Jaundice

- definition of jaundice
  Increased concentration of bilirubin in the blood resulting in a yellowish staining of the skin surface and/or visible mucous membranes or sclerae. Internal organs may also be affected.
- Jaundice can be caused by:
  - increase of unconjugated bilirubin, hydrophobic (liposoluble) product, which cannot be excreted with urine; it can accumulate in the blood, in the skin and in the mucous membranes)
  - increase of conjugated bilirubin (water-soluble), which can be excreted in the urine
  - mixture of conjugated and unconjugated bilirubin
- These different types of bilirubin depend on the problem that causes the disease.
- what is bilirubin?
  bilirubin is the toxic end product of heme degradation that is processed in the liver, excreted in the bile
- explain the normal metabolism of bilirubin
  1. **heme** (from senescent erythrocytes, erythrocyte precursors, P450 cytochrome enzymes, etc) is taken inside a phagocytic cell where it is oxidized by **heme oxygenase** into **biliverdin**, which is in turn converted into **unconjugated bilirubin** by **biliverdin reductase**
  2. **unconjugated bilirubin** is lipid-soluble, so it binds serum **albumin** and transported to the liver
  3. bilirubin is conjugated with one or two molecules of **glucuronic acid** in the **ER** by bilirubin uridine diphosphate glucoronyl transferase (**UGT**)
  4. conjugated bilirubin is nontoxic and water soluble, it diffuses through the cytoplasm into the **biliary canaliculi** and eventually into the gallbladder where it will form bile (together with bile salts, phospholipids, and cholesterol)
  5. in the intestine most of it is de-conjugated by the flora (bacterial β-glucuronidases) and degraded to colorless **urobilinogen** (or bilinogen)
  6. fate of urobilinogen:
     - 80-90% oxidized by other intestinal bacteria and together with bile pigment residues is excreted in feces: **stercobilin**
     - 10-20% is reabsorbed through the enterohepatic circulation (terminal ileum and colon) and returned to the liver (portal circulation) and excreted into bile
     - a small amount of reabsorbed urobilinogen reaches the systemic circle and is excreted in the urine: **urobilin**

- what is bile made up of?
  - bile salts (2/3)
  - bilirubin
  - phospholipids
  - cholesterol
- normal blood bilirubin levels
  0.3-1.2 mg/dL
  Hyperbilirubinemia: > 1.2 mg/dL
  2 there's jaundice

- what is the function of bile
  - emulsion and absorption of dietary lipids in the gut lumen through the detergent properties of bile salts (they solubilize water-insoluble dietary lipids)
  - neutralize stomach acid
  - helps to eliminate waste products (excess cholesterol and bilirubin)
- how are bile salts formed
  by the conjugation of bile acids with taurine or glycine
  bile acids are major catabolic products of cholesterol; they are water-soluble sterols with carboxylated side chains
- what amount of bile acids are made and excreted by the liver in a day? what is their fate?
  The liver secretes from 12 to 36 g of bile acids a day and their fecal loss is from 0.2 to 0.6 g a day.
- what happens to bile acids once in the gut lumen
  95% are reabsorbed by the liver via the enterohepatic circulation
- clinical features of jaundice
  Approach to the jaundiced patient: Clinical features
  - Urine color
  - Faeces color
  - Presence of associated symptoms
    - itch
    - ache
    - nausea, vomiting
    - asthenia
    - temperature
  - Key Questions
    - Taking toxic substances?
    - Ingestion of suspect foods?
    - Contact with blood or derivatives
    - History of cholelithiasis?
    - Family history of jaundice?
- describe pre-hepatic jaundice
  It occurs when there is an **excessive breakdown of red blood cells**

that happens so fast that the liver is not able to process all of the bilirubin, leading to an accumulation of the substance in the blood. Often caused by
    - increased hemolysis
        - sickle cell anemia, thalassemia, hemolytic anemia, favism or G6PD defect, spleen hyper-functionality, spherocytosis, elliptocytosis, bacterial infections, autoimmune diseases, erythroblastosis *fetalis* (Rh-, Rh+)
    - defects in erythropoiesis
        - thalassemia, mediterranean anemia (hemoglobin def), pernicious anemia (B12 def), sideroblastic anemia (iron def), leukemia, etc.
- In sickle cell anemia and thalassemia, the red blood cells are abnormal and have a shorter lifespan than normal red blood cells, leading to an increased breakdown of these cells. Hemolytic anemia, on the other hand, is caused by the destruction of red blood cells by the immune system or by external factors such as infections or exposure to certain medications or chemicals.
    - Pleiochromic (dark) feces due to excess **stercobilin**
    - Hyper-chromic urine with lots of **urobilin**
    - in the fetus or newborn if severe accumulation unconjugated bilirubin (20 mg/dl) it can lead to **kernicterus**(bilirubin induced brain damage) The blood–brain barrier is not fully functional in neonates and therefore bilirubin is able to cross into the central nervous system.
- describe hepatic jaundice
  Due to alteration of hepatic function impairing either the uptake, the conjugation of bilirubin, or the excretion
  Uptake defect:
    - decrease in ligandins amount or function:
        - neonatal physiological jaundice (liver is not mature until 2 weeks post birth)
    - hepatic cellular damage (hepatitis)
        - viral, drug induced.
    - Rotor syndrome (autosomal recessive mutation leads to loss of function of the Organic Anion Transporter Proteins (OATP1)→ less bilirubin taken up by the liver)
- Conjugation defect
    - UGT deficiency
        - neonatal physiological jaundice
        - Crigler-Najjar type I: complete absence or severe deficiency → **fatal** around the time of birth
        - Crigler-Najjar type II or Gilbert syndrome: decreased UGT
    - some drugs

- Hepatocellular jaundice with conjugated bilirubin:
  - congenital defect of conjugated bilirubin **excretion** (non lethal)
    - Rotor syndrome
    - Dubin-Jhonson syndrome: MRP2 transport protein deficient (for the transport of conjugated bilirubin from hepatocyte to bile duct) and up-regulation of MRP3 for its transport to the blood
  - acquired cellular hepatic injury.
    - drugs, pregnancy, hepatocellular damage, etc.
- Jaundice with mixed defects (uptake, conjugation and secretion):
  - **Mixed hyperbilirubinemia: acute or chronic hepatopathies**
- ❓
- describe post-hepatic jaundice
  Also called stasis jaundice or cholestatic jaundice
  obstruction of bile excretion that leads to an accumulation of conjugated bilirubin and bile.
  The detergent properties of bile acids damage cells and activate apoptosis; bile acids are hepatotoxic.
  Clinical diagnosis:
  - increase in blood of compounds usually transferred to bile (bilirubin, bile acids, CHOLESTEROL...)
  - itching (Excess of bile salts in the circulation cause irritation of cutaneous nerve terminations)
  - steatorrhea (reduced bile formation → decreased absorption of fats, and hypo-chromic feces)
  - hyper-chromic (dark) urine
  - Hepatomegaly
  - Chronic:
    - Nutritional deficiency of liposoluble vitamin (A, D and K) related to intestinal malabsorption.
    - Cutaneous xanthomas (focal accumulation of cholesterol) due to hyperlipidemia and altered cholesterol excretion
- Subtypes
  - **Intrahepatic cholestasis**: obstructions or alterations of the intrahepatic **biliary tract** (between hepatocytes and main interlobular bile ducts) due to
    - biliary cirrhosis
    - viral, bacterial, neoplastic, or toxic factors
    - drugs (oral contraceptives, anabolic steroids)
  - **Extrahepatic cholestasis**: Occlusion of **extrahepatic bile ducts**
    - gallstones (cholesterol, calcium salts),
    - biliary tract tumors
    - pancreatic tumors
    - chronic inflammatory processes of the biliary tract

        - lymphopathies of the hepatic hilum
        - chronic sclerosing pancreatitis, etc.
- describe the histology of cholestasis
    - enlarged hepatocytes with bile droplets accumulating inside
    - dilated canaliculi
    - apoptotic cells (Detergent properties of bile acids damage cells and activate apoptosis; bile acids are hepatotoxic.)
- Mechanisms of cholestasis
    - **Damage of the canalicular plasma membranes**(drugs, toxic compounds..)causing a reduction in the bile transport
    - **Alterations of canalicular membrane permeability:** e.g: in pregnancy, increase in estrogen can increase membrane permeability of the biliary canaliculi favoring the retro-diffusion of the bile components, causing cholestasis.
    - **Alterations or inhibitions of contractile properties (actin) of the canaliculus**
        - e.g. **phalloidin toxin** (found in death cap mushroom) binds to actin and impairs the peristaltic-like activity of hepatocytes promotes canalicular flow of bile.)
- **urine and stool color for the 3 types of jaundice**

• type	• pre-hepatic	• hepatic	• post-hepatic / cholestatic	•

• pathophysiology	• increased hemolysis, or defective erythropoiesis → amount of unconjugated (indirect) bilirubin exceeds liver capacity to process it in time so it accumulates in blood	• a. issue in liver uptake (unconjugated hyperbilirubinemia) b. conjugation defect (unconjugated hyperbilirubinemia) c. excretion defect (conjugated hyperbilirubinemia) d. mixed defects (uptake, conjugation, and secretion) lead to mixed hyperbilirubinemia	• Decreased bile flow through bile canaliculus (defect in bile transport) due to (1) hepatocellular	•
• dysfunction or (2) intrahepatic cholestasis or (3) extrahepatic cholestasis	•	•	•	•

• urine color	• dark (unconjugated/indirect bilirubin is hydrophobic so not present in the urine however its elevation indirectly leads to an accumulation of conjugated bilirubin)	• dark in defects of excretion	• dark	•
• feces color	• dark	• normal / lighter (not steatorrhea)	• CLAY: Reduced bile formation and excretion in the intestine leads to decreased absorption of fats = steatorrhea	•
• pruritus	• no	• no (or very mild)	• yes! excess bile salts in blood cause irritation of nerve terminations.	•

• diseases	• favism/ Glucose-6-phosphate-dehydrogenase deficiency, sickle cell, spherocytosis, spleen hypefunctionality, autoimmune, erythroblastosis fetalis, leukemia, thalassemia, pernicious anemia, etc.	• a. uptake issue can be caused by hepatocellular damage or ligandins deficiency (neonatal; Gilbert syndrome)	•	•

• b. conjugation defects: neonatal, Crigler-Najjar type I and type II syndromes; Gilbert syndrome; drugs... c. excretion defects: Rotor syndrome, Dubin-Johnson syndrome, hepatocellular damage, pregnancy. d. diffuse hepatocellular damage by drugs, viral, toxic.	• - Intrahepatic: biliary cirrhosis, biliary tract alterations , viral, bacterial, neoplastic, or toxic factors, drugs (oral contraceptives and anabolic derivatives of testosterone , estrogens, etc.)	•	•	•
• - Extrahepatic cholestasis: gallstones (cholesterol, calcium salts), tumors (liver, gallbladder, head of pancreas)	•	•	•	•

•	• AST and ALT are normal, GGT and ALP normal,	• ALP and GGT are normal or mildly elevated, AST and ALP are elevated,	• hypercholesterolemia, ALP and GGT very elevated. ALT and AST should be normal	•
•	• in pre hepatic jaundice there's an increase in unconjugated bilirubin that reaches the liver, therefore higher amounts than normal are conjugated and an increased amount of conjugated bilirubin reaches the intestine. This causes a higher absorption of intestinal bilinogen back to the liver and higher amounts of stercobilin (darker feces). The liver is	• in hepatocellular jaundice, when there's an ongoing hepatic injury, unconjugated bilirubin cannot be completely transformed into conjugated bilirubin due to hepatocellular defects, therefore part of this unconjugated bilirubin stays in the blood "imprefectly conjugated" and is eliminated by the kidneys. Therefore there will be less stercobilin content, so	• in post-hepatic jaundice there is an obstruction in bile flow, bile does not reach the intestine so it is instead poured into the blood circulation and therefore it also ends up in the urine. In the feces there is no stercobilin (due to lack of bile in the intestine), in the urine there is no urobilin, there's instead bile salts and conjugated bilirubin (so hyperchromic urine)	•

	unable to conjugate all the bilirubin present so blood unconjugated bilirubin rises. in the urine there is more urobilin and bilirubin is absent (only conjugated bilirubin accumulates in urine)	feces will be lighter than normal, an elevated urobilin and bilirubin in the urine		
•	•	•	•	•

- Describe neonatal jaundice
  - Transient and mild **unconjugated** hyperbilirubinemia
  - considered physiological
  - (70%) of newborns; more pronounced in premature infants
  - Mechanisms of hepatic **uptake**, **conjugation** and biliary **excretion** have nor been matured fully until about 2 weeks of age (normal ligandin levels take longer)
    - Low ligandin levels; hepatic UGT activity is 100 times lower than that of the adult.
  - During pregnancy, Fetal bilirubin passes placenta and is conjugated and excreted from the maternal liver.
  - May be exacerbated by breastfeeding: bilirubin-deconjugating enzymes in breast milk.
  - Treatment with **Phototherapy** (blue light fluorescent lamps) light absorption by unconjugated bilirubin generates water-soluble isomers that can be excreted in the urine.
- What is mixed hyperbilirubinemia? describe its clinical characteristics
  Hepatocellular damage caused by acute or chronic hepatopathies can cause deficits in bilirubin uptake, glucuronation (conjugation) or hepatocyte excretion. This is defined as mixed hyperbilirubinemia.
  Clinical characteristics:
  Excess in both an unconjugated and conjugated bilirubin can cause:
  - Bilirubin deposit in the subcutaneous fatty tissues (**yellow pigmentation**)
  - conjugated bilirubin passes through the renal filter **(dark urine**)
  - increased **transaminases**

    - decreased **albumin** in the blood
    - reduced lipid absorption due to the deficit of bile salt production (**fattier stools but no steatorrhea)**
    - **Hypocholic feces**
    - **Reduced bowel transit**
- Intrahepatic pregnancy cholestasis?
    - central-lobular cholestasis
    - Rare pathology characterized by **increase in total bile acids** and intense itching, cholestasis, and jaundice.
    - It occurs in the last trimester of gestation (0.8%-1.5%) and has a benign prognosis (complete remission after delivery).
    - Associated with premature birth, fetal distress and placental insufficiency.
    - Uro-desoxycholic acid therapy attenuates itching
- Prolonged conjugated hyperbilirubinemia in the newborn?
  Prolonged conjugated hyperbilirubinemia in the newborn (affects ≈ 1:2500 live birth)
    - Infants who have jaundice beyond 14-21 days after birth risk of neonatal cholestasis
- Major causes:
    - **cholangiopathies**: genetic and acquired biliary disorders. Can be caused by:
        - cystic fibrosis
        - biliary atresia
        - fibro-polycystic diseases
        - disordered immunity (primarily biliary cirrhosis..)
        - infectious agents (cytomegalovirus, bacteria...)
        - ischemia
        - toxic compounds (drugs, toxins..
    - **primarily biliary atresia**: complete/partial obstruction of the lumen of the extrahepatic biliary tree within the first 3 months of life (1/3 infants with neonatal cholestasis).
        - aberrant intrauterine development
        - destruction following birth due to
            - viral infection : rotavirus, reovirus, cytomegalovirus
            - auto-immune reactions);
    - **Various disorders causing conjugated hyperbilirubinemia (referred to neonatal hepatitis)**