Neonatal Jaundice

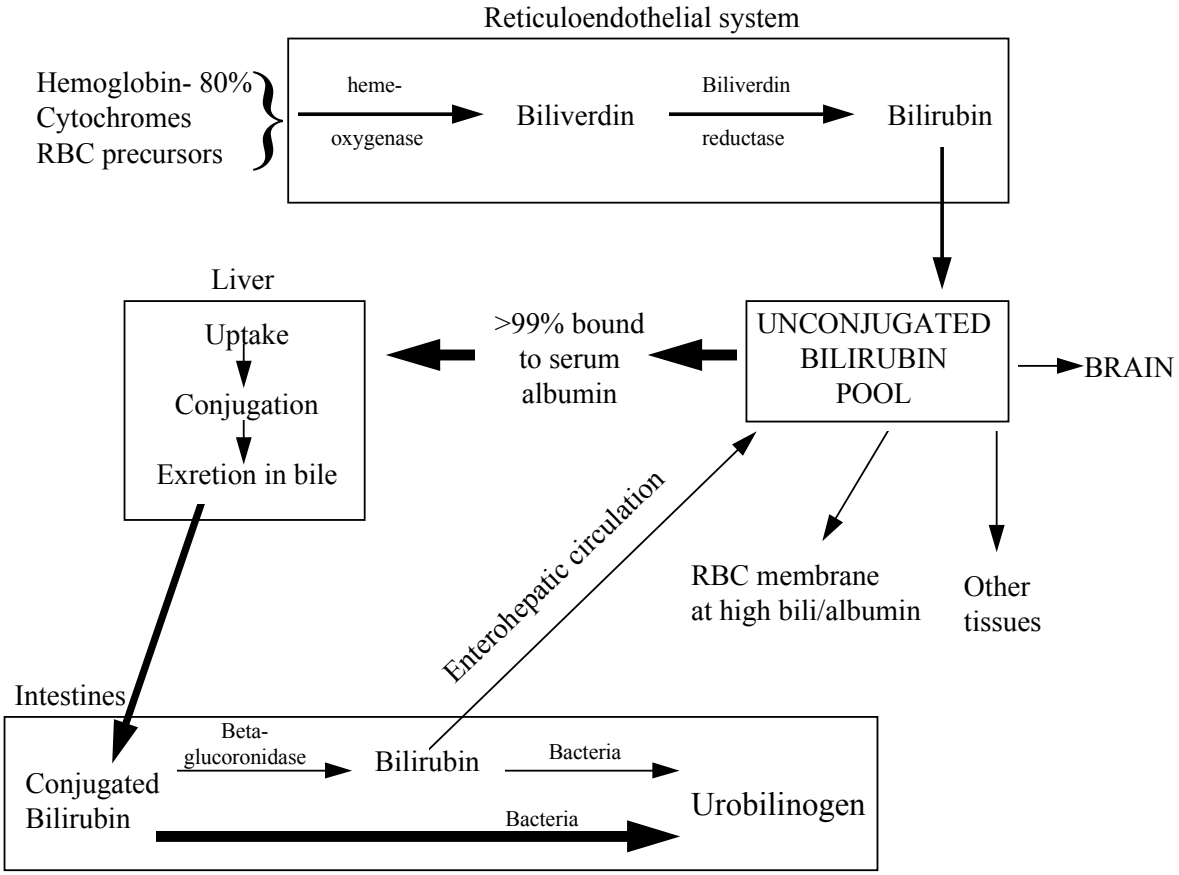
I. Bilirubin Metabolism

A. Chemical structure and properties of bilirubin

- tetrapyrrole ring with intramolecular hydrogen bonding
- poorly soluble in water and highly lipophilic
- native configuration is designated 4z,15z-bilirubin IXα
- >99% of unconjugated bilirubin is transported in serum tightly bound to albumin, although at high concentrations, the bilirubin will bind to proteins in RBC membranes, and other tissues.
- Under normal circumstances the CNS blood-brain barrier is relatively impermeable to albumin bound bilirubin, however unbound bilirubin readily enters the CNS.

B. Bilirubin production

- 80% of bilirubin is derived from the breakdown of senescent RBCs.
- Remainder derived from the degradation of RBC precursors, myoglobin, and cytochromes.
- Heme oxygenase is the rate limiting enzyme for bilirubin production in the reticuloendothelial system.



C. Hepatic uptake conjugation and excretion

- Transfer of albumin bound bilirubin to the hepatocyte protein “ligandin”
- Carrier proteins “Y” and “Z” are the intracellular carriers that translocate bilirubin to the smooth ER.
- UDP glucoronyl transferase: bilirubin-monoglucoronide
- UDP glucoronate glucoronyl transferase: bilirubin-diglucoronide
- Both mono and diconjugated bilirubins are excreted in the bile

- Small intestine β-glucoronidase deconjugates some of the bilirubin which is then reabsorbed. (enterohepatic circulation)
- The majority of conjugated bilirubin is metabolized to urobilinogen by intestinal bacteria, which is then excreted in the stool.

II. Jaundice

- Clinically apparent jaundice occurs when the serum unconjugated bilirubin level is 5-7mg/dl. Occurs in about 50% of term newborns.
- Can be classified as either conjugated (direct), or unconjugated (indirect) hyperbilirubinemia.

Table 1. Differential Diagnosis of an Unconjugated Hyperbilirubinemia

Increased production	Decreased Clearance
Physiologic Jaundice	Physiologic Jaundice
Isoimmunization (ABO, Rh, other)	Breast milk Jaundice
RBC biochemical defects	Deficient conjugation (Crigler-Najjar)
RBC structural abnormalities	Prematurity
hemoglobinopathies	Increased enterohepatic circulation
Infections	Infant of a diabetic mother
Polycythemia	Hypothyroidism
Sequestered blood	? deficient hepatic uptake

Table 2. Differential Diagnosis of a Conjugated Hyperbilirubinemia

Intrahepatic	Extrahepatic
Idiopathic Neonatal Hepatitis	Extrahepatic Biliary Atresia
Inborn errors of metabolism	Bile duct stenosis
Other genetic diseases	Bile duct perforation
Congenital infections	Choledocal cyst
Congenital hepatitis	Cholelithiasis
Toxic hepatitis (TPN and certain drugs)	Bile duct plug

III. Physiologic Jaundice

A. Term infants

- Rise in serum unconjugated bilirubin to a peak of 5-7mg/dl by 72 hours of life, followed by a progressive decrease over the next several days.
- An increased load of bilirubin presented to the liver (↑ enterohepatic circulation)
- Decreased ability of the liver to conjugate and excrete the bilirubin (decreased activity of UDP glucoronyl transferase, and endogenous inhibitors of this enzyme)
- Genetic predisposition in certain ethnic groups (Mediterranean and Asian ancestry).

B. Prematurity

- Peak bilirubin concentrations of 10-12mg/dl are not reached until the 5th day of life.
- There is also a delay in the rate of decline of the bilirubin levels.
- This is primarily the result of delayed maturation of the UDP glucoronyl transferase in preterm infants, and the prolonged intestinal transit time in preterm infants.
- It may take up to one month for the bilirubin levels to decline completely.

IV. Breast Feeding Jaundice

A. Early onset

- Onset in the first week of life, occurs in approximately 12-13% of term newborns.
- Peak bilirubin concentration of >12mg/dl
- Very slow decline over the next three weeks.
- Felt to be due to dehydration/starvation until mothers breast milk “comes in”.
- Possible role for inhibitors of intestinal colonization or inhibitors of glucoronyl transferase in the breast milk.

B. Late Onset

- Onset at about 7 days of age, with a peak serum bilirubin of >10mg/dl.
- Usually takes several months for bilirubin levels to normalize.
- See above for possible etiologic factors.

V. Bilirubin Encephalopathy

A. Presentation

- Kernicterus: is a pathologic finding of yellow staining and necrosis of neurons.
- The basal ganglia, hippocampal cortex, subthalamic nuclei, and cerebellum are the areas most commonly affected.
- Most infants with kernicterus at autopsy, also show evidence of injury to other organ systems as well. (kidney, pancreas, intestines, etc.)
- Abnormalities in BAER may be the first sign, detectable at levels as low as 15mg/dl
- Classic presentation is the progressive development of lethargy, rigidity, opisthotonus, high pitched cry, fever, and seizures. Death then follows in 50%.

B. Pathogenesis

- Unconjugated bilirubin enters the CNS neurons.
- Appears the albumin binding ability is the most critical determinant of the serum bilirubin level at which this occurs.
- Certain factors predispose an infant to developing bilirubin encephalopathy either through a reduction in the albumin binding capacity, competition for the binding sites, or increasing the permeability of the blood brain barrier.
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Factors predisposing to bilirubin encephalopathy:

Prematurity	Hemolysis
Certain drugs	Sepsis
Hypoalbuminemia	hypoglycemia
Acidosis	Asphyxia/Hypoxia

- Bilirubin appears to interfere with synaptic transmission, $Na^{+}K^{+}$ATPase function, decreased mitochondrial activity, decreased substrate transport, and decreased cell viability

C. Sequelae

- Choreoathetoid cerebral palsy and upward gaze palsy
- High frequency deafness
- Mental retardation occurs less often.
- Some develop mild abnormalities in motor function and cognition, termed minimal brain dysfunction.

VI. Diagnosis

If jaundice is clinically apparent in the first 24 hours of life, or if the total bilirubin level rises at a rate >5mg/dl/day, or if the direct bilirubin is >1.5-mg/dl or >10% of the indirect fraction, then you should be highly suspicious that the etiology is not physiologic jaundice. In these infants further evaluation is warranted.

Minimal diagnostic evaluation for clinically jaundiced infants

Fractionated serum bilirubin	Hematocrit
Blood type and Rh testing on baby and mom	Blood smear for RBC morphology
Direct coomb's test on baby	Reticulocyte count
Blood for G-6-PD levels in high risk infants	

VII. Treatment

A. Phototherapy:

- Photooxidation of bilirubin (irreversible)
- Isomerization
  - -Configurational 4z,15z to 4z 15e (reversible)
  - -Structural isomerization to lumirubin (irreversible)
- Side effects

B. Exchange transfusion

C. Novel therapies: Tin mesoporphyrin & Oral agar feedings