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Liver Function Test

★ Agenda:

Diagnosis of jaundice.

Pathophysiology of bilirubin.

Differential diagnosis.

How to approach jaundice: Hx, Px, Labs.

Further Investigations.

Doctors Notes, Extra explanation, Important notes.

★ Resources Used in This lecture:

Step Up, Slides and Doctor notes

Done by: Manal Alhamdan Maram Al aqel
Revised by: Reem Labani & Hussain Alkaff

Contact us at InternalMedicineTeam434@gmail.com

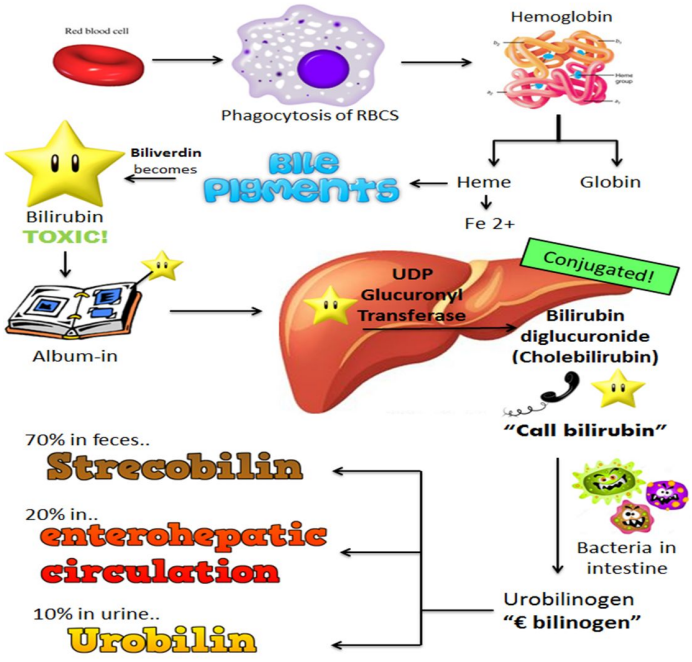
Physiology of bilirubin

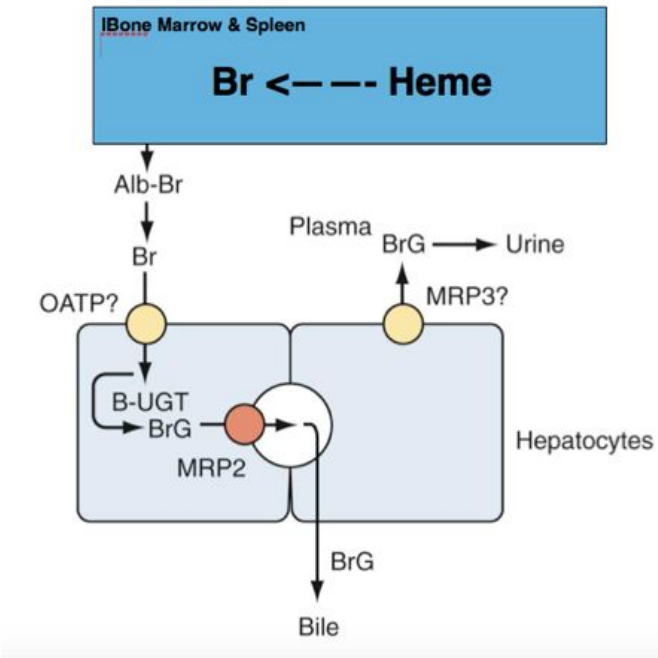
1. **Heme** from hemoglobin is converted to bilirubin (Br) in spleen.
2. **Br** is released into plasma (in its unconjugated form), where it is tightly bound to albumin (Alb). → Br is then taken up by **hepatocytes.**
3. **Br is conjugated**, via the activity of bilirubin UDP-glucuronyl transferase (B-UGT), to form bilirubin mono- and di-glucuronides **(BrG)**.
4. **Majority of BrG is eliminated in bile going to stool.**
5. **Small amounts of BrG are back into plasma, Plasma BrG** enters the renal circulation, elimination into urine.

Note: 95% of bilirubin in plasma is present in the unconjugated form.

Conjugated bilirubin (direct)	Unconjugated bilirubin (indirect)
Loosely bound to albumin (water soluble)	Tightly bound to albumin (Lipid soluble→ can cross BBB in neonates → causing kerticture)
Excreted in urine (dark urine)	Can't be excreted in urine (high blood levels)
Nontoxic	Toxic

Dark urine and pale stool signal a diagnosis of conjugated hyperbilirubinemia.





Jaundice

Definition

It is yellow discoloration of skin, mucous membrane, and sclera due to overproduction or under clearance causing total bilirubin to be more than 2mg/dL.(in the sclera is the most clear jaundice.)

Causes

Unconjugated Hyperbilirubinemia (indirect)	Excess production of bilirubin	Hemolytic enemies
	Decreased hepatic intake of bilirubin or impaired conjugation	**Gilbert syndrome: autosomal dominant, characterized by decreased the activity of** UDP-glucuronyl transferase and mostly asymptomatic.
		Crigler najjar syndrome ★ Type 1 : completely absent of UDP-glucuronyl transferase **activity → severe Unconjugated Hyperbilirubinemia → brain damage** ★ Type 2 : **decreased the activity of** UDP-glucuronyl transferase and less severe than Type 1
		Diffuse liver diseases such as liver cirrhosis , hepatitis
		Drugs such as rifampicin,penicillin, sulfonamide and radiocontrast agent.
Conjugated Hyperbilirubinemia (direct)	Decrease intrahepatocellular excretion of bilirubin. (ALT/AST elevated)	Hepatocellular disease: ➢ Viral and Alcoholic hepatitis ➢ NASH/ASH
		Inherited disorders: dubin-johnson, rotor syndrome
		Drug induced: Oral contraceptive, Tylenol OD, idiosyncratic reaction or toxins as cocain.
		PBC and PSC[1]
		Pregnancy related
		Vascular injury: such as in prolong hypotension(shock) , vascular outflow obstruction.
	Extrahepatic biliary obstruction. (ALP & GGT elevated)	• Gallstones • Periampullary tumors • Cholchcarinoma • Carcinoma of head pancreas • Cholangiocarcinoma • Extrahepatic biliary atresia

[1] primary sclerosing cholangitis

- Pseudo-Jaundice due to Carotenemia, in which case the sclera is intact.
- PSC can be both intra (seen in liver biopsy) and extrahepatic but mostly extra in the bile duct.

Diagnosis of jaundice:

❑ History and Physical Examination:

- Biliary stone obstruction: Fever Pale stool dark urine & Tender abdomen.
- Biliary malignant obstruction : Associated constitutional symptoms.
- Liver cirrhosis: Lower edema ,dilated veins, splenomegaly and ascites.
- Alcohol abuse: Parotid gland enlargement, gynaecomastia, and a Dupuytren's contracture.

❑ Laboratory Test:

➢ Total bilirubin with fractionation of the bilirubin (direct and indirect)

- **Indirect hyperalbuminemia →** CBC, Reticulocyte count, haptoglobin ,LDH, peripheral smear may aid in the diagnosis of hemolysis.
- **Direct hyperalbuminemia→** LFT's may point to the cause.

➢ CBC, Creatinine

- **Leukocytosis** might indicate the presence of biliary tract obstruction or other inflammatory disorder that may be associated with cholestasis.
- **Anemia** leaves open the possibility that a hemolytic disorder is responsible for bilirubin overload.
- **Thrombocytopenia (Low platelet count)** is suggestive of portal hypertension or alcohol abuse.

➢ PT,INR, Albumin

- **An increased PT and INR when coupled with a low albumin** is indicative of synthetic liver dysfunction and suggestive of cirrhosis or acute liver failure.

➢ LFT (ALT, AST, ALP, GGT)

- **Aminotransferases** (ALT and AST):
  - ALT is more specific and sensitive than AST for liver damage
  - ALT and AST usually have similar increase, exception in alcoholic hepatitis AST is higher that ALT ratio may be >2:1.

Why? Due to Pyridoxine deficiency in alcoholics , and for ALT to be produced in the serum we need pyridoxal phosphatase.

- ALT & AST are mildly elevated in→ chronic viral hepatitis or alcoholic hepatitis
- ALT & AST are moderately elevated in → acute viral hepatitis
- ALT & AST severely elevated in →Severe viral hepatitis or extensive hepatic necrosis due to: 1- Ischemia (vascular injury) 2- acetaminophen toxicity
- ALT & AST are normal or low in Cirrhosis or metastatic liver disease.
- ALT & AST can be elevated in asymptomatic patients.

- **Alkaline phosphatase** (ALK-P)
  - Not specific to liver, also found in bone gut and placenta.
  - ALK-P is elevated when there is an obstruction to bile flow (cholestasis).
  - If levels are high measure GGT to confirm obstruction, if it was normal suspect bone,intestinal disease or pregnancy.
- **Gamma-glutamyl- transferase** (GGT)
  - Often is used to confirm that AKL-P elevation is of hepatic origin.
- **Prothrombin time**
  - PT is not prolong until most of liver's synthetic capacity (80%) is lost.
  - It reflects the severity of damage and advanced liver disease.

- Acetylcysteine is given for acetaminophen toxicity.
- Low or normal aminotransferases is due to reduce number of functioning hepatocyte.
- The liver synthesizes all clotting factors except factor 8 and VWF.
- GGT is sensitive also for alcohol abuse⟶ liver might be normal yet GGT is still elevated.

❑ Specific test (based on result)

➢ High levels of ALP, GGT (suspected extrahepatic obstruction) :

- CT or US (for fatty liver or cirrhosis)
- ERCP (Endoscopic retrograde cholangiopancreatography)
- PTC (Percutaneous transhepatic cholangiography)
- MRCP (Magnetic resonance cholangiopancreatography)

➢ High levels of ALT, AST (suspected intrahepatic)

- Viral Hepatitis serologies
- Alcohol level
- Drug level for Tylenol
- Urine toxins: cocaine
- Doppler US
- ANA[2], ASMA[3],IgG, AMA[4], celiac screen
- Serum Ceruloplasmin
- Fibroscan

❑ **Liver Biopsy** should be considered if needed (unknown reason yet)

- Normal LFT and Conjugated hyperbilirubinemia ⟶ Rotor syndrome or dubin johnson syndrome.
- Normal LFT and Unconjugated hyperbilirubinemia ⟶ hemolysis or gilbert syndrome.

[2] Antinuclear antibody
[3] Anti smooth muscle antibody
[4] Anti mitochondrial antibody

Summary

Liver function tests

Markers of liver dysfunction		Markers of hepatocellular injury		Markers of cholestasis	
Bilirubin (serum)	• High bilirubin levels are observed in gallstones, acute and chronic hepatitis • It is the yellowish pigment observed in jaundice: Types of jaundice: 1- Pre-hepatic or hemolytic ↑ Unconjugated → hemolytic anemia 2- Hepatic or Hepatocellular ↑ Unconjugated and conjugated → hepatitis 3- Post-hepatic ↑ conjugated →gallstones	**Aspartate aminotransferase (AST)**	• A marker of hepatocellular damage • High serum levels are observed in chronic hepatitis, cirrhosis and liver cancer	**Alkaline phosphatase (ALP)**	• Modearte elevation observed in Infective hepatitis, alcoholic hepatitis and hepatocellular carcinoma • High levels are observed in Extrahepatic obstruction (obstructive jaundice) and intrahepatic cholestasis • Very high levels are observed in Bone diseases
urobilinogen(UBG) and urine bile salts(urine)	• Normally : bile salts are not present in the urine and only a little amount of UBG is present in the urine • High UBG and the presences of bile salts in the urine indicates biliary obstruction	**Alanine aminotransferase (ALT)**	• More liver-specific than AST • High serum levels are observed in acute hepatitis • Moderate elevation is observed in alcoholic hepatitis • Minor elevation is observed in cirrhosis, hepatitis C and non-alcoholic steatohepatitis • Appears in plasma many days before clinical signs appear • A normal value does not always indicate absence of liver damage	**g-glutamyltransferase (GGT)**	• Moderate elevation observed in Infective hepatitis and prostate cancers • GGT is increased in alcoholics despite normal liver function tests • Highly sensitive in detecting alcohol abuse
Albumin(Serum)	• decreases in all chronic liver diseases				
Globulin(Serum)	High serum g-globulins are observed in chronic hepatitis and cirrhosis: • IgG in autoimmune hepatitis • IgA in alcoholic liver disease				
Albumin to globulin (A/G) ratio	• Globulin levels increase in hypoalbuminemia as a compensation • The ratio decreases				
Prothrombin Time (PT)	• PT is prolonged only when liver loses more than 80% of its reserve capacity • Vitamin K deficiency also causes prolonged PT				