed of fibrous CT

Don’t biopsy or mistake for mets

**Focal nodular hyperplasia (pseudotumor) = Central Scar**

Female, Young to middle-aged

Cause: hepatic blood flow / anabolic hormones/oral contraceptives.

Well demarcated subcapsular, circumscribed nodule, variable size

**central gray-white stellate scar**

mix of benign hepatocytes and bile ducts.

Good Px

**Liver cell adenoma (Oral Contraceptives)**

young women, oral contraceptives, may regress when discontinued.

Any location, often sub-capsular, solitary / multiple, up to 30 cm.

Subcapsular + pregnant → inappritional hemorrhage

Mutations transcription factors  →  HNF1α in 50%

B-catenin 15%

Maturity onset-diabetes of young + HNF1 → multiple

Glycogen storage or B-catenin → carcinoma

Histopathology:

Normal hepatocytes : Sheets and cords, var size and shape.

abundant glycogen  →  Clear cytoplasm

Steatosis commonly present

unpaired arteries and draining veins but no portal tracts or bile ducts

Differentiated from hepatocellular carcinoma: absence of atypia or parenchymal invasion

**Malignant tumors**

**Metastatic tumors most common** Mets:primary 30:1.

colon, breast, lung and pancreas (surrounding organs)

solitary / multiple, replace most of parenchyma

outgrow blood supply → central necrosis

**Absence** of clinical or laboratory signs

Destruction of parenchyma + bile obstruction → elevation of liver enzymes or jaundice

cirrhosis primary cancer is more common

**Hepatocellular carcinoma (Most Common primary 90%)**

HBV infection (Asia and Africa (82% of all cases) vertical transmission 200x risk

US, cirrhosis (75 to 90%)

Risk: (HBV and HCV)

Chronic alcoholism

**Clinical features**

RUQ pain, ascites, weight loss, hepatomegaly

alpha-fetoprotein levels (AFP) in 75% of cases (only if large)

DDx: yolk sac tumors, cirrhosis, pregnancy, fetal death, and neural tube

Imaging < 2 cm

Poor Px in general

Death occurs from cachexia, variceal bleeding, coma, hemorrhage.

**Pathology = Absent Bile ducts → contains bile**

Single large mass, multifocal / diffusely infiltrative tumor.

soft, paler than liver, may be bile stained.

vascular invasion: snakelike portal vein or inferior vena cava

satellite nodules or intrahepatic metastases.

**Lymph node mets** to lungs occur later in the disease.

Histo: hepatocytes, no bile ducts , thick trabeculae (> 3 cells thick),

with loss of reticulin network.

Low grade look like adenomas

High-grade tumors look like mets

Fibrolamellar variant of HCC (oncocytic hepatocytes with infiltrating fibrous stroma), young adults , better Px

**Treatment**

- Resection, if possible.

- Small → Radiofrequency ablation or chemoembolization

- Large → transplantation is an option.

**Hepatoblastoma** early childhood, increasing incidence

Wnt/B-catenin signaling pathway (80%).

familial adenomatous polyposis and Beckwith-Wiedmann

Histo → epithelial or mixed epithelial/mesenchymal pattern (fetal development)

Tx: → chemotherapy and complete surgical resection.

5 year survival: 80%.

**Angiosarcoma**

- vinyl chloride, arsenic or thorotrast.

long latency period after exposure

highly aggressive with metastasis and death within a year.

**Cholangiocarcinoma**

Histo = atypical cancer cells