به نام خدا

CLASSIFICATION OF HYPERBILIRUBINEMIA IN THE NEWBORN

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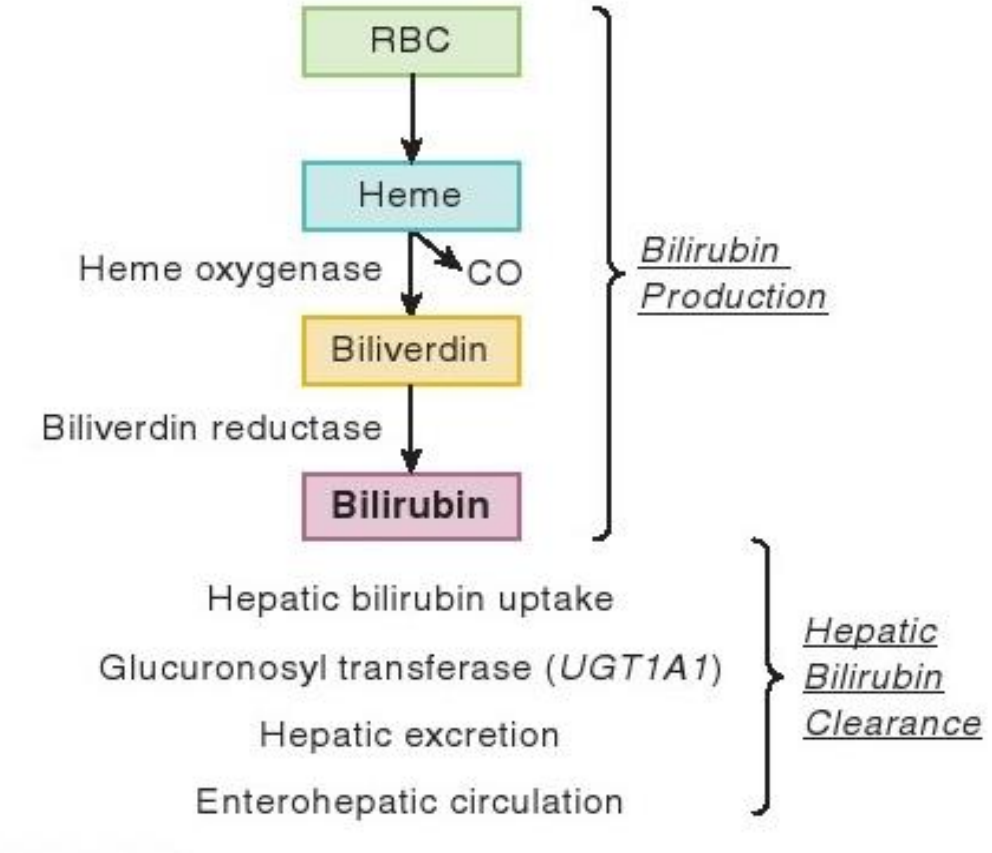
Indirect Unconjugated Hyperbilirubinemia

- Jaundice is observed during the 1st wk. after birth in approximately 60% of term infants and 80% of preterm infants.
- The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin.
- This unconjugated bilirubin (designated indirect-acting by nature of the van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and nonenzymatic reducing agents in the reticuloendothelial cells.

Schematic of bilirubin production and bilirubin clearance



Glucuronidation

Hyperbilirubinemia

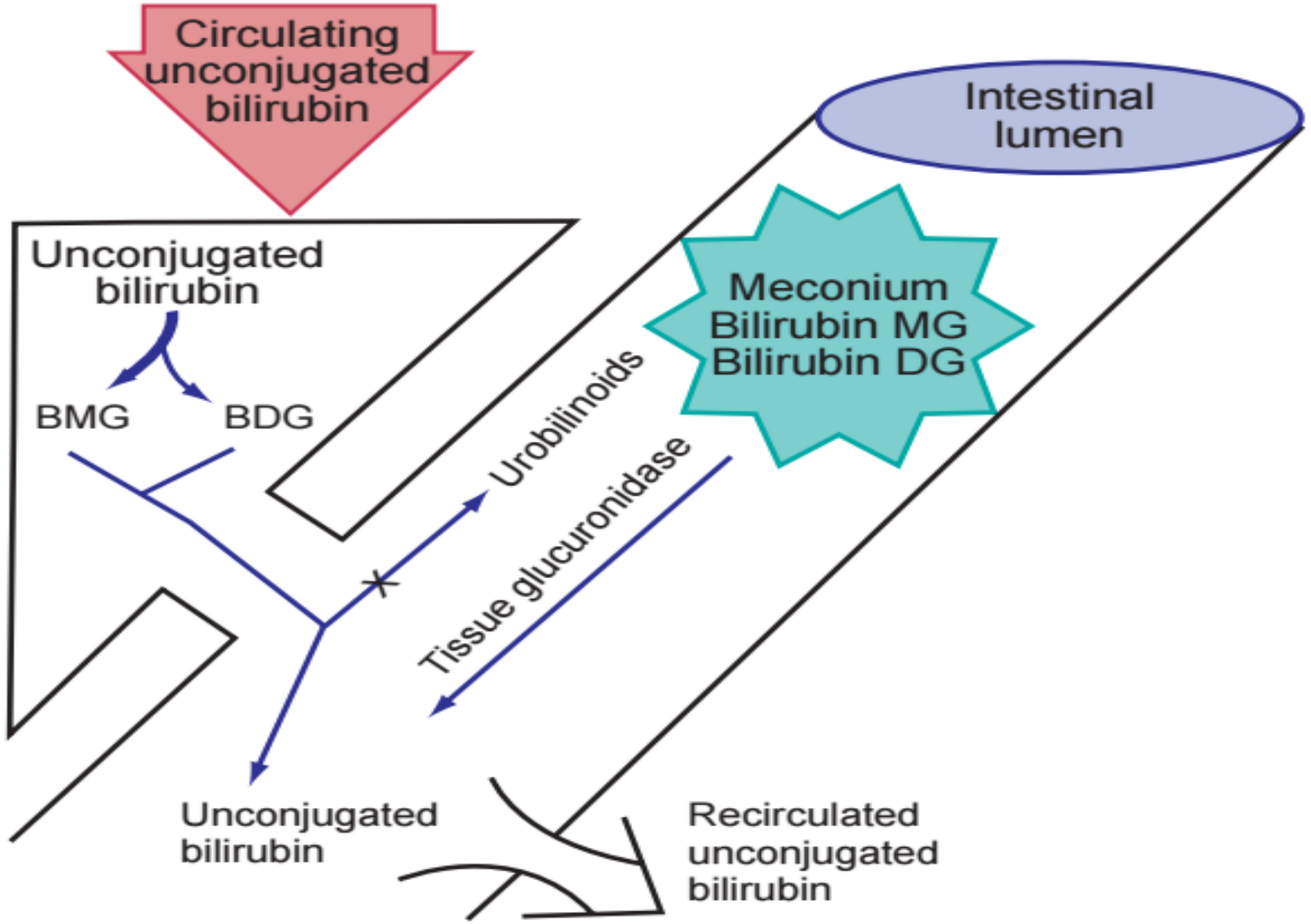
- One gram of hemoglobin produces 35 mg of bilirubin.
- Newborns have a twofold to threefold greater rate of bilirubin production
  - 6-10 mg/kg/24 hr. vs. 3 mg/kg/24 hr.
- This increased production is caused, in part, by an increased RBC mass and a shortened erythrocyte life span of 70-90 days compared with the 120-day erythrocyte life span in adults.
- Increased transcription of the heme oxygenase gene.

Hyperbilirubinemia

- Unconjugated bilirubin binds to albumin on specific bilirubin binding sites; 1 g of albumin binds 8.5 mg of bilirubin in a newborn.
- If the binding sites become saturated or if a competitive compound binds at the site, displacing bound bilirubin
  - Organic acids such as free fatty acids and drugs such as sulfisuxasole can displace bilirubin from its binding site on albumin.
- Bilirubin dissociates from albumin at the hepatocyte and becomes bound to a cytoplasmic liver protein Y (ligandin).
- The enzyme glucuronosyltransferase represents the rate-limiting step of bilirubin conjugation.
- The concentrations of ligandin and glucuronosyltransferase are lower in newborns, particularly in premature infants,

Hyperbilirubinemia (Enterohepatic recirculation)

- Some bilirubin may undergo hydrolysis back to the unconjugated fraction by **intestinal glucuronidase.**
- In addition, **bacteria n the neonatal intestine** convert bilirubin to urobilinogen and stercobilinogen, which are excreted in urine and stool and usually limit bilirubin reabsorption.
- Delayed passage of meconium which contains 1 mg bilirubin/dL


Circulating unconjugated bilirubin
Intestinal lumen
Unconjugated bilirubin
Meconium
Bilirubin MG
Bilirubin DG
BMG
BDG
Urobilinoids
Tissue glucuronidase
Unconjugated bilirubin
Recirculated unconjugated bilirubin

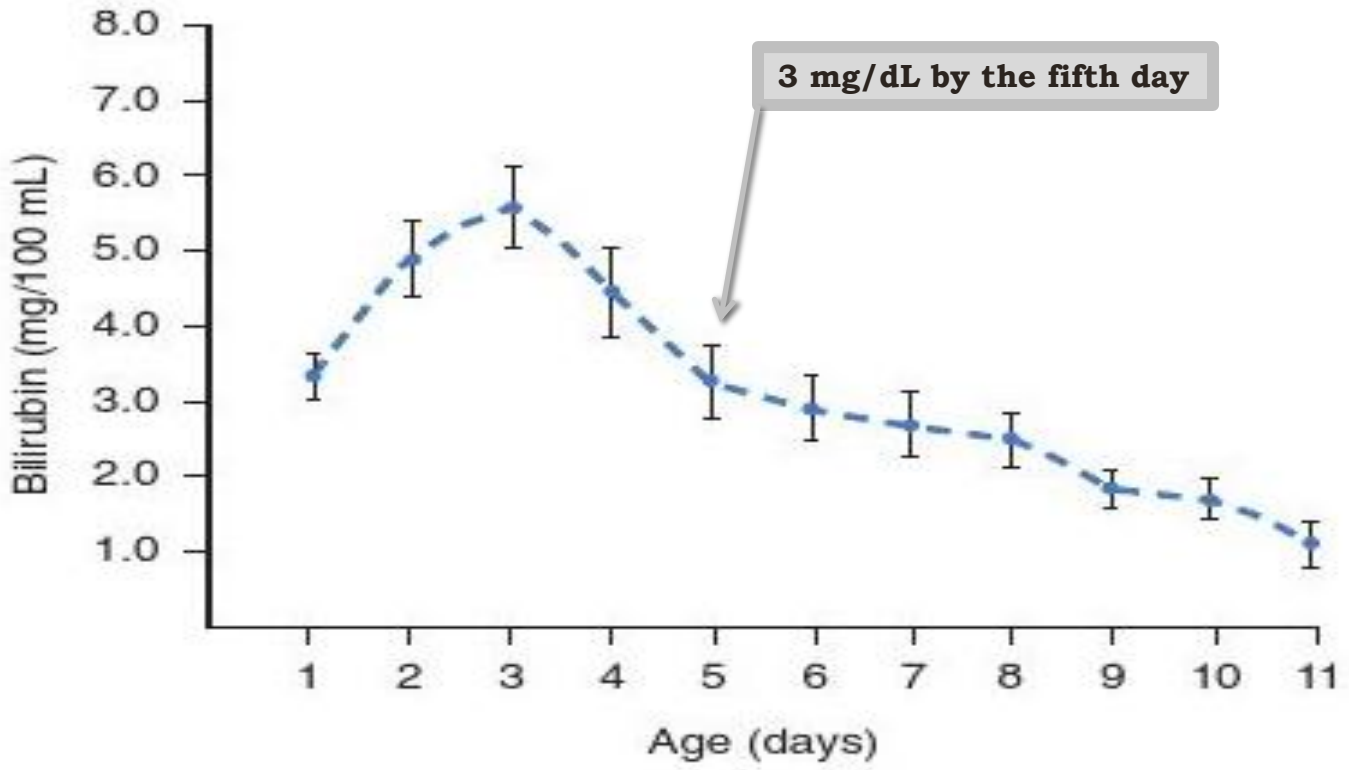
Physiologic jaundice

- The clinical pattern of physiological jaundice in term infants includes a peak indirect-reacting bilirubin level of no more than 12 mg/dL on day 3 of life.
- In premature infants, the peak is higher (15 mg/dL) and occurs later (fifth day).
- The peak level of indirect bilirubin during physiological jaundice may be higher in **breast milk–fed infants than in formula-fed infants (15-17 mg/dL versus 12 mg/dL).**
  - This higher level may be partly a result of the decreased fluid intake of infants fed breast milk. **(starvation jaundice/non-breastfeeding jaundice/breastfeeding failure jaundice)**

Physiologic jaundice

In white and the African:
Infant peak is 5-6 mg/dL between 48 to 120 hr. of age (most reached the peak between 72-96 hr.)

Asian neonates:
TSB peak is 10-14 mg/dL
Time of peak is 72 to 120 hr. of age
TSB reached 3 mg/dL by 7 to 10 days of age



Breast milk jaundice

- unconjugated hyperbilirubinemia
- First to second week of life.
- Bilirubin levels rarely increase to more than 20 mg/dL.
- Interruption of breast feeding for 1-2 days results in a rapid decline of bilirubin levels, which do not increase significantly after breast feeding resumes.
- **Breast milk may contain:**
  - **Inhibitor of bilirubin conjugation**
  - **Increase enterohepatic recirculation of Bilirubin because of breast milk glucuronidase**
  - **Lipase in breast milk**

Unphysiological or Pathological

- Jaundice is unphysiological or pathological:
  - If it is clinically evident on the first day of life
  - If the bilirubin level increases more than 0.5 mg/dL/h
    - TB is about 2 mg/dL in UC and normally rate of rise less than 0.2 mg/dL/h
  - If the peak bilirubin is greater than 13 mg/dL in term infants
  - If the direct bilirubin fraction is greater than 1.5 mg/dL
  - If hepatosplenomegaly and anemia are present

Jaundice on the First Day of Life is Always Pathological

(jaundice is observed in infants when bilirubin levels reach 5-10 mg/dL vs 2-3 mg/dL in adults)

- Early onset jaundice often is a result of:
  - Hemolysis,
  - Internal hemorrhage (cephalhematoma, hepatic or splenic hematoma)
  - Infection
    - Infection also is often associated with **direct-reacting bilirubin** resulting from perinatal congenital infections or from bacterial sepsis
- When jaundice is observed, the laboratory evaluation for hyperbilirubinemia should include:
  - total bilirubin measurement to determine the magnitude of hyperbilirubinemia.
    - Bilirubin levels greater than 5 mg/dL on the first day of life or greater than 13 mg/dL thereafter in term infants should be evaluated further with measurement of indirect and direct bilirubin levels,
  - Blood typing,
  - Coombs test.
  - Complete blood count.
  - Blood smear, and reticulocyte count.

Etiology of Unconjugated Hyperbilirubinemia

	Hemolysis Present	Hemolysis Absent
Common	▪ Blood group incompatibility: ABO Rh, Kell, Duffy, … ▪ Infection	▪ Physiological jaundice ▪ Breast milk jaundice ▪ Internal hemorrhage ▪ Polycythemia ▪ Infant of diabetic mother
Rare	▪ Red blood cell enzyme defects: G6PD Pyruvate kinase ▪ Red blood cell membrane disorders: Spherocytosis, Ovalocytosis ▪ Hemoglobinopathy: ▪ Thalassemia	▪ Mutations of glucuronyl transferase ▪ Crigler-Najjar syndrome ▪ Gilbert disease ▪ Pyloric stenosis ▪ Hypothyroidism ▪ Immune thrombocytopenia

Direct Conjugated Hyperbilirubinemia

- Direct-reacting hyperbilirubinemia defined as a direct bilirubin level >2 mg/dL or >20% of the total bilirubin
- Direct-reacting bilirubin (composed mostly of conjugated bilirubin) is not neurotoxic to the infant but signifies a serious underlying disorder involving cholestasis or hepatocellular injury.
- The diagnostic evaluation of patients with direct-reacting hyperbilirubinemia involves the determination of the levels of liver enzymes:
  - Aspartate aminotransferase,
  - Alkaline phosphatase,
  - Alanine aminotransferase, and γ-glutamyl transpeptidase
  - Bacterial and viral cultures,
  - Metabolic screening tests,
  - Hepatic ultrasound,
  - Sweat chloride test,
  - Liver biopsy.
- Dark urine and gray-white (acholic) stools with jaundice after the second week of life suggests biliary atresia.

Direct Conjugated Hyperbilirubinemia

Etiology of Conjugated Hyperbilirubinemia	
Common	Uncommon
• Hyperalimentation cholestasis • CMV infection • Other perinatal congenital infections (TORCH) • Inspissated bile from prolonged hemolysis • Neonatal hepatitis • Sepsis	• Hepatic infarction • Inborn errors of metabolism (galactosemia, tyrosinemia) • Cystic fibrosis • Biliary atresia • Choledochal cyst • α1-Antitrypsin deficiency • Neonatal iron storage disease (neonatal hemochromatosis) • Alagille syndrome (arteriohepatic dysplasia) • Byler disease, progressive familial intrahepatic cholestasis types

Transient Familial Neonatal Hyperbilirubinemia (Lucey-Driscoll Syndrome)

- Lucey-Driscoll syndrome is a rare familial disorder in which neonates of certain mothers may develop severe **unconjugated hyperbilirubinemia** during the first 48 hours of life.
- The sera of these neonates and their mothers contain high concentrations of an inhibitor of UGT1A1 when tested in vitro.
- The serum inhibitory effect gradually declines after delivery coincident with gradual decline in TB levels.

Prolonged jaundice

Definition:

- TSB >5 mg/dL (>85 micro mol/L) that persists beyond 14 days of life in a term or 21 days in a preterm infant
- Indirect-reacting bilirubin 2 mg/dL or greater that persists beyond 14 days of life in a term or 21 days in a preterm infant

Prolonged jaundice

Increased bilirubin load on liver cell

- Increased degradation of hem
- Increased enterohepatic circulation

Decreased clearance of bilirubin from the plasma

- Uptake
- Conjugation
- Excretion

Prolonged jaundice (Increased Degradation of Hem)

Isoimmunization

- ABO Heterospecificity
  - A1, IgG3, Number of Ag, Maternal HLA
- Rh incompatibility (Rh system comprises more than 40 Ags)
  - D phenotypes:
    - Partial D (D I, D II, … D VII)
      - Have more than 30 variants
    - Weak D
    - DEL
    - RhD ψ (RhD-negative)
    - RhD-CE-D (RhD-negative)
  - C, c, E
- Duffy, Kell, Diego, Kidd, MNSs, P, Half-life of IgG is about 28 days and hemolysis resolved within the 3 or 4 months

Prolonged jaundice (Increased Degradation of Hem)

- Erythrocyte Biochemical Defects
  - G6PD deficiency
    - Associated with Gilbert syndrome
- Structural Abnormalities of Erythrocytes
  - Hereditary spherocytosis
  - Infantile pyknocytosis
- Infection
  - Oxidative stress and Heinz body formation
  - Heme oxygenase induced
  - Impairing of UGT activity
- Sequestered Blood
- Polycythemia

Prolonged jaundice (Increased Enterohepatic Circulation)

- Breast Milk Jaundice
  - β-glucuronidase
  - Inhibit activity of UGT
    - Pregnanediol isomer
    - Nonesterified long-chain fatty acids
- Intestinal Tract Disease
  - Hirschsprung Disease
  - Duodenal and jejunal obstruction
  - Pyloric Stenosis
    - Associated with Gilbert syndrome

Prolonged jaundice (Decreased clearance of bilirubin from the plasma)

- Uptake (Y protein, Z protein)
  - Hypothyroidism
    - Decreased UGT activity
  - Gilbert syndrome
  - G6PD deficiency

Prolonged jaundice (Decreased clearance of bilirubin from the plasma)

- Conjugation (UGT activity before 30 wks of gestational is 0.1% adult and 1% at term)
  - Crigler-Najjar
  - Gilbert Syndrome

Characteristic	CN-1	CN-2	Gilbert
Inheritance	AR	AR/AD	AR/AD
UGT1 activity	Absent	<10%	50%
bilirubin	>20 mg/dL	5-15 mg/dL	3-5 mg/dL

Causes of Prolonged Jaundice

Indirect

- Urosepsis
- Hypothyroidism
- Hemolysis
- Galactosemia
- Gilbert
- CN
- Breast Milk Jaundice
- Down Syndrome

Direct

- Biliary Tree Abnormalities
- Urosepsis
- TORCHES
- Inborn Error Metabolism
- Idiopathic Neonatal Hepatitis