Pathophysiology of Jaundice

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- Jaundice, also known as hyperbilirubinemia, is defined as a yellow discolouration of the body tissue resulting from the accumulation of excess bilirubin.
- Deposition of bilirubin happens only when there is an excess of bilirubin, and this indicates increased production or impaired excretion.
- The normal serum levels of bilirubin are less than 1 milligram per deciliter (mg/dL).
- the clinical presentation of jaundice with peripheral yellowing of the eye sclera is best appreciated when serum bilirubin levels exceed 3 mg/dl.
- The skin will progressively discolour ranging from lemon yellow to apple green, especially if the process is long-standing; the green colour is due to **biliverdin**.
- Bilirubin has two components: **unconjugated (**indirect) and **conjugated** (direct), and hence elevation of any of these can result in jaundice.
- Icterus acts as an essential clinical indicator for liver disease, apart from various other insults.
- **Bilirubin** is the catabolic product of haemoglobin.
- **Bilirubin** exists in two main forms; **conjugated and unconjugated bilirubin**.
- The metabolism of bilirubin takes place predominantly in the liver. Bilirubin enters the liver in the **unconjugated** form and is thereby converted to the conjugated form after some metabolic conversions.
- Conjugated bilirubin is also referred to as direct bilirubin, and unconjugated bilirubin is referred to as indirect bilirubin.

- Direct Bilirubin or the conjugated form of bilirubin is covalently modified bilirubin that has increased solubility.
- Direct Bilirubin is soluble due to the conjugation reaction with glucuronic acid, which takes place in the liver.
- Indirect Bilirubin is the type of bilirubin that is not attached or conjugated to any other chemical compound.
- Indirect bilirubin is bound to albumin, which is the common carrier protein of bilirubin.
- The **key difference** between Direct and Indirect bilirubin is that **direct bilirubin is the bilirubin that is conjugated with glucuronic acid while indirect bilirubin is not conjugated to the liver and attaches to the carrier protein albumin**.
- Yellowing of skin-sparing the sclera is indicative of carotenoderma which occurs in healthy individuals who consume excessive carotene-rich foods.

UNCONJUGATED HYPERBILIRUBINEMIA

Excess production of bilirubin

- Hemolytic anaemias, extravasation of blood in tissues, dyserythropoietic

Reduced hepatic uptake of bilirubin

- Gilbert syndrome

Impaired conjugation

- Crigler–Najjar syndrome type 1 and 2
- Hyperthyroid
- Estrogen

CONJUGATED HYPERBILIRUBINEMIA

Decreased intrahepatic excretion of bilirubin

- Hepatocellular disease - Viral hepatitis A, B, D; alcoholic hepatitis; cirrhosis, nonalcoholic steatohepatitis, EBV, CMV, HSV, Wilson, autoimmune

- Cholestatic liver disease-Primary biliary cholangitis, primary sclerosing cholangitis
- Infiltrative diseases (e.g., amyloidosis, lymphoma, sarcoidosis, tuberculosis)
- Sepsis and hypoperfusion states
- Total parenteral nutrition
- Drugs & Toxins - oral contraceptives, rifampin, probenecid, steroids, chlorpromazine, herbal medications (e.g., Jamaican bush tea, kava), arsenic
- Hepatic crisis in sickle cell disease
- Pregnancy

Extrahepatic cholestasis (biliary obstruction)

- Choledocholithiasis
- Tumours (e.g., cholangiocarcinoma, head of pancreas cancer)
- Extrahepatic biliary atresia
- Acute and chronic pancreatitis
- Strictures
- Parasitic infections (e.g., Ascaris lumbricoides, liver flukes)

➢ Around 20 per cent of term babies are found with jaundice in the first week of life, primarily due to an immature hepatic conjugation process.

➢ Congenital disorders, overproduction from hemolysis, defective bilirubin uptake, and defects in conjugation are also responsible for jaundice in infancy or childhood.

➢ Hepatitis A was found to be the most cause of jaundice among children.

➢ Bile duct stones, drug-induced liver disease, and malignant biliary obstruction occur in the elderly population.

- The pathophysiology of jaundice is best explained by dividing the metabolism of bilirubin into three phases: **prehepatic, hepatic, and post-hepatic.**

PREHEPATIC

- **Production** - Bilirubin is the end product of heme, which is released by defective RBCs. In the reticuloendothelial cells of the spleen, liver and bone marrow.
- heme released from the RBC undergoes a series of reactions to form the final product bilirubin:
- Heme-->Biliverdin-->Bilirubin (insoluble due to tight hydrogen bonding)

HEPATIC

1. **Hepatocellular uptake** - The bilirubin released from the reticuloendothelial system is in an unconjugated form (i.e., non-soluble)⟹ bound to albumin which accomplishes solubility in blood ⟹ and gets transported to the hepatocytes.⟹ The albumin-bilirubin bond is broken, ⟹and the bilirubin alone is then taken into the hepatocytes through a carrier-membrane transport ⟹and bound to proteins in the cytosol to decrease the efflux of bilirubin back into the plasma.
2. **Conjugation of bilirubin** - This unconjugated bilirubin then proceeds to the endoplasmic reticulum,⟹ where it undergoes conjugation to glucuronic acid resulting ⟹in the formation of conjugated bilirubin, which is soluble in the bile.

POSTHEPATIC

1. **Bile secretion from hepatocytes**- Conjugated bilirubin is now released into the bile canaliculi ⟹ into the bile ducts, ⟹ stored in the gallbladder, ⟹ reaching the small bowel through the ampulla of Vater and⟹or finally enters the colon.

2. **Intestinal metabolism and renal transport**- The intestinal mucosa does not reabsorb conjugated bilirubin due to its hydrophilicity and large molecular size.

   The colonic bacteria deconjugate and metabolize bilirubin into **urobilinogen**, 80% of which gets excreted into the faeces as **stercobilin** and the remaining (10 to 20%) undergoes enterohepatic circulation. Some of this urobilin is excreted through the kidneys imparting the yellow pigment of urine.

- Dysfunction in the prehepatic phase results in elevated serum levels of **unconjugated** bilirubin
- while defects in post hepatic phase mark elevated conjugated bilirubin.
- Hepatic phase impairment can elevate both unconjugated and conjugated bilirubin.
- Increased urinary excretion of urobilinogen can be due to
  - ✓ increased production of bilirubin,
  - ✓ increased reabsorption of urobilinogen from the colon,
  - ✓ or decreased hepatic clearance of urobilinogen.
- As mentioned earlier, the serum level of bilirubin is a balance between production and hepatic excretion.
- After reaching the colon, the bacteria metabolize it into urobilinogen.
- A vast majority of urobilinogen is converted into stercobilin and excreted in faeces.
- About 10 to 20% of urobilin gets reabsorbed in the brush border of the gut and facilitates enterohepatic circulation and is re-excreted by the liver;
- less than 3mg/dl escapes the hepatic uptakes and filters into the urine.
- Owing to its lipid-soluble nature, bilirubin may cross the blood-brain barrier and thus enter the brain.

- bilirubin clearance from the brain is ensured by the presence of an enzyme on the inner mitochondrial membrane, which aids in the oxidation of bilirubin, thus protecting against its neurotoxic effects.
- However, in newborns, since the blood-brain barrier is yet to develop, a pathological increase in serum levels of bilirubin can result in death in the neonatal period or survival with disastrous neurological sequelae called **kernicterus.**
- Also, newborns are at increased risk due to a lack of colonic bacteria resulting in deconjugation and enterohepatic reabsorption resulting in hyperbilirubinemia.

History

- yellowish discolouration of skin along with pruritus.
- A thorough questioning regarding the use of drugs, alcohol or other toxic substances, risk factors for hepatitis (travel, unsafe sexual practices),
- HIV status and personal or family history of any inherited disorders or hemolytic disorders are vital.
- Other important points include the duration of jaundice; and the presence of any coexisting signs and symptoms, like a joint ache, rash, myalgia, and changes in urine and stool.
- A history of arthralgias and myalgias before yellowing indicates hepatitis, either due to drugs or viral infections.
- Further, fever, chills, and severe right-upper-quadrant-abdominal pain as seen in cholangitis and anorexia.
- malaise as seen in hepatitis.
- significant weight loss suggesting malignancy obstructing the bile ducts provide additional information for diagnosis.
- The abdominal examination should provide information on the presence of hepatosplenomegaly, or ascites.

- Jaundice with ascites indicates either cirrhosis or malignancy with peritoneal spread.
- Right upper quadrant tenderness with palpable gallbladder suggests obstruction of the cystic duct due to malignancy.
- **Serum Bilirubin -** whether there is a rise in unconjugated or conjugated bilirubin
- In addition to the liver panel, all jaundiced patients should have additional tests such as albumin and prothrombin time – which are indicative of chronic and acute liver function, respectively.
- The results of the bilirubin, enzymes, and liver function tests will direct the diagnosis towards a hepatocellular or cholestatic cause and offer some idea of the duration and severity of the disease.

Complications

- Indirect (insoluble) bilirubin is harmful to cells and cellular structures.
- Due to the physiologic mechanisms that protect against elevated bilirubin, the toxic effects are on neonates due to the poorly developed blood-brain barrier.
- High levels of bilirubin are neurotoxic and can lead to permanent neurologic injury (kernicterus) (Bilirubin-induced neurologic dysfunction).