NEONATAL HYPERBILIRUBENEMIA

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Definition

- The accumulation of bilirubin manifests as yellow discoloration of the skin, sclera (icterus), and mucosa called **jaundice**.

- Hyperbilirubinemia presents as either

1. **unconjugated hyperbilirubinemia**
2. **conjugated hyperbilirubinemia**

- In most infants unconjugated hyperbilirubinemia reflects a **normal transitional** phenomenon.

- unconjugated bilirubin is neurotoxic (fat soluble).

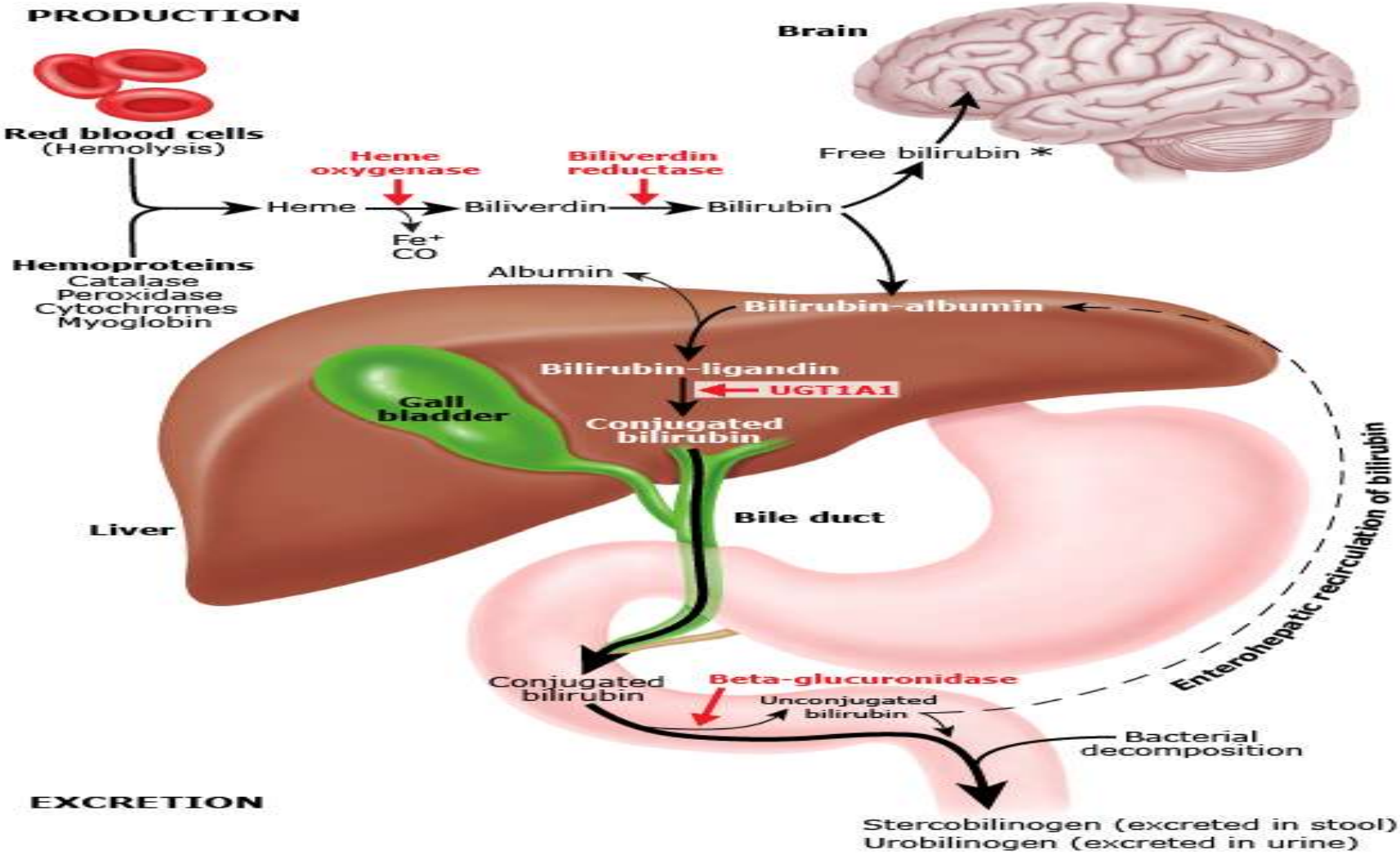
- **Conjugated hyperbilirubinemia is always pathologic** and requires thorough investigation.

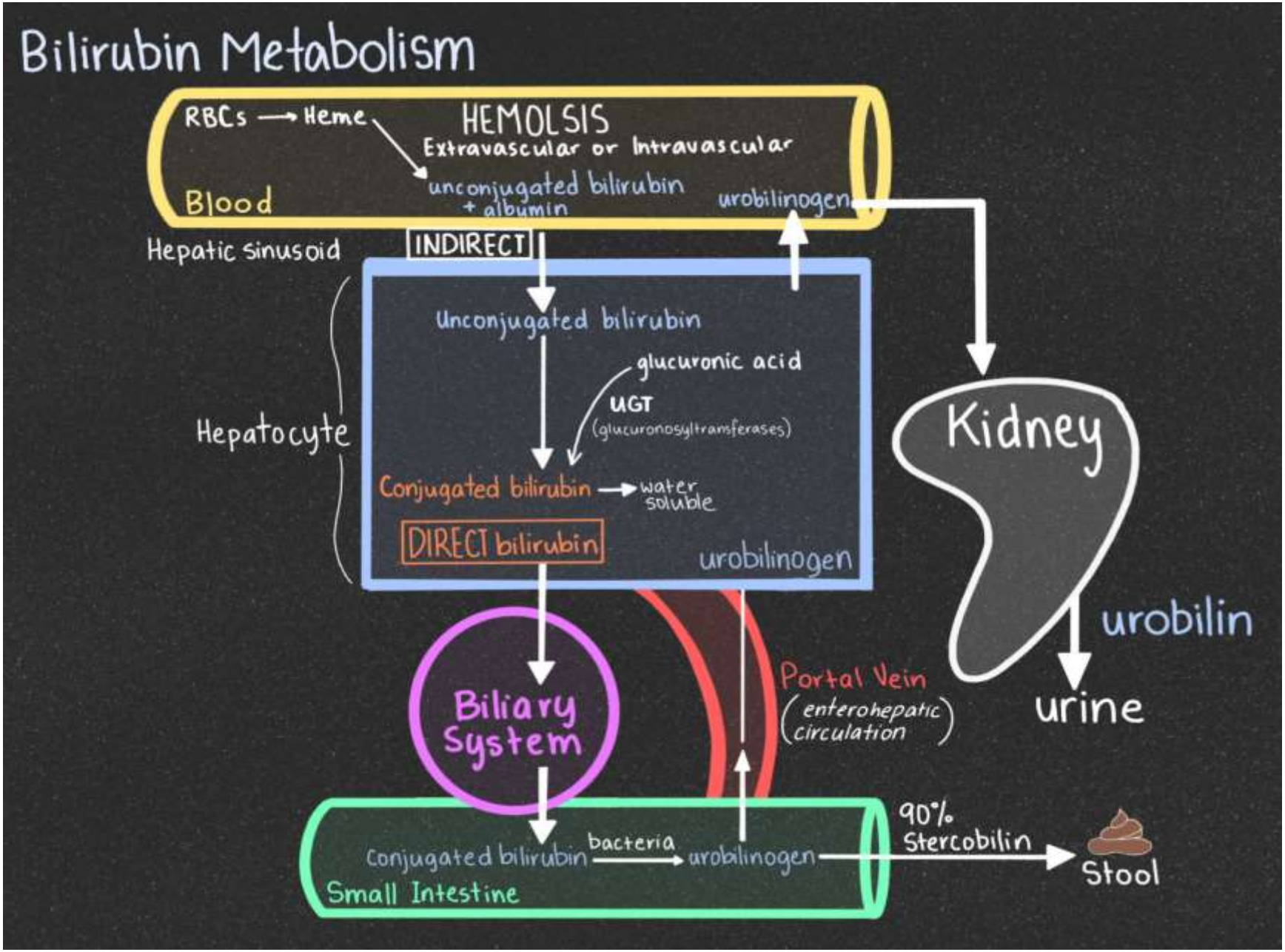
Incidence

- It occurs in approximately 60% to 70% of term and approximately 80% of preterm infants in the first week of life.

- The incidence of severe hyperbilirubinemia is approximately 0.14%.

Pathophysiology




Bilirubin Metabolism
RBCs → Heme
HEMOLSIS
Extravascular or Intravascular
unconjugated bilirubin
+ albumin
Blood
urobilinogen
Hepatic sinusoid
INDIRECT
Unconjugated bilirubin
glucuronic acid
UGT
(glucuronosyltransferases)
Hepatocyte
Conjugated bilirubin → water soluble
DIRECT bilirubin
urobilinogen
Kidney
urobilin
urine
Biliary System
Portal Vein
(enterohepatic circulation)
Conjugated bilirubin
bacteria
urobilinogen
Small Intestine
90% Stercobilin
Stool

Pathophysiology

“Physiologic” unconjugated hyperbilirubinemia.

- Neonatal physiologic jaundice results from simultaneous occurrence of the following 2 phenomena:
  1. **Bilirubin production** is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes

  2. **Hepatic excretory capacity** is low both because of :
     A. low concentrations of the binding protein ligandin in the hepatocytes
     B. low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).

Pathophysiology

“Physiologic” unconjugated hyperbilirubinemia.

- Accepted “normal” or physiologic ranges of TSB levels vary widely because levels are influenced by many diverse factors such as:

1. **gestational age**
2. **Birthweight**
3. **disease state**
4. **degree of hydration**
5. **nutritional status**
6. **racial background**
7. **breast feeding**
8. **other genetic and epidemiologic factors**.

- Although **most of these infants are healthy and will not need therapy**, **they need to be monitored closely**.

Pathophysiology

"**Physiologic**" unconjugated hyperbilirubinemia.

- **Term neonates** characterized by:
  - Most infants presenting at **72 to 96 hours of age with TSB levels of 10 to 14 mg/dL**
  - This is followed by a rapid decline by the 5-7 day of life.

- **Premature neonates** is more severe than in full-term neonates
  - Mean peak **TSB 10 to 12 mg/dL by the fifth day of life**.
  - This **delay in reaching the maximum** concentration as compared with the full-term neonates primarily reflects the delay in maturation of hepatic UGT activity.
  - **All degrees of visible jaundice** in *premature neonates* should be monitored closely and investigated fully

Pathophysiology

Exclusion criteria for diagnosis of "physiologic" jaundice

1. **Jaundice appearing within the first 24 hours of life.**

2. **Total serum bilirubin level >95th percentile** for age in hours based on a nomogram for hour-specific serum bilirubin concentration.

3. **Bilirubin level increasing at a rate** >0.2 mg/dL/h or >5 mg/dL/d.

4. **Direct serum bilirubin level** >1.0 mg/dL if the total serum bilirubin is ≤5 mg/dL or >20% of the TSB.

5. **Jaundice persisting for >2 weeks in full-term infants and >3 weeks in preterms.**

Pathophysiology

Mechanisms that predispose newborn infants to hyperbilirubinemia

1. **Increased bilirubin synthesis** due to **larger RBC mass, increased hemoglobin breakdown due to shorter RBC life span** in neonates, (t1/2 of adult RBC's is 120 days, of **HbF containing RBC's is 90 d)**and increased rate of RBC degradation within the bone marrow before release to the circulation.

2. **Decreased binding and transport.** Decreased hepatic uptake of bilirubin from plasma due to **decreased plasma albumin and the liver transfer protein ligandin**.

3. **Impaired conjugation and excretion. Reduced UDPGT activity** in the newborn liver results in bilirubin conjugates that can be excreted in the bile.

4. **Enhanced enterohepatic circulation.** Conjugated bilirubin is unstable and can be hydrolyzed by the intestinal enzyme β-glucuronidase to its unconjugated form; this can be readily absorbed through the intestinal mucosa and move back to the liver (enterohepatic circulation). **Sterility of intestinal mucosa prevents further formation of the more excretable products** namely, urobilin and stercobilin.

Pathophysiology

Early-onset Breast-feeding jaundice.

- **Begins in the first week** of life due to **dehydration, caloric deprivation with greater than average weight loss , and increased enterohepatic circulation**.
- **Treatment should focus on establishing adequate lactation**

Late-onset Breast milk jaundice.

- **Prolonged indirect hyperbilirubinemia** has been reported to occur in up to 30% of breastfed infants startrted 2nd week til 2-3 months.
- **Genetic pathogenesis** characterized by **polymorphism of the *UGT1A1* gene, Gilbert syndrome and presence of high level of β-glucuronidase in BM**.
- Usually **with family history** of prolonged jaundice in previous sibblings.

Pathophysiology

Disorders of production

A. Immune-mediated hemolytic disease

- **is the most common cause of pathologic hyperbilirubinemia in the newborn period.** The process may begin in fetal life or immediately after birth.

1. Rh (D antigen) incompatibility as well as other antigens in the Rh blood-group system (c, C, e, E, cc, and Ce) can cause immune-mediated hemolytic disease.

- Alloimmunization occurs when as little as 0.1 mL of RBCs from an Rh(D)-positive fetus cross the placenta into the circulation of an Rh(D)-negative mother.
- The initial response in the maternal circulation is the production of immunoglobulin (Ig) M that does not cross the placenta, **which is then later followed by IgG, which in subsequent pregnancies crosses the placenta** and causes a hemolytic process that can begin in utero.
- The severe form of this process can result in erythroblastosis fetalis with hydrops.

Pathophysiology

Disorders of production

A. Immune-mediated hemolytic

2. ABO incompatibility.

- Antigens present on the surface of RBCs react with antibodies in the plasma of opposing blood types, resulting in ABO incompatibility with sensitization.
- Hemolysis is generally limited to **group A or B infants born to group O mothers**.
- **Occur in the first pregnancy.**
- **Risk of recurrence can be as high as 88%** in infants with the same blood type .
- **ABO incompatibility is somewhat protective of Rh sensitization** because the fetal ABO incompatible RBCs are rapidly destroyed in the maternal circulation, thereby decreasing the opportunity of Rh antigen to mount an immune response.

Pathophysiology

Disorders of production

B. Red blood cell enzyme deficiencies

1. Glucose-6-phosphate dehydrogenase deficiency is the **most common RBC enzyme deficiency**.

- The major function of G6PD is preventing oxidative damage of cells.
- The G6PD gene is located on the **X chromosome**.
- The rapid rise in TSB in infants with this enzyme deficiency may not be **accompanied by evidence of a hemolytic process**.
- It presents in the newborn period with jaundice, anemia, and reticulocytosis.

2. Pyruvate kinase deficiency is inherited in an autosomal recessive manner.

Pathophysiology

Disorders of production

C. Red blood cell membrane defects

1. Hereditary spherocytosis (HS).

- The **inheritance is dominant** in 75% of the cases, but some cases of de novo mutations.
- Jaundice can range from mild to severe, causing kernicterus.
- A simple way to screen in neonates is the **HS ratio (MCHC/MCV when >0.36** has 97% sensitive and 99% specific) + blood film.
- The **incubated osmotic fragility test** is considered the gold standard for making the definitive diagnosis of HS.

2. Hereditary elliptocytosis is an autosomal dominant.

Pathophysiology

Disorders of production

D. Hemoglobinopathies.

- These conditions **generally do not present in the newborn period**.
- patients with **deletion of 3 α-globin genes (hemoglobin H) are often born with hypochromic hemolytic anemia and are at risk for developing severe hyperbilirubinemia**.

E. Infection

- causes hyperbilirubinemia by increasing bilirubin concentrations via **hemolysis, and it may impair conjugation, leading to decreased excretion of bilirubin**.
- Both **early- and late-onset jaundice** are reported to be some of the more common clinical manifestations of **urinary tract infection**.

F. Increased erythrocyte load

1. **Blood sequestration. The catabolism of 1 g of hemoglobin yields 35 mg of bilirubin**. Occult hemorrhages, such as bruising, cephalohematomas, and intracranial bleeding.
2. **Polycythemia.**
3. **Infants of diabetic mothers.** have high erythropoietin levels, leading to polycythemia.

Pathophysiology

Disorders of bilirubin clearance

A. Crigler-Najjar syndrome type I.

- Autosomal recessive disease characterized by almost complete absence of hepatic UDPGT activity.
- TSB is commonly >20 mg/dL.
- The diagnosis of Crigler-Najjar syndrome type I (CNS-I) can usually be made by microassay of UDPGT activity or by measurement of menthol glucuronide in urine after oral menthol.
- TSB is unresponsive to phenobarbital therapy.

C. Gilbert syndrome

- Relatively common disorder characterized by mild, lifelong, unconjugated hyperbilirubinemia in the absence of hemolysis or evidence of liver disease.
- Autosomal dominant and recessive.
- **Hepatic glucuronidation activity is 30% of normal**, resulting in an increased proportion of monoglucuronide.

B. Crigler-Najjar syndrome type II ,

- more common than CNS-I and typically benign.
- autosomal recessive and dominant inheritance.
- It is caused by a single base pair mutation leading to **decreased but not totally absent UDPGT enzyme activity**.
- TSB rarely exceeds 20 mg/dL.
- Diagnosis by identifying the genetic defect.
- For routine clinical practice, CNS-I and CNS-II can be differentiated by their **response to phenobarbital therapy and bile analysis**. In CNS-I, bile is totally devoid of bilirubin conjugates, whereas bilirubin monoconjugates are present in CNS-II, and some diconjugates may be detectable after phenobarbital treatment.

Pathophysiology

Metabolic and endocrine disorders

A. Galactosemia.

- Jaundice may be 1 of the presenting signs such as poor feeding, vomiting, and lethargy.
- **Hyperbilirubinemia during the first week of life is almost always unconjugated, and then it becomes mostly conjugated during the second week, reflective of developing liver disease.**

B. Hypothyroidism.

- Prolonged jaundice is found in up to 10% of newborns diagnosed with hypothyroidism.
- **It is due to a deficient activity of UDPGT.**
- **Early-onset hyperbilirubinemia** has been reported as the only presenting sign of congenital hypothyroidism.
- **Treatment with thyroid hormone improves hyperbilirubinemia.**

Pathophysiology

Increased enterohepatic circulation of bilirubin

A. Conditions that cause gastrointestinal obstruction (eg, pyloric stenosis, duodenal atresia, annular pancreas) or a decrease in gastrointestinal motility may result in exaggerated jaundice due to increased enterohepatic recirculation of bilirubin. **Blood swallowed during delivery and decreased caloric intake** may also be contributing factors.

B. Breast-feeding jaundice and breast milk jaundice.

Substances affecting binding of bilirubin to albumin.

- Certain drugs occupy bilirubin-binding sites on albumin and increase the amount of free unconjugated bilirubin that can cross the blood–brain barrier.
- Drugs in which this effect may be significant include aspirin, moxalactam, ceftriaxone, sulfisoxazole, penicillin and gentamicin.

Risk factors

1. Sepsis
2. Acidosis
3. Lethargy
4. Asphyxia
5. Temperature instability
6. G6PD deficiency
7. Hemolytic disease (ABO or G6PD deficiency)
8. Late preterm (34–36 weeks) and early term gestation (37–38 weeks)
9. Exclusive breast feeding
10. Cephalohematoma or significant bruising
11. Male sex
12. Maternal diabetes
13. Family history of neonatal jaundice
14. Use of oxytocin in labor

Clinical presentation

Monitor for jaundice.

- Jaundice is **clinically visible when the serum bilirubin level approaches 5 mg/dL**.

- The yellow color is seen more easily in the “fingerprint” area than in the surrounding skin.

- **Progression is cephalocaudal**, so that for a given bilirubin level, the face appears more yellow than the rest of the body.

Clinical presentation

Clinical history.

- Gestational age.
- Mother and baby blood group.
- Family history of jaundice, anemia, splenectomy, or metabolic disorder is significant and may suggest underlying etiology for jaundice.
- Maternal history of infection or diabetes may increase the newborn’s risk for jaundice.
- Breast feeding and factors affecting normal gastrointestinal function in the newborn period increase the tendency for more severe jaundice.

Clinical presentation

Physical examination.

- **Weight**
- Areas of bleeding such as **cephalhematoma, petechiae, or ecchymoses** indicate blood extravasations.
- **Hepatosplenomegaly** may signify hemolytic disease, liver disease, or infection.
- Physical signs of **prematurity, plethora** with polycythemia, **pallor** with hemolytic disease, and macrosomia with maternal diabetes all can be associated with jaundice.
- **Omphalitis, chorioretinitis, microcephaly, petechiae, and purpuric lesions** suggest infectious causes.
- **Neurologic examination.**
  - Severe hyperbilirubinemia can result in **hearing loss and encephalopathy**.
  - The appearance of subtle abnormal neurologic signs heralds the onset of early bilirubin encephalopathy.
  - Clinical signs may include **lethargy, poor feeding, vomiting, hypotonia, and seizures**.

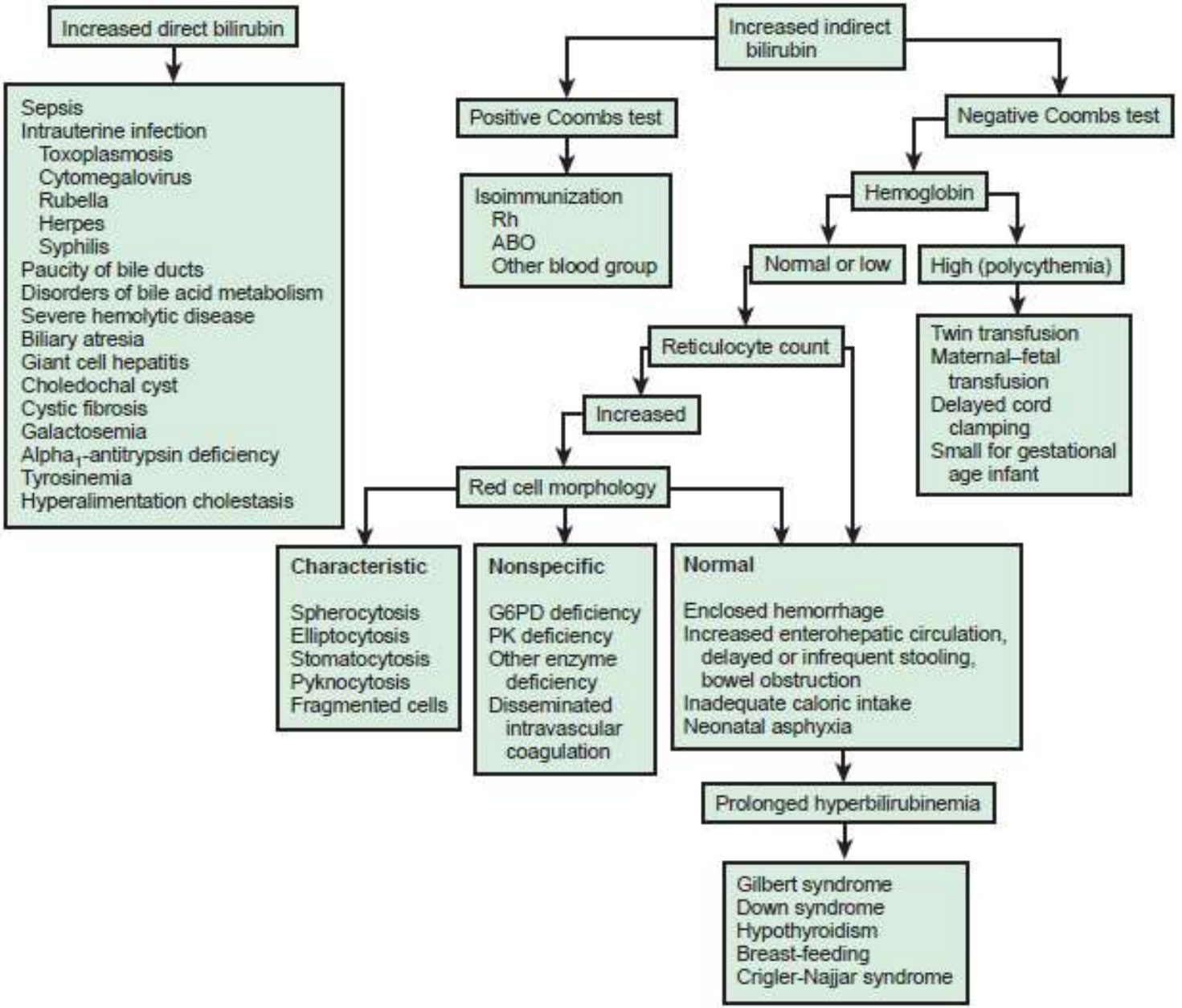
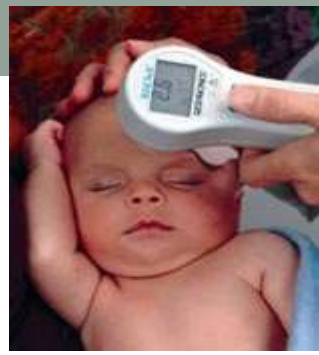


Figure 102-7 Schematic approach to the diagnosis of neonatal jaundice. G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase. *(From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, editors:* Schaffer and Avery's diseases of the newborn, *ed 6, Philadelphia, 1991, WB Saunders.)*

Diagnosis



1. Total and direct serum bilirubin (total bilirubin interpreted based on age in hours).

- **Transcutaneous bilirubinometry** TcB value of >15 mg/dL should be correlated with TSB.

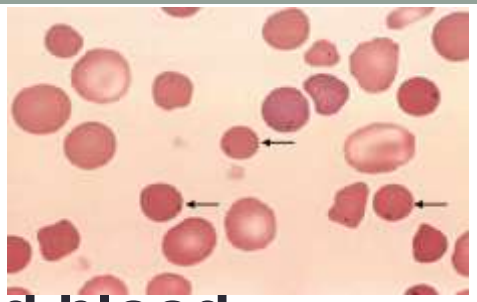
2. Blood type and Rh status in both mother and infant (Cord blood can be sent for DAT and routine blood typing).

3. Hemoglobin electrophoresis, G6PD level, or osmotic fragility testing may be required, In the absence of ABO or Rh incompatibility.

4. Direct antiglobulin test is also known as direct Coombs test

- **Detects antibodies** bound to the surface of RBCs.
- **Usually positive in hemolytic disease** resulting from isoimmunization.
- **Does not correlate with severity** of jaundice.
- **Can be obtained from the cord blood.**
- **Poor test in ABO incompatibility** due to the relative lack of type specific antigen on the surface of neonatal RBC's, **therefore often negative**

Diagnosis



5. Complete blood count with differential and blood film

- **Presence of anemia** may be suggestive of a hemolytic process; **polycythemia**.
- **Evaluate red blood cell morphology;** spherocytes suggest ABO incompatibility or HS.
- **Look for MCHC/MCV ratio >0.36** is highly suggestive of congenital spherocytosis
- **Evaluate for indices suggestive of infection** (leukopenia, neutropenia, and thrombocytopenia).

6. Reticulocyte count **(Elevation suggests hemolytic disease, cases of chronic occult or overt hemorrhage).**

Diagnosis

7. Prolonged jaundice may require additional tests

1. Thyroid function
2. Liver function,
3. Blood and urine cultures, (may include CMV urine culture for TORCH)
4. Metabolic screening workup, such as plasma amino acid and urine organic acid and reducing substances measurements.
5. Blood film
6. Urine culture

8. Measurement of serum albumin. Help assess the fraction of unbound bilirubin in the circulation and thereby determine the need of an albumin infusion.

9. Blood gas measurements:

The risk of bilirubin CNS toxicity is increased in acidosis

10. Ultrasonography:

Ultrasonography of the liver and bile ducts is warranted in infants with laboratory or clinical signs of cholestatic disease.

Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Practice guidelines.

The recommendations include the following:

1. to promote and support successful breast feeding,

2. to perform a risk assessment for severe hyperbilirubinemia prior to discharge,

3. to provide early and focused follow-up for the high-risk patient,

4. to initiate immediate therapeutic intervention when indicated.

Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Phototherapy

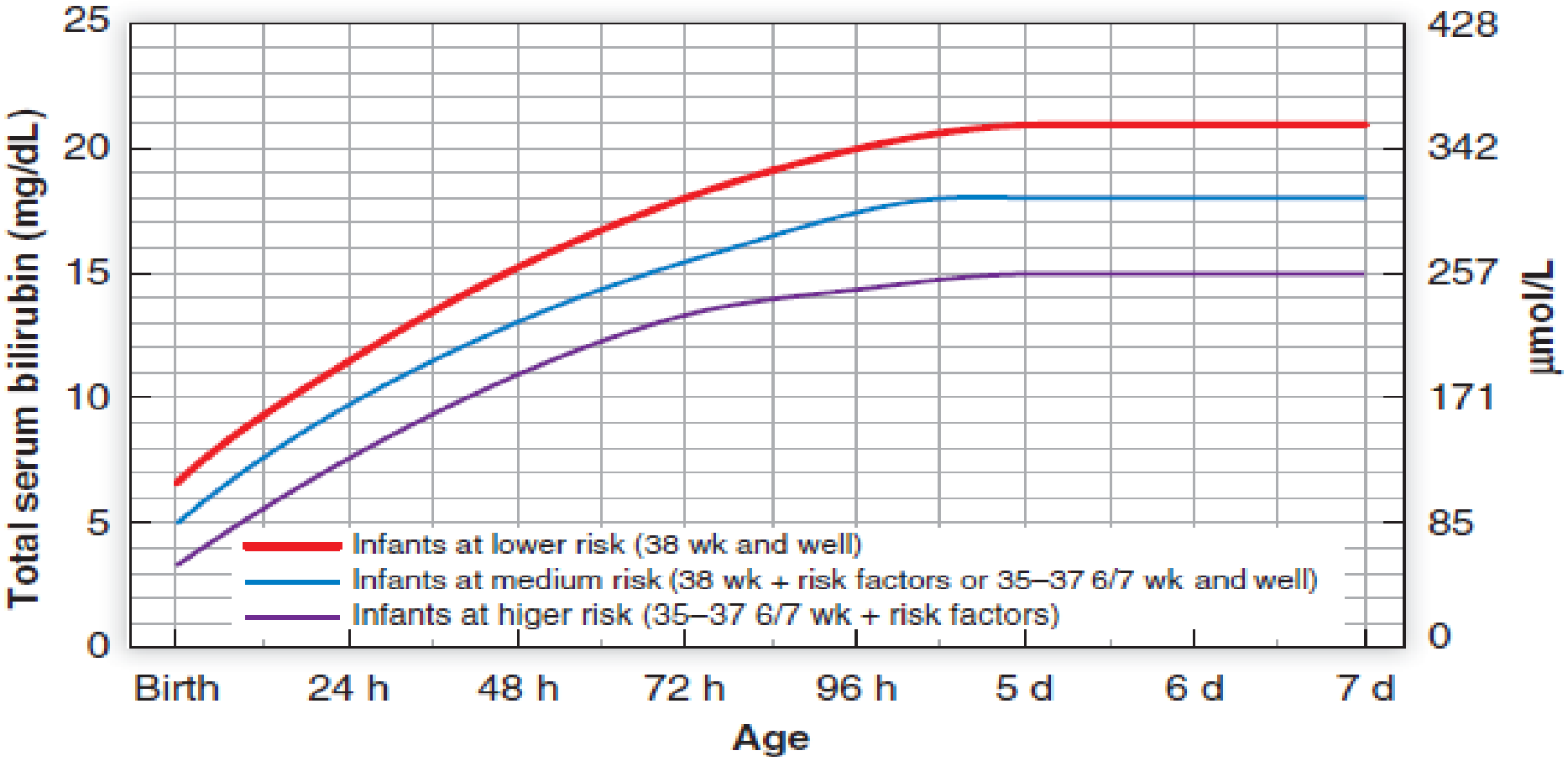
- **Mechanism of action:**

1. Reduces serum bilirubin level through structural (irreversible) isomerization to lumirubin, which is a more soluble substance that is excreted without conjugation into bile and urine.
2. Photoisomerization (reversible) and photo-oxidation of bilirubin to less toxic and more soluble forms that can be eliminated in bile and urine.

- **Indication.** when it is believed that bilirubin levels reaches the phototherapy levels.

- **Factors influencing effective phototherapy**
  - **Spectrum of light delivered.** The **blue region of the spectrum (460–490 nm).**
  - **Energy output.** Intensity of phototherapy and distance from infant (**best 30–40 cm**).
  - **Surface area exposed.** The infant **should be naked** in servo-controlled incubators **but covering the eyes and genitalia**.


JAUNDICE
PHOTOTHERAPY



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors–isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35–37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

For < 35 wks gestation infants

* Currently no consensus guidelines are available for employing phototherapy or exchange transfusion in preterm babies.

* The proposed TSB cutoffs are arbitary and clinical judgement is needed before phototherapy or exchange transfusion decision making in cases.

Postmenstual age (weeks)	TSB cuttoffs (mg/dl)	
	PHOTOTHERAPY	EXCHANGE TRANSFUSION
< 28 0/7	5 – 6	11 – 14
28 0/7 – 29 6/7	6 – 8	12 – 14
30 0/7 – 31 6/7	8 – 10	13 – 16
32 6/7 – 33 0/7	10 - 12	15 – 18
34 0/7 – 34 6/7	12 - 14	17 - 19

Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Phototherapy

Side effects.

- Phototherapy is relatively safe and easy to use.

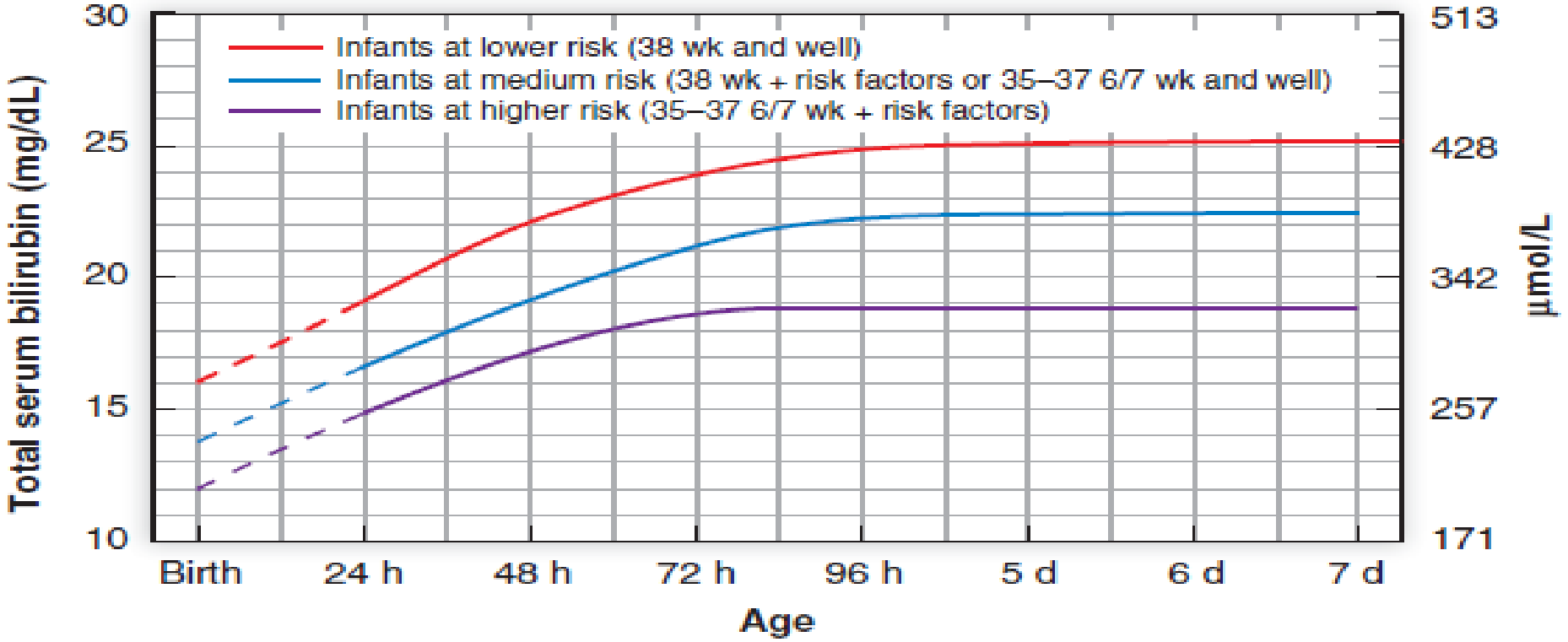
1. Minor side effects include **macular rashes, dehydration, loose stools and overheating**.
2. **Bronze baby syndrome.** With conjugated hyperbilirubinemia.
3. **Congenital erythropoietic porphyria** in which phototherapy is contraindicated. Exposure produces severe bullous lesions on exposed skin and may lead to death.
4. **Retinal and corneal effects.** Retinal degeneration may occur. Eye shields must be used.
5. **No Potential long-term effects** .

Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Exchange transfusion.

- **Double volume exchange (DVET)** is replacing the neonatal blood volume twice, leaving the volume the same.

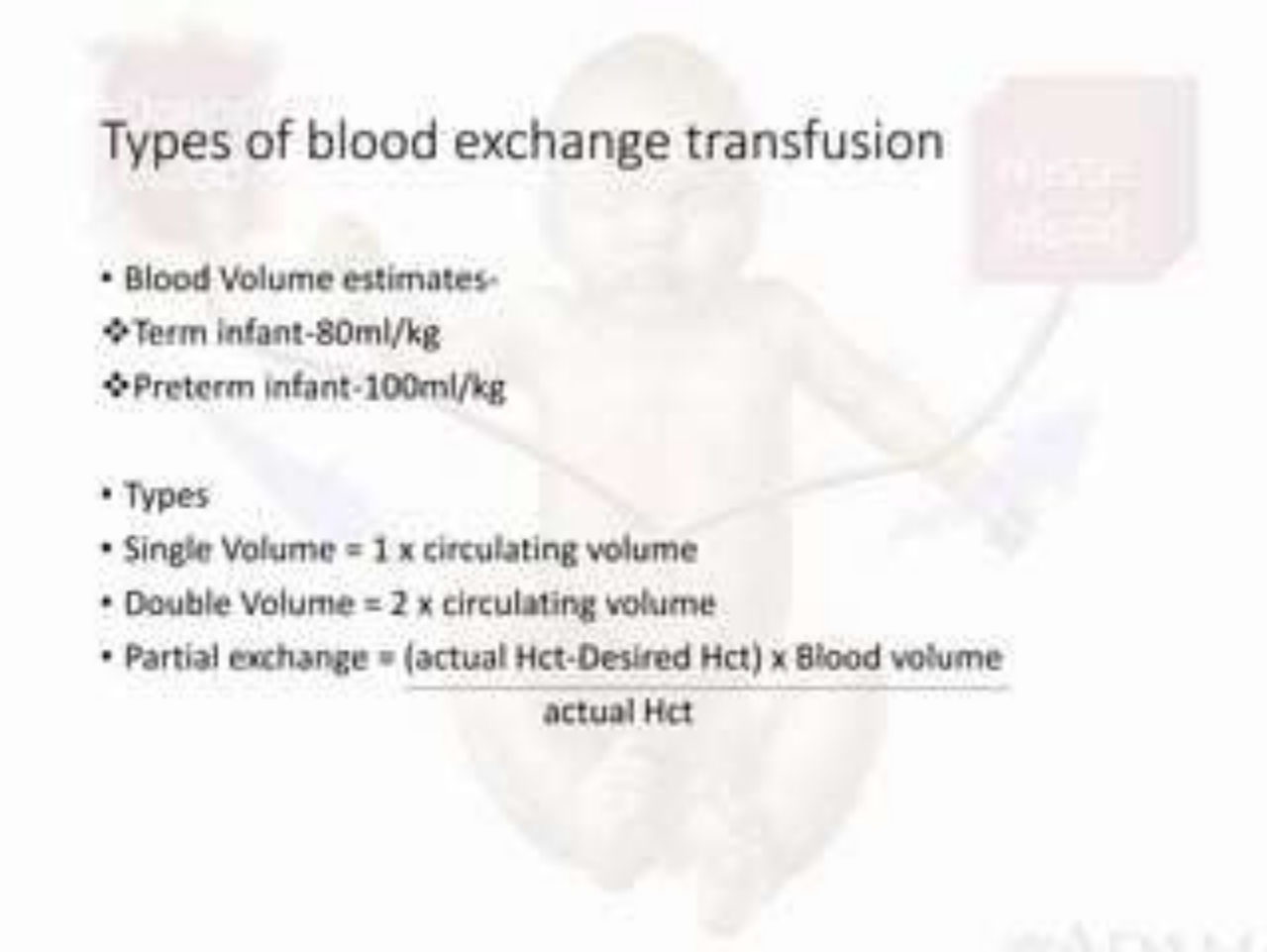
- **Indications**:
  1. **There is evidence of an ongoing hemolytic process** and high TSB (exchange threshold) **failed to decline by 1 to 2 mg/dL with 4 to 6 hours of intensive phototherapy**.
  2. **Rate of rise** indicates that the level will reach 25 mg/dL within 48 hours.
  3. **High concentration of total serum bilirubin and early signs of bilirubin encephalopathy**.
  4. **Ongoing Hemolysis causing anemia and hydrops fetalis**.



- The dashed lines for the first 24 h indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is 5 mg/dL (85 µmol/L) above these lines.
- Risk factors: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.

Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy.

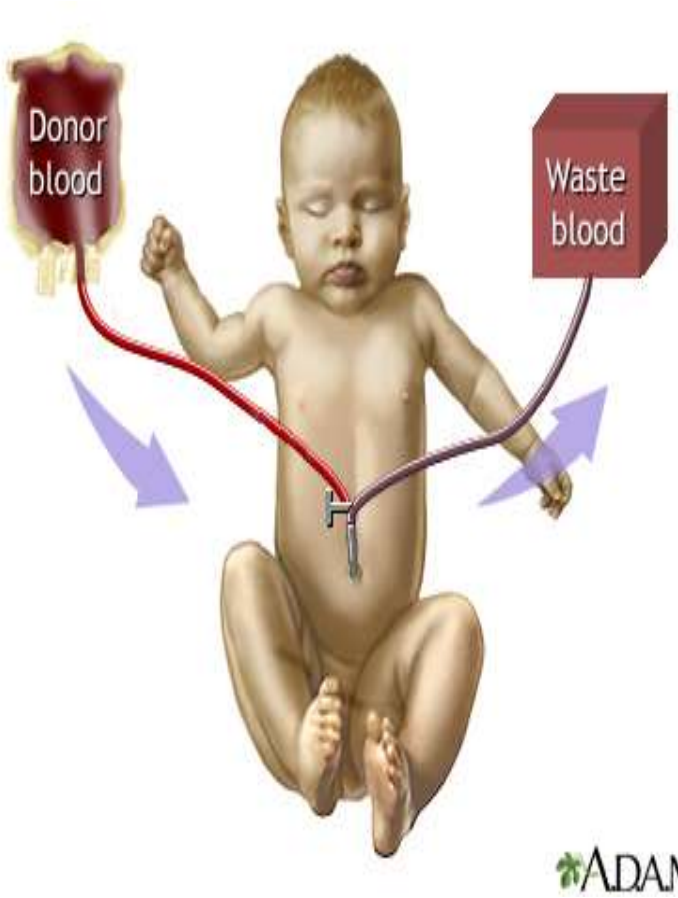
Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.



Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Exchange transfusion.

- **General guidelines for exchange transfusion**
  - **Generally, type O Rh-negative blood** is used for ABO or Rh incompatibility.
  - **Donor blood must always be crossmatched with maternal serum**, **CMV negative, irradiated**, **warmed (37 C) and fresh (<4 days)**
  - **Make the NPO.**
  - **Continuous cardiac monitor during the procedure**
  - **Continue phototherapy during the procedure.**
  - **Consider calcium gluconate** during the exchange because citrate chelates calcium.



Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Exchange transfusion.

- **Post procedure care.**
  - Repeat **Total and direct bilirubin, Na, K, Ca and CBC immediately** with strict **glucose montoring**.
  - **Rebound increase in TSB is expected** as bilirubin in tissues "migrates" back into circulation.
  - **Resume feeding after 4-6 hours**.

- **Adverse events.**

1. Bloodborne infections (eg, cytomegalovirus)
2. Thrombocytopenia and coagulopathy
3. Graft-versus-host disease
4. Necrotizing enterocolitis
5. Portal vein thrombosis
6. Electrolyte abnormalities (eg, hypocalcemia and hyperkalemia)
7. Cardiac arrhythmias

Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Pharmacologic therapy

1. Phenobarbital

- **increases the concentration of ligandin in liver cells, inducing production of UDPGT and enhancing bilirubin excretion**.
- It is used for treatment of **CNS-II and Gilbert syndrome**.
- It takes 3 to 7 days to be effective
- it is **not helpful in acute management**.

Management of indirect hyperbilirubinemia in infants ≥ 35 weeks' gestation.

Pharmacologic therapy

2. Albumin.

- **Neurotoxicity is caused by the unconjugated bilirubin not bound to albumin** (**free bilirubin**).
- Administration of intravenous albumin (1 g/kg over 2–3 hours) increases bilirubin-binding capacity, resulting in reduced free bilirubin.
- Albumin infusion may be considered **when albumin level is <3.0 g/dL, when TSB/albumin ratio is >6, and prior to DVET**.

3. Intravenous γ-globulin. (IVIG)

- works by **competing with sensitized neonatal RBCs at the Fc receptors** in the reticuloendothelial system thus **preventing further hemolysis**.
- It is recommended **in patients with isoimmune hemolysis when TSB is rising despite intensive phototherapy**.
- Dose is 1 g/kg given over 2 to 4 hours; it can be repeated if needed in 12 to 24 hours (2 doses).

Prognosis

- Outcome of hyperbilirubinemia is generally excellent, with minimal to no additional risk of adverse outcome if identified and treated appropriately.

- Unconjugated bilirubin in high concentration can cross the blood–brain barrier and lead to neuronal dysfunction and death.

Prognosis

Encephalopathy

1. Transient.

- Early (Bilirubin Induced Neural Damage) BIND is transient and reversible.

Prognosis

Encephalopathy

2. Acute bilirubin encephalopathy

- It is a **preventable** neurologic sequela of untreated severe hyperbilirubinemia.
- The major clinical features involve disturbances in level of consciousness, tone and movement, and brainstem function, especially relating to feeding and cry.
- The severity correlates with both the **severity and duration of hyperbilirubinemia**.

a. Initial phase.

- Initial phase is noted by **lethargy**, **hypotonia**, **decreased movement, and poor suck**.
- Clinical findings are nonspecific.

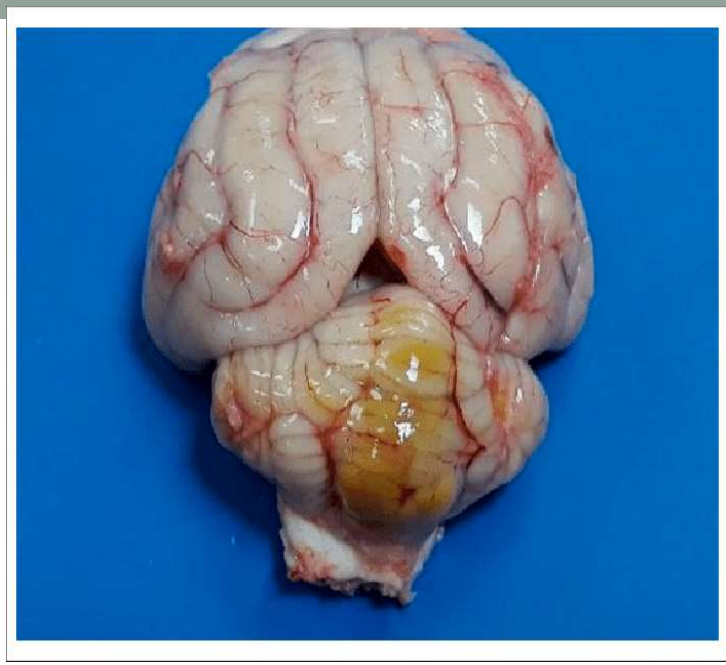
b. Intermediate phase

- It has cardinal signs of **moderate stupor**, **irritability, Fever, and increased tone**.
- Infant may exhibit backward arching of the **neck (retrocollis) or of the back (opisthotonos).**

c. Advanced phase

- It is characterized by **deep stupor or coma**, **increased tone, Seizures**, **inability to feed, and a shrill cry**.
- Suggesting **irreversible** central nervous system injury and the later development of chronic bilirubin encephalopathy (kernicterus) in most infants.

Prognosis



Encephalopathy

3. Chronic bilirubin encephalopathy (kernicterus)

- It is characterized by the following **clinical**:
  1. choreoathetoid cerebral palsy;
  2. high-frequency sensorineural hearing loss;
  3. palsy of vertical gaze;
  4. dental enamel hypoplasia.
  5. Mental retardation.

- **Kernicterus** is a pathologic diagnosis, describing the yellow discoloration of the deep nuclei of the brain.
  1. **Mildly affected** individuals remain highly functional;
  2. **Moderately affected** individuals have more prominent dystonia and are likely to have athetoid movements.
  3. **Severely affected** individuals have speech difficulty and a more disabling dystonia to the point of not being ambulatory.

- This is a form of **static encephalopathy**, in which the degree of disability may change slightly over time but only within limits and never dramatically.

THANK YOU