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Editorial

Bilirubin metabolism & pathophysiology of neonatal jaundice

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ABSTRACT

Jaundice is a visible yellowish color change in skin and sclera, secondary to elevated serum bilirubin which accumulates in the skin. Visibility of jaundice depends upon the age of the patient, color/complexion of the skin and level of bilirubin in blood. It is more easily visible in fair complexioned and new born (particularly, pre term) babies. In the new born, jaundice is visible during the 1st week of life in 60% of full term and 80% preterm infants.

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1. Bilirubin Metabolism^{1,2}

Bilirubin is the end product of heme catabolism, derived mainly from hemoglobin of senescent RBC (75%) and prematurely destroyed red cells in marrow (ineffective erythropoiesis). It is also derived from other heme containing proteins like enzymes catalase & cytochromes, tryptophan pyrrolase & peroxidase as well as from myoglobin. One gram of hemoglobin yields 35 mg of bilirubin.

1.1. Formation of bilirubin

1. Heme is a four pyrroles ring molecule joined by carbon bridges and a central iron atom. Bilirubin is generated by its catalytic degradation in the cells of reticuloendothelial system (RES) in spleen, phagocytes and Kupfer cells of liver. After heme is taken in these cells, it is acted upon by enzyme heme oxygenase at microsomes, liberating iron, equimolar amount of carbon mono-oxide and a green pigment biliverdin. Biliverdin is then acted upon by NADPH (nicotinamide adenine dinucleotide phosphate) dependent enzyme

biliverdin reductase in cytosol releasing orange-yellow pigment called bilirubin. This fully bonded structure is designated as Bilirubin IX-alpha-ZZ.

2. Bilirubin formed by degradation of Hb is unconjugated, non-polar, lipid soluble bilirubin (UCB) and it is hydrophobic in nature. This unconjugated bilirubin is designated as indirect reacting as, in Van den Bergh reaction, it needs addition of alcohol for estimation.
3. Part of jaundice may be by deposition of conjugated bilirubin which is the end product from indirect unconjugated bilirubin that undergoes conjugation in liver cells microsomes.
4. While bilirubin has a physiologic role as anti-oxidant, elevated indirect / unconjugated bilirubin levels are potentially neurotoxic. Direct reacting conjugated bilirubin is not neurotoxic, but its elevation indicates serious hepatic disorder or systemic illness.

1.2. Bilirubin transport

1. From RES, bilirubin is released into plasma, bound with albumin with a reversible covalent bond. Albumin has two sites: first with high affinity and second with

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low affinity. Other molecules like FFA, sulfonamides may also compete for binding and in situations of low albumin, UCB may bind with high molecular weight lipoprotein as well.

2. Under normal conditions, there is no or very little unbound (free) UCB in plasma. Binding with albumin limits escape of bilirubin from vascular space, minimizes glomerular filtration and prevents tissue precipitation of it. However, if albumin bilirubin binding is saturated or bilirubin is displaced, this increases the risk of free bilirubin in plasma and tissue escape, particularly to neural tissues in neonates.

2. Hepatic Transport Mechanism

When bilirubin-albumin complex reaches liver on the sinusoidal surface of hepatocytes, pigment dissociates from albumin. Bilirubin is taken up by hepatocytes from liver sinusoids mainly by active transport mediated by not well understood carrier proteins – Y Protein or Ligandin or now recognized as Glutathione Transferase B.

2.1. Hepatocyte conjugation

1. Conjugation within hepatocyte makes unconjugated bilirubin water soluble, facilitating its secretion across canalicular membrane for excretion in bile.
2. Conjugation of bilirubin is carried out with glucuronic acid by enzyme uridine-diphosphoglucuronic glucuronosyl transferase (UDPGT1A1). Conjugation involves disruption of hydrogen bonds and is essential for its excretion by liver / kidney.
3. Two / one molecules of glucuronic acid are conjugated with one molecule of bilirubin forming bilirubin diglucuronide (80%) or bilirubin mono glucuronide (20%). But, if amount of bilirubin for conjugation is very high, proportion of monoglucuronide may increase, reversing the ratio.

2.2. Excretion of conjugated bilirubin

1. Conjugated bilirubin to be excreted in bile is actively transported across bile canalicular membrane of hepatocyte. Of the transporters identified, multidrug resistance protein-2 (MRP2) is predominant. This is the rate limiting step in bilirubin throughput.
2. A part of conjugated bilirubin may leak back into sinusoidal blood thro' MRP-3 from where it is re-up-taken by hepatocyte via organic anion transport protein 1B1 and 1B3 (OATP 1B1 and OATP 1B3). (also known as soluble carrier organic anion transporter. SLCO1B1).
3. Some conjugated and unconjugated bilirubin may revert back to circulation from hepatocyte, it is re-up-taken. only conjugated bilirubin enters bile.

4. If hepatic excretion capacity is exceeded, conjugated bilirubin may accumulate in plasma and fraction of it may be bound to albumin (called δ bilirubin or δ fraction of bili-protein). δ bilirubin clearance takes 12-14 days (~ half-life of albumin) cf. normal of 2-4 hours (~half-life of bilirubin).
5. Conjugation of bilirubin promotes its excretion by (a) makes it water soluble so that it can be excreted in bile or urine. (b) obviates need for a protein carrier during transport (c) increases molecular size which is hydrophilic—thus prevents passive absorption of bilirubin from intestinal mucosa (d) modestly reduces its affinity to albumin.

2.3. Degradation in digestive tract

1. Conjugated bilirubin is not absorbed from proximal intestine, whereas, unconjugated bilirubin spilled into intestine may be absorbed across the lipid cell membrane of small intestine leading to entero-hepatic circulation.
2. As conjugated bilirubin reaches distal ileum and colon, it is rapidly reduced and deconjugated into compounds called as urobilinoids. Major of them in stool are urobilinogen and stercobilinogen.

3. Etiopathogenesis of Neonatal Jaundice³

Bilirubin metabolism in a neonate is in transitional state from fetus to adult. In fetus, placenta is the principal route for elimination of lipid soluble, indirect bilirubin via maternal liver whereas in adults, water-soluble conjugated form is excreted from hepatic cells via bile into GI system or sometimes via kidneys into the urine.

Mostly, neonatal jaundice or bilirubin toxicity is result of a combination of events.

3.1. Unconjugated bilirubin in serum may occur due to any of the

3.1.1. Increase in UCB load to be metabolized.

Increased rate of bilirubin production (neonatal rate of 6-8 mg/kg/d cf. adult rate of 3-4 mg/kg/d) leads to increased UCB load. (increased hemolysis, polycythemia, enhanced entero-hepatic circulation, shorter RBC life due to immature/ transfused RBCs, infection, bruising/ internal hemorrhage). Sometimes, breast feeding per se as in cases of breast milk jaundice.

1. Inability of liver to clear sufficient bilirubin from plasma. Reduced activity of transferase enzyme (Y protein or ligandin or glutathione S transferase B) leads to decreased uptake by hepatocyte. (developmental for first 5-10 days, prematurity, genetic deficiency, hypoxia, infection, hypothermia, thyroid dysfunction).

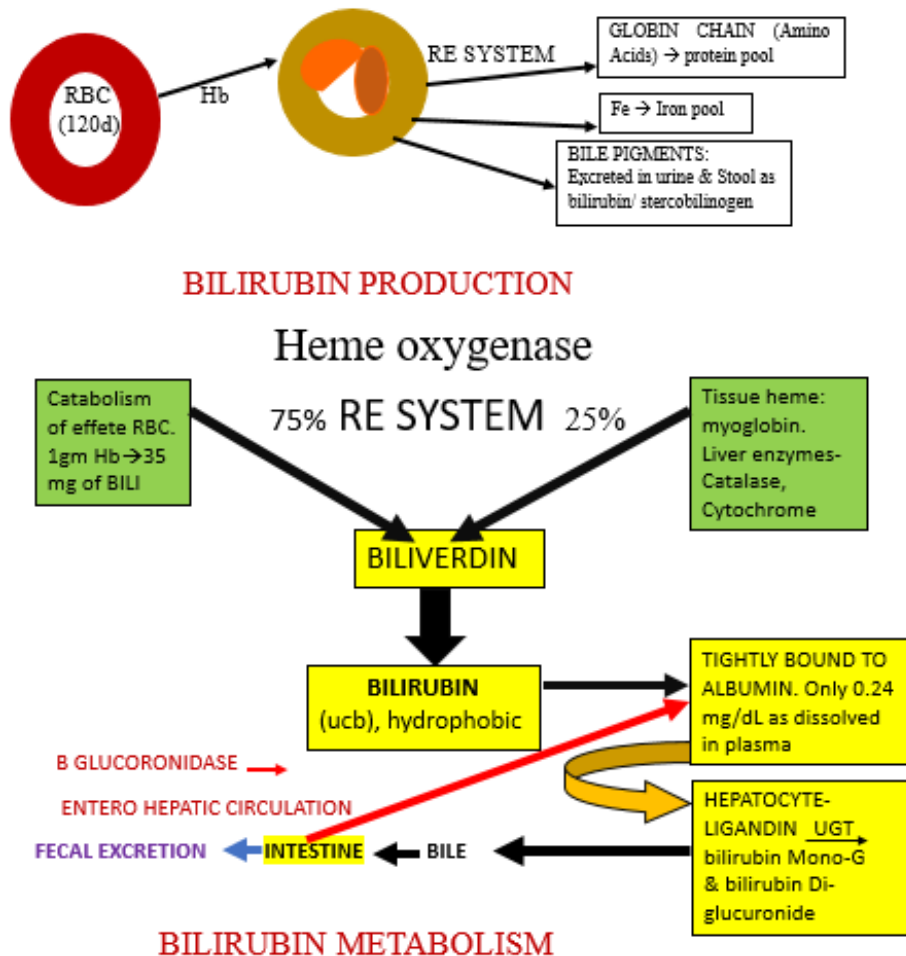


Fig. 1:

- Decreased conjugation due to deficiency (1% of adult of UGT1A1 Competition / blockade of transferase enzyme (developmental (particularly in preterm babies), drugs / substances requiring glucuronic acid conjugation for excretion).
- Increased absorption from gut (entero-hepatic circulation) due to relatively sterile gut and higher β glucuronidase activity to deconjugate bilirubin. Also, if delayed passage of meconium (contains 1mg/dl bilirubin).
- Drugs: oxytocin to mother, and chemicals used in nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia.
- Multifactorial risk factors include infections, infants of diabetic mothers, prematurity.

3.2. Toxic UCB effects enhanced by factors \rightarrow \downarrow bilirubin retention in blood

Less efficient albumin binding in plasma causing increased free UCB (hypoproteinemia, higher pre-albumin fraction as

in preterm neonates) -displacement from albumin binding sites by drugs (sulfonamides, diazepam, moxalactam), higher FFA (starvation, hypothermia, hypoglycemia, as a part of parenteral nutrition—particularly in preterm babies who clear FFP slowly cf. term neonates), acidosis-increased blood brain barrier or nerve cell permeability or neuronal susceptibility to injury: (asphyxia, prematurity, hyperosmolarity, infection,)-delayed early feeding, dehydration causing raised bilirubin levels.

4. Normal Serum Bilirubin Levels & natural history of Neonatal Jaundice

4.1. In utero

- UCB effectively transported via placenta into maternal blood for clearance
- Mean total serum bilirubin (TSB) levels in cord blood: 1-3 mg/dL

4.2. Term infants

TSB increases since birth, peaks on d3/d4 of life and then reduces to normal levels by d7-10

4.3. Late preterm

Significantly different cf. term infants and peak occurs after 96h

4.4. Preterm babies of <34 weeks gestation

Appears late and more sustained, elevated levels may persist in 2nd week of life.

4.5. Pathological jaundice

Jaundice & associated hyperbilirubinemia are considered pathologic if their time of appearance, duration or pattern of serially determined TSB varies significantly from that of physiological jaundice.

Search to determine the cause of jaundice should be made if.

1. Jaundice appears within first 24 -36 h of life.
2. TSB >12 mg/dL in full term and >15 mg/dL in preterm baby.
3. Rate of rise is >5 mg/dL /day or > 0.2 mg/dL / h (may be more than 0.5mg/dL/h in cases of severe Rh hemolytic disease).
4. Direct reacting bilirubin >2 mg/dL at any time of life.
5. Jaundice persists for >14 days.
6. Factors like pallor, hepato/splenomegaly, light colored stools, s/s of illness like poor feeding, apnoea, lethargy, poor vitals, Rh negative mother are recorded.
7. S/S of kernicterus.
8. In cases of severe Rh hemolytic disease, pallor / severe pallor may be the only feature at birth as bilirubin is cleared by placenta.

In evaluation of neonatal jaundice, it is important to assess the time of appearance, extent, duration, clinical clues to causes and presence of any complications due to jaundice. To assess extent, Kramer's staging⁴ for cephalocaudal progression may be applied. There are standard guidelines for management of neonatal hyperbilirubinemia.⁵⁻⁷


5. Conflict of Interest

None.

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