Jaundice and Hyperbilirubinemia in the Newborn

Introduction

- Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st wk of life 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.

- Although bilirubin may have a physiologic role as an antioxidant, elevated levels of indirect, unconjugated bilirubin are potentially neurotoxic.
- Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates potentially serious hepatic disorders or systemic illnesses.

ETIOLOGY:.

(1) Increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, shortened red cell life as a result of immaturity or transfused cells, increased enterohepatic circulation, infection);

(2) Damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency);

(3) Competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation); or

(4) Absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, and prematurity).

Factors that reduce the retention of bilirubin in the circulation :

1- Hypoproteinemia.

2- Displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam.

3- Chuen-Lin herbal tea.

4- Acidosis.

5- Increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia.

Neurotoxic effects adversely influenced by :-

- Asphyxia, prematurity, hyperosmolality, and infection.
- Early and frequent feeding decreases whereas breast-feeding and dehydration increase serum levels of bilirubin.
- Delay in passage of meconium,increases the enterohepatic circulation after deconjugation by intestinal glucuronidase.
- Drugs such as oxytocin and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia

Major Risk Factors for Development of Severe Hyperbilirubinemia

Predischarge TSB or TcB level in the high-risk zone
Jaundice observed in the first 24 hr
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race

Minor Risk Factors for Development of Severe Hyperbilirubinemia

Predischarge TSB or TcB level in the intermediate-risk zone
Gestational age 37–38 wk
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a diabetic mother
Maternal age ≥25 yr
Male gender

Laboratory Evaluation of the Jaundiced Infant

INDICATIONS	ASSESSMENTS
Jaundice in first 24 hr	Measure TcB and/or TSB
Jaundice appears excessive for age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly and unexplained by history and physical examination.	Blood type and Coombs test
	CBC& smaer,TSB &Direct bilirubin
	Reticulocyte count, G6PD
	Repeat TSB in 4–24 hr.
TSB approaching exchange evels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin.
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture. Evaluate for sepsis if suspected clinicaly.
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level
	If direct bilirubin elevated, look for the causes.
	Check the thyroid and galactosemia screen.

DIFFERENTIAL DIAGNOSIS

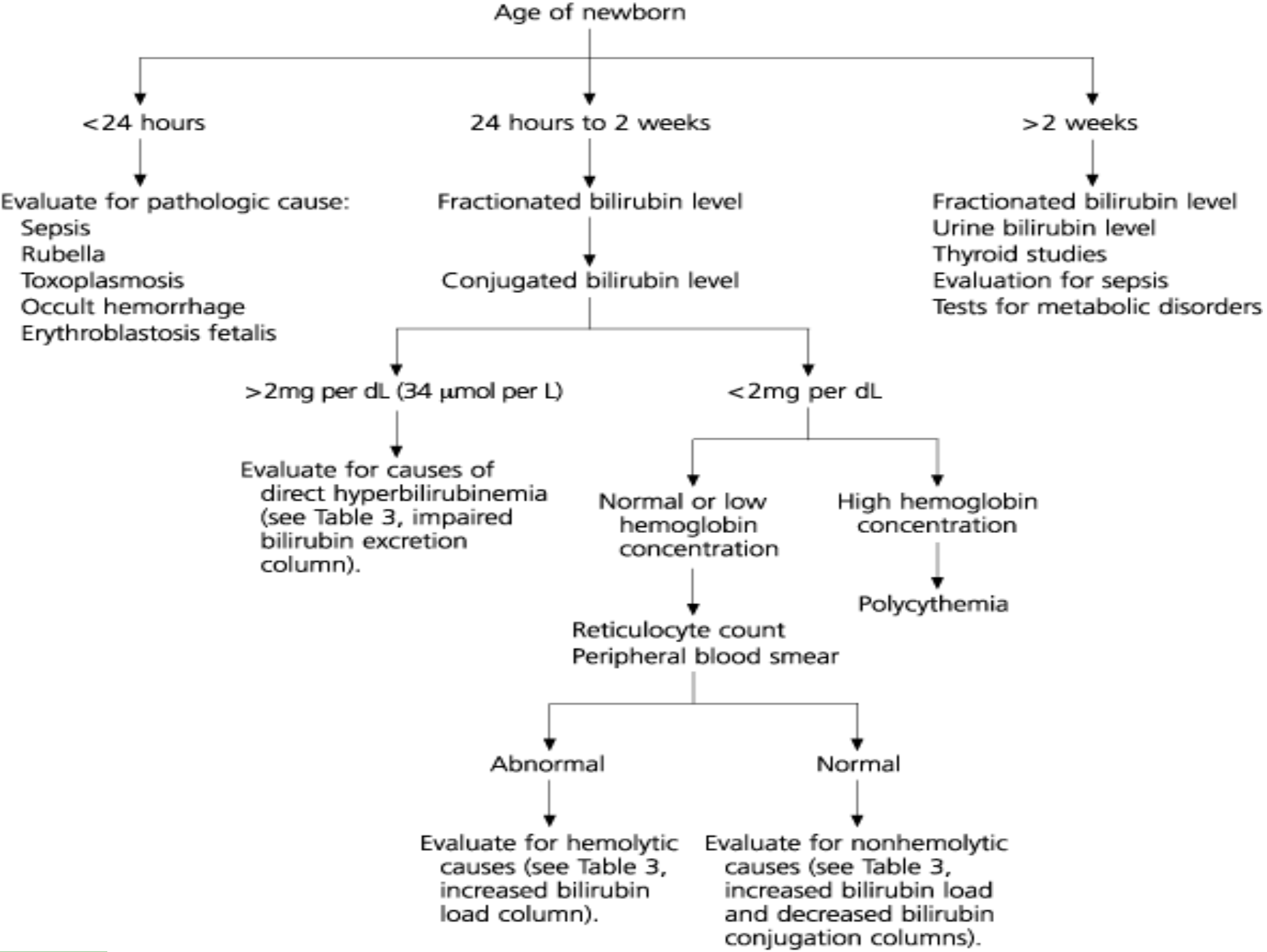
Jaundice that is present at birth or appears within the 1st 24 hr of life:

1- Erythroblastosis fetalis.

2- Concealed hemorrhage.

3- Sepsis.

4-Congenital infections, including syphilis, cytomegalovirus, rubella, and toxoplasmosis


Age of newborn
<24 hours
24 hours to 2 weeks
>2 weeks
Evaluate for pathologic cause:
Sepsis
Rubella
Toxoplasmosis
Occult hemorrhage
Erythroblastosis fetalis
Fractionated bilirubin level
Conjugated bilirubin level
Fractionated bilirubin level
Urine bilirubin level
Thyroid studies
Evaluation for sepsis
Tests for metabolic disorders
>2mg per dL (34 µmol per L)
<2mg per dL
Evaluate for causes of direct hyperbilirubinemia (see Table 3, impaired bilirubin excretion column).
Normal or low hemoglobin concentration
High hemoglobin concentration
Polycythemia
Reticulocyte count
Peripheral blood smear
Abnormal
Normal
Evaluate for hemolytic causes (see Table 3, increased bilirubin load column).
Evaluate for nonhemolytic causes (see Table 3, increased bilirubin load and decreased bilirubin conjugation columns).

Hemolytic jaundice

Hemolysis is suggested by:-

1-Rapid rise in serum bilirubin (>0.5 mg/dL/hr).

2-Anemia.

3-Pallor.

4-Reticulocytosis.

5-Hepatosplenomegaly.

6-Positive family history.

Jaundice that 1st appears on the 2nd or 3rd day:

1-**Physiological jaundice.**

2-Familial non-hemolytic icterus **(Crigler-Najjar syndrome)** .

3-Early-onset breast-feeding jaundice are seen initially on the 2nd or 3rd day

Jaundice appearing after the 3rd day and within the 1st wk :-

1-bacterial sepsis.

2-Urinary tract infection.

3-Jaundice secondary to extensive ecchymosis or blood extravasation .

Jaundice 1st recognized after the 1st wk of life:

1-breast-milk jaundice.

2-Septicemia.

3-Congenital atresia or paucity of the bile ducts.

4-Hepatitis.

5-Galactosemia.

6-Hypothyroidism.

7- Cystic Fibrosis.

8-Congenital hemolytic anemia crises related to red cell morphology and enzyme deficiencies.

Persistent jaundice during the 1st mo of life

1-Hyperalimentation-associated cholestasis.
2-Hepatitis.
3-Cytomegalic inclusion disease.
4-Syphilis.
5-Toxoplasmosis.
6-Familial non-hemolytic icterus.
7-Congenital atresia of the bile ducts.
8-Galactosemia.
9-Inspissated bile syndrome following hemolytic disease of the newborn.
10-Rarely, physiologic jaundice may be prolonged for several wk, as in infants with hypothyroidism or pyloric stenosis.

PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)

- bilirubin in umbilical cord serum is 1–3 mg/dL and rises at a rate of <5 mg/dL/24 hr.
- jaundice becomes visible on the 2nd–3rd day, usually peaking between the 2nd and 4th days at 5–6 mg/dL and decreasing to below 2 mg/dL between the 5th and 7th days of life.

- physiologic is the result of increased bilirubin production from the breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

- 6–7% of full-term infants have indirect bilirubin levels >12.9 mg/dL and less than 3% have levels >15 mg/dL .

EJAUNDICE ASSOCIATED WITH BREAST-FEEDING

- 2% of breast-fed term infants after the 7th day of life.
- maximal concentrations as high as 10–30 mg/dL reached during the 2nd–3rd week .
- If breast-feeding is continued, the bilirubin gradually decreases but may persist for 3–10 wk at lower levels .
- If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal levels within a few days .
- With resumption of breast-feeding, bilirubin levels seldom return to previously high levels.

- Phototherapy may be of benefit
- Although uncommon, kernicterus can occur in patients with breast-milk jaundice.
- The etiology of breast-milk jaundice is not entirely clear, but may be attributed to the presence of glucuronidase in some breast milk.

Unconjugated hyperbilirubinemia known as breast-feeding jaundice

- occurs in the 1st week of life, in breast-fed infants .
- normally have higher bilirubin levels than formula-fed infants .
- Hyperbilirubinemia (>12 mg/dL) develops in 13% of breast-fed infants in the 1st wk of life.
- may be due to decreased milk intake with dehydration and/or reduced caloric intake.

- Giving supplements of glucose water to breast-fed infants is associated with higher bilirubin levels, in part because of reduced intake of the higher caloric density of breast milk.
- Frequent breast-feeding (>10/24 hr), rooming-in with night feeding, discouraging 5% dextrose or water supplementation, and ongoing lactation support may reduce the incidence of early breast-feeding jaundice.


A


B

Kernicterus

- bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei .
- Disruption of the blood-brain barrier by disease, asphyxia, and other factors and maturational changes in blood-brain barrier permeability affect risk.
- kernicterus is rare in healthy term infants and in the absence of hemolysis if the serum level is <25 mg/dL

- Onset is usually in the 1st wk of life, but may be delayed to the 2nd–3rd wk .
- The duration of exposure needed to produce toxic effects is unknown .
- the more immature the infant is the greater the susceptibility to kernicterus .

CLINICAL MANIFESTATIONS

ACUTE FORM

Phase 1 (1st 1–2 days): poor sucking, stupor, hypotonia, seizures.

Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever

Phase 3 (after the 1st wk): hypertonia

CHRONIC FORM

First year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills.

After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

INCIDENCE AND PROGNOSIS

- kernicterus will develop in ⅓ of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25–30 mg/dL.

- Neurologic signs have a grave prognosis; more than 75% of such infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common .

PREVENTION

- Protocols using the hour-specific bilirubin nomogram.
- Physical examination.
- Clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management.

preventable causes of kernicterus:

(1) early discharge (<48 hr) with no early follow-up (within 48 hr of discharge); this problem is particularly important in near-term infants (35–37 wk gestation).

(2) failure to check the bilirubin level in an infant noted to be jaundiced in the 1st 24 hr.

(3) failure to recognize the presence of risk factors for hyperbilirubinemia.

(4) underestimation of the severity of jaundice by clinical (visual) assessment.

(5) lack of concern regarding the presence of jaundice.

(6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels.

(7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy.

TREATMENT OF HYPERBILIRUBINEMIA

- Regardless of the cause, the goal of therapy is to prevent indirect-reacting bilirubin related neurotoxicity .
- Phototherapy and, if unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below the pathologic levels.
- Because phototherapy may require 6–12 hr to have a measurable effect, it must be started at bilirubin levels below those indicated for exchange transfusion

- Underlying medical causes of elevated bilirubin should be treated (antibiotics for septicemia and correction of acidosis).

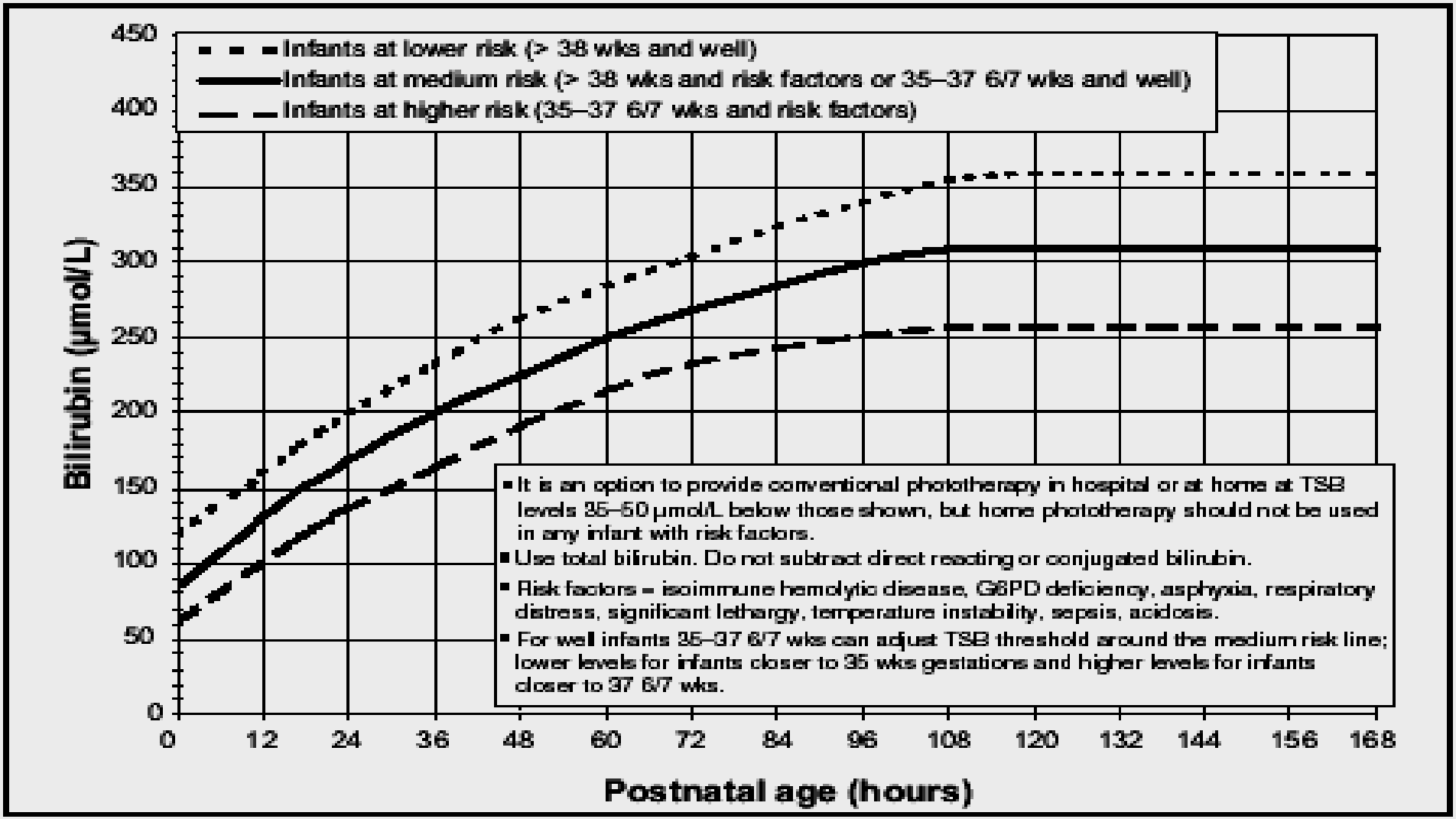


Figure 2) *Guidelines for intensive phototherapy in infants of 35 or more weeks' (wk) gestation. These guidelines are based on limited evidence and the levels shown are approximations. Intensive phototherapy should be used when the total serum bilirubin (TSB) concentration exceeds the line indicated for each category. G6PD Glucose-6-phosphate dehydrogenase*

Phototherapy

- Bilirubin absorbs light maximally in the blue range (420–470 nm).
- Photo-isomerization reaction converting the toxic native unconjugated 4Z, 15Z-bilirubin into an unconjugated configurational isomer 4Z,15E-bilirubin, which can then be excreted in bile without conjugation.
- A major product from phototherapy is lumirubin, which is converted from native bilirubin and can be excreted by the kidneys in the unconjugated state.

Phototherapy

1-The light energy emitted in the effective range of wavelengths.

2-The distance between the lights and the infant(30cm).

3-The surface area of exposed skin.

4-The rate of hemolysis and in vivo metabolism and excretion of bilirubin.

5-Dark skin does not reduce the efficacy of phototherapy.

6-Phototherapy is contraindicated in the presence of porphyria.

Complications

1-loose stools.

2-Erythematous macular rash.

3-Purpuric rash associated with transient porphyrinemia.

4-Overheating.

5-Dehydration (increased insensible water loss, diarrhea),

6-Hypothermia from exposure.

7-A benign condition called *bronze baby syndrome.*

bronze baby syndrome

- Grayish-brown skin discoloration in infants undergoing phototherapy .
- Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease.
- Due to photo-induced modification of porphyrins, which are often present during cholestatic jaundice.
- Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immunoglobulin

- Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions including phototherapy.

- Intravenous immunoglobulin (0.5–1.0 g/kg/dose; repeat in 12 hr) has been shown to reduce the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.

Metalloporphyrins:

- The metalloporphyrin Sn-mesoporphyrin (SnMP) offers promise as a drug candidate .
- The proposed mechanism of action is by competitive enzymatic inhibition of the rate limiting conversion of heme-protein to biliverdin .
- A single intramuscular dose on the 1st day of life may reduce the need for phototherapy .
- Complications from metalloporphyrins include transient erythema if the infant is receiving phototherapy

Exchange Transfusion

- Double volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels.
- The appearance of clinical signs suggesting kernicterus is an indication for exchange transfusion at any level of serum bilirubin.
- A healthy full-term infant with physiologic or breast-milk jaundice may tolerate a concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level.

Complications from exchange transfusion

- Metabolic acidosis.
- Electrolyte abnormalities.
- Hypoglycemia.
- Hypocalcemia.
- Thrombocytopenia.
- Volume overload.
- Arrhythmias.
- NEC (necrotizing enterocolotis).
- Infection.
- Graft versus host disease.