# NEONATAL HYPERBILIRUBENEMIA

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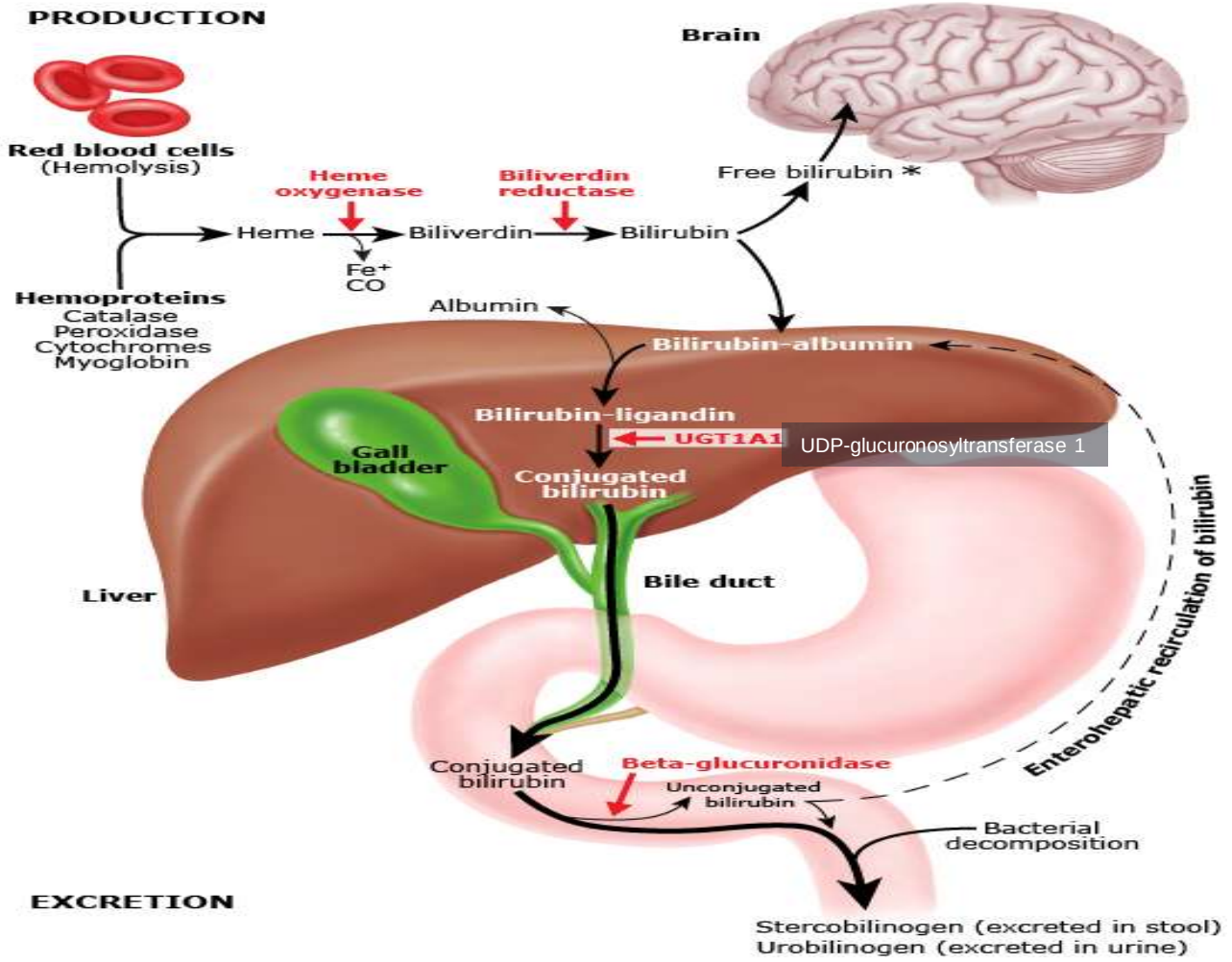
# Definition

- In most infants <u>unconjugated hyperbilirubinemia</u> reflects a **normal transitional** phenomenon (is neurotoxic (fat soluble)), **Conjugated hyperbilirubinemia is always pathologic**

- Neonatal physiologic jaundice results from:
  1. **Bilirubin** is elevated because of increased breakdown of fetal erythrocytes (short lifespan)
  2. **Hepatic**
     - A. low concentrations of ligandin
     - B. low activity of glucuronyl transferase (bind bilirubin to glucuronic acid -> water souble)

- physiologic jaundice 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.



# Pathophysiology

**“Physiologic” unconjugated hyperbilirubinemia.**

A. **Term neonates =** presenting at **72 to 96 hours of age with TSB levels of 10 to 14 mg/dL**

B. **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

**Exclusion criteria for diagnosis of “physiologic” jaundice = pathological**

1. **Jaundice appearing within the first 24 hours of life.**
2. **Jaundice persisting for >2 weeks in full-term infants and >3 weeks in preterms.**
3. **Total serum bilirubin level >95th percentile** for age
4. **Bilirubin level increasing at a rate** >0.2 mg/dL/h or >5 mg/dL/d.
5. **Direct serum bilirubin level** >1.0 mg/dL if the total serum bilirubin is ≤5 mg/dL or >20% of the TSB.

TSB = Total serum bilirubin levels

# 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 = adequate lactation**

## Late-onset Breast milk jaundice.

- **Prolonged indirect hyperbilirubinemia** 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**

# Disorders of production

## A. Immune-mediated hemolytic disease

**is the most common cause of pathologic hyperbilirubinemia in the newborn period**

**Hemolytic disease of the fetus and newborn** — Also called erythroblastosis fetalis.

| | Rh hemolytic disease | ABO hemolytic disease |
|---|---|---|
| INTERACTION | Rh ⊖ pregnant patient; Rh ⊕ fetus. | Type O pregnant patient; type A or B fetus. |
| MECHANISM | First pregnancy: patient exposed to fetal blood (often during delivery) → formation of maternal anti-D IgG. Subsequent pregnancies: anti-D IgG crosses placenta → attacks fetal and newborn RBCs → hemolysis. | Preexisting pregnant patient anti-A and/or anti-B IgG antibodies cross the placenta → attack fetal and newborn RBCs → hemolysis. |
| PRESENTATION | Hydrops fetalis, jaundice shortly after birth, kernicterus. | Mild jaundice in the neonate within 24 hours of birth. Unlike Rh hemolytic disease, can occur in firstborn babies and is usually less severe. |
| TREATMENT/PREVENTION | Prevent by administration of anti-D IgG to Rh ⊖ pregnant patients during third trimester and early postpartum period (if fetus Rh ⊕). Prevents maternal anti-D IgG production. | Treatment: phototherapy or exchange transfusion. |

# Pathophysiology

**B. Red blood cell enzyme deficiencies**

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

**2. Pyruvate kinase deficiency**

**C. Red blood cell membrane defects**

**1. Hereditary spherocytosis (HS).**

- The **incubated osmotic fragility test** is considered the gold standard for making the definitive diagnosis

**2. Hereditary elliptocytosis**

**D. Hemoglobinopathies =** not present in the newborn period.

**E. Infection =** more common clinical manifestations of urinary tract infection.

**F. Increased erythrocyte load**

1. Blood sequestration
2. Polycythemia.
3. Infants of diabetic mothers

## Disorders of bilirubin clearance

### Crigler-Najjar syndrome type I.

1. absence of hepatic UDPGT activity.
2. TSB is commonly >20 mg/dL.
3. unresponsive to phenobarbital therapy

### Crigler-Najjar syndrome type II ,

1. more common than CNS-I and typically benign.
2. decreased but not totally absent UDPGT enzyme activity.
3. TSB rarely exceeds 20 mg/dL.
4. response to phenobarbital therapy and bile analysis

### Gilbert syndrome

1. mild, lifelong, unconjugated hyperbilirubinemia, no hemolysis or liver disease.
2. Hepatic glucuronidation activity is 30% of normal

# Pathophysiology

### Metabolic and endocrine disorders

**A. Galactosemia.**

- *first week* of life is almost always unconjugated, → conjugated during the *second week*, reflective of developing liver disease.

**B. Hypothyroidism.**

- It is due to a deficient activity of UDPGT.
- Early-onset hyperbilirubinemia
- Treatment with thyroid hormone

### Increased enterohepatic circulation of bilirubin

**A. Conditions that cause GIT obstruction** (eg, pyloric stenosis, duodenal atresia, annular pancreas)

**B. Breast-feeding jaundice and breast milk jaundice.**

### Substances affecting binding of bilirubin to albumin.

- drugs occupy bilirubin-binding sites on albumin (aspirin, ceftriaxone, 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.**

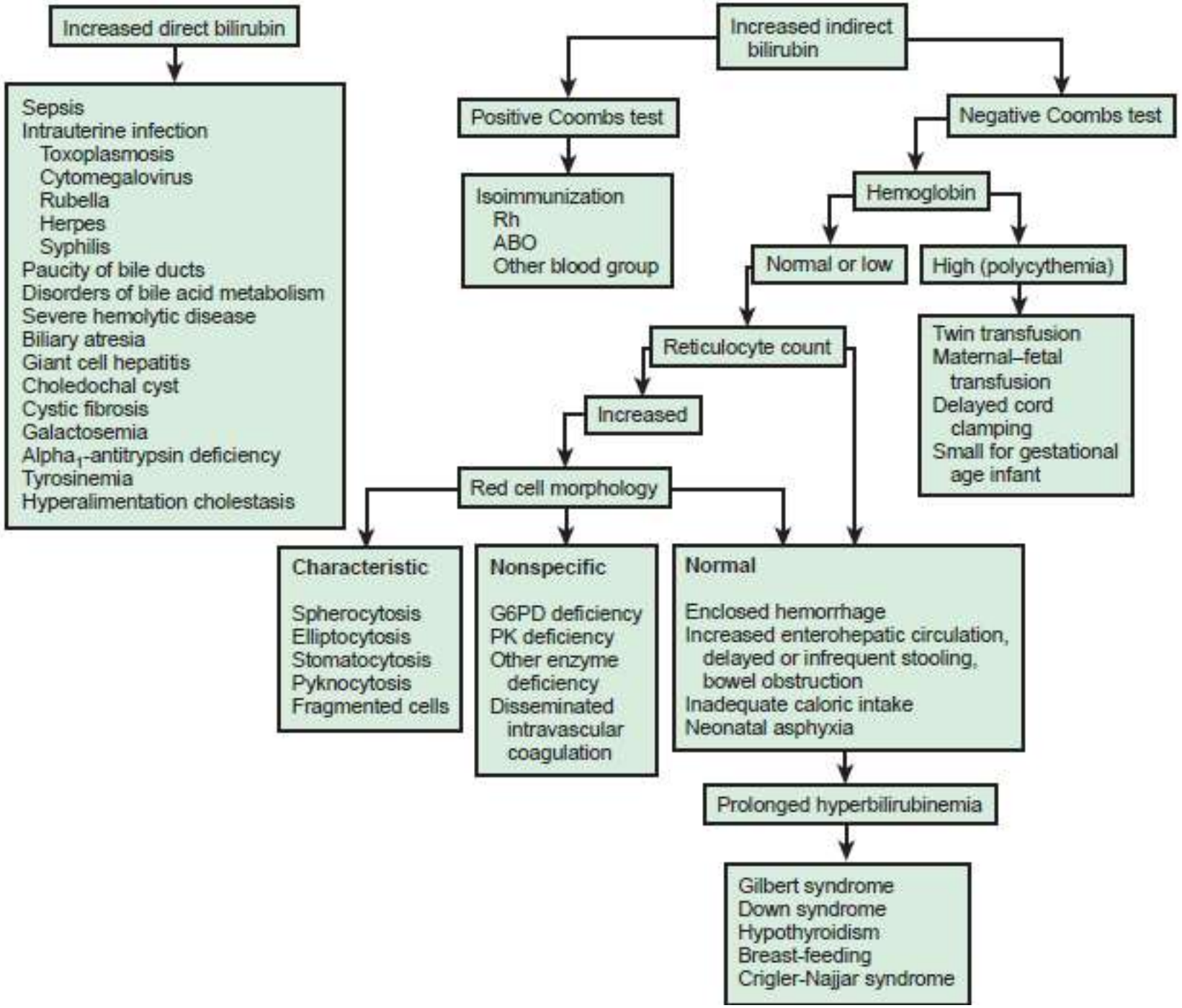
- Jaundice is **clinically visible when the serum bilirubin level approaches 5 mg/dL**. → Sclera icterus → **Progression is cephalocaudal** (head to toe)

## Clinical history.

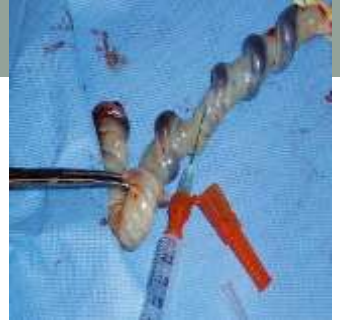
1. Gestational age.
2. Mother and baby blood group.
3. Family history of jaundice, anemia, splenectomy, or metabolic disorder is significant and may suggest underlying etiology for jaundice.
4. Maternal history of infection or diabetes
5. Breast feeding and factors affecting normal gastrointestinal function

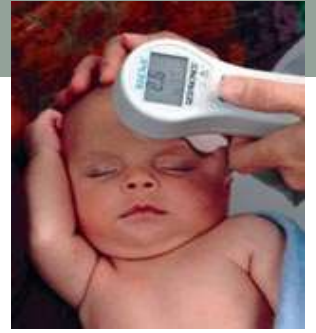
## Physical examination.

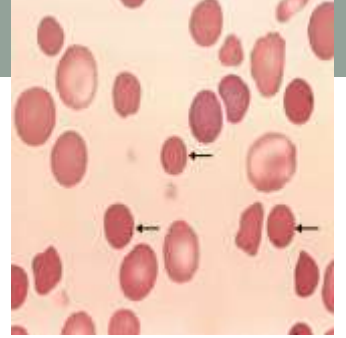
- **Weight**
- Areas of bleeding such as **cephalhematoma, petechiae, or ecchymoses** indicate blood extravasations.
- **Hepatosplenomegaly** may signify hemolytic disease, liver disease, or infection.
- Physical signs of **prematurity, plethora** with polycythemia, **pallor** with hemolytic disease, and macrosomia with maternal diabetes all can be associated with jaundice.
- **Signs of infections = Omphalitis, chorioretinitis, microcephaly, petechiae, and purpuric lesions**
- **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**.


Increased direct bilirubin
Sepsis
Intrauterine infection
Toxoplasmosis
Cytomegalovirus
Rubella
Herpes
Syphilis
Paucity of bile ducts
Disorders of bile acid metabolism
Severe hemolytic disease
Biliary atresia
Giant cell hepatitis
Choledochal cyst
Cystic fibrosis
Galactosemia
Alpha1-antitrypsin deficiency
Tyrosinemia
Hyperalimentation cholestasis
Increased indirect bilirubin
Positive Coombs test
Isoimmunization
Rh
ABO
Other blood group
Negative Coombs test
Hemoglobin
Normal or low
High (polycythemia)
Twin transfusion
Maternal–fetal transfusion
Delayed cord clamping
Small for gestational age infant
Reticulocyte count
Increased
Red cell morphology
Characteristic
Spherocytosis
Elliptocytosis
Stomatocytosis
Pyknocytosis
Fragmented cells
Nonspecific
G6PD deficiency
PK deficiency
Other enzyme deficiency
Disseminated intravascular coagulation
Normal
Enclosed hemorrhage
Increased enterohepatic circulation, delayed or infrequent stooling, bowel obstruction
Inadequate caloric intake
Neonatal asphyxia
Prolonged hyperbilirubinemia
Gilbert syndrome
Down syndrome
Hypothyroidism
Breast-feeding
Crigler-Najjar syndrome

# 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**

**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**:

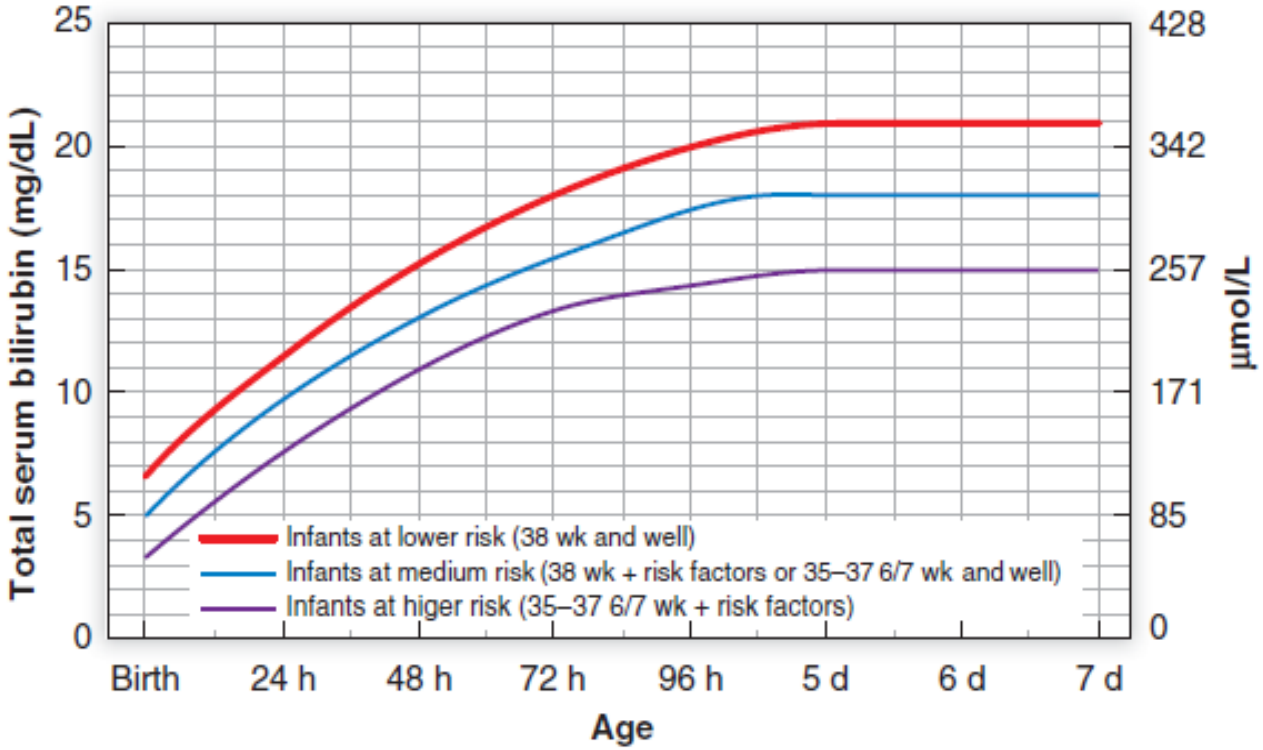
Ultrasonography of the liver and bile ducts is warranted in infants with laboratory or clinical signs of cholestatic disease.

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

## Phototherapy

- **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**.




- 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.

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

## Phototherapy

**Side effects.**

- Phototherapy is relatively safe and easy to use.

1. **macular rashes, dehydration, loose stools and overheating**.
2. **Bronze baby syndrome.**
3. **Congenital erythropoietic porphyria**
4. **Retinal and corneal effects**
5. **No Potential long-term effects** .

## Exchange transfusion.

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

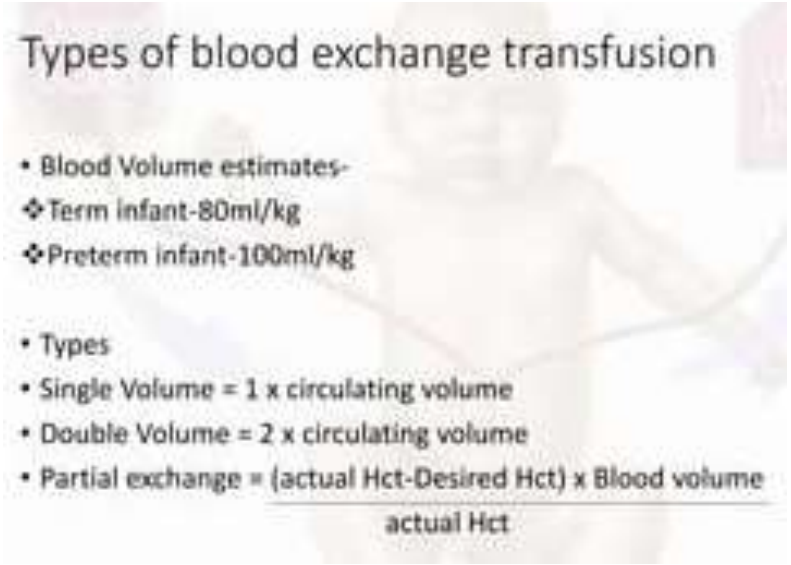
- **Indications**:
  1. **There is evidence of an ongoing hemolytic process** and high TSB (exchange threshold) **failed to decline by 1 to 2 mg/dL with 4 to 6 hours of intensive phototherapy**.
  2. **Rate of rise** indicates that the level will reach 25 mg/dL within 48 hours.
  3. **High concentration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

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

## Exchange transfusion.

- **Adverse events.**

1. Blood borne infections (eg, cytomegalovirus)
2. Thrombocytopenia and coagulopathy
3. Electrolyte abnormalities (eg, hypocalcemia and hyperkalemia)
4. Cardiac arrhythmias




## Pharmacologic therapy

### 1. Phenobarbital

- **increases the concentration of ligandin in liver cells,**
- It is used for treatment of **CNS-II and Gilbert syndrome**.
- it is **not helpful in acute management**.

### 2. Albumin.

- **Neurotoxicity is caused by the unconjugated bilirubin not bound to albumin (free bilirubin).**

### 3. Intravenous γ-globulin. (IVIG)

- **in patients with isoimmune hemolysis when TSB is rising despite intensive phototherapy.**

# Prognosis of hyperbilirubinemai

## Encephalopathy

**1. Transient =** Early (Bilirubin Induced Neural Damage) BIND is transient and reversible.

**2. Acute bilirubin encephalopathy =** It is a **preventable** neurologic sequela, The severity depend on both the **severity and duration of hyperbilirubinemia**.

**a. Initial phase = lethargy, hypotonia, decreased movement, and poor suck**.

**b. Intermediate phase =** It has cardinal signs of **moderate stupor, irritability, Fever, and increased tone**.

- backward arching of the **neck (retrocollis) or of the back (opisthotonos).**

**c. Advanced phase (irreversible) = deep stupor or coma, increased tone, Seizures, inability to feed, and a shrill cry**.

**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.