

Jaundice in the Newborns

Satish Mishra, Ramesh Agarwal, Ashok K Deorari, Vinod K Paul

Division of Neonatology, Department of Pediatrics

All India Institute of Medical Sciences

Ansari Nagar, New Delhi –110029

Address for correspondence:

Dr Ashok Deorari

Professor

Department of Pediatrics

All India Institute of Medical Sciences

Ansari Nagar, New Delhi 110029

Email: sdeorari@yahoo.com

Abstract

Hyperbilirubinemia is the commonest morbidity in the neonatal period and 5-10% of all newborns require intervention for pathological jaundice. Neonates on exclusive breast-feeding have a different pattern and degree of jaundice as compared to artificially fed babies.. Latest guidelines from American Academy of Pediatrics (AAP) for management of jaundice in a normal term newborn have been included in the protocol. Separate guidelines have been provided for the management of jaundice in sick term babies, preterm and low birth weight babies, for hemolytic jaundice and prolonged hyperbilirubinemia.

1. Introduction

Jaundice is an important problem in the first week of life. It is a cause of concern for the physician and a source of anxiety for the parents. High bilirubin levels may be toxic to the developing central nervous system and may cause neurological impairment even in term newborns. Nearly 60% of term newborn becomes visibly jaundiced in the first week of life.¹ In most cases, it is benign and no intervention is required. Approximately 5-10 % of them have clinically significant hyperbilirubinemia mandating the use of phototherapy.²⁻³

2. Physiological jaundice

Jaundice attributable to physiological immaturity of neonates to handle increased bilirubin production. Visible jaundice usually appears between 24-72 hours of age. Total serum bilirubin (TSB) level usually rises in full-term infants to a peak of 6 to 8 mg/dL by 3 days of age and then falls. A rise to 12mg/dL is in the physiologic range. In premature infants, the peak may be 10 to 12 mg/dL on the fifth day of life, possibly rising over 15 mg/dL without any specific abnormality of bilirubin metabolism. Levels under 2mg/dL may not be seen until one month of age in both full term and premature infants.⁴ Safe bilirubin levels in preterms vary according to gestational age.⁵

3. Pathological jaundice

TSB concentrations have been defined as non-physiologic if concentration exceeds 5 mg/dl on first day of life in term neonate, 10 mg/dL on second day, or 12-13 thereafter.⁶ Any TSB elevation exceeding 17 mg/dL should be presumed pathologic and warrants investigation for a cause and possible intervention, such as phototherapy.⁷ Appearance of jaundice within 24 hours, peak TSB levels above the expected normal range (Fig. 1)⁸, presence of clinical

jaundice beyond 3 weeks and conjugated bilirubin (dark urine staining the clothes and light colored stool) would be categorized under pathological jaundice.

4. Breast-feeding and jaundice

Exclusively breast-fed infants have a different pattern of physiological jaundice as compared to artificially fed babies.^{7,9,10} Jaundice in breast-fed babies usually appears between 24-72 hours of age, peaks by 5-15 days of life and disappears by the third week of life. They have also been reported to have higher bilirubin levels. Schneider's meta-analysis of 25 studies has shown that 13% of breast-fed babies had peak TSB levels of 12 mg/dL or higher as compared to 4% of artificially fed babies.¹¹ One third of all breast-fed babies are detected to have mild clinical jaundice in the third week of life, which may persist into the 2nd to 3rd month of life in a few babies.

Authors have stated that this increased frequency is not related to characteristics of breast milk but rather to the pattern of breast-feeding. Decreased frequency of breast-feeding is associated with exaggeration of physiological jaundice. Encouraging a mother to breast-feed her baby at least 10-12 times per day would be helpful in the management of jaundice in a term healthy baby.

5. Breast milk jaundice

Approximately 2-4% of exclusively breast-fed term babies have jaundice in excess of 10 mg/dL in the third week of life.^{12,13} These babies with TSB beyond 10 mg/dL after the third week of life should be investigated for prolonged jaundice. A diagnosis of breast milk jaundice should be considered if the TSB is predominantly unconjugated, other causes of prolonged jaundice have been excluded and the infant is in good health. Mothers should be advised to continue breast-feeding frequently intervals and TSB levels usually decline over

a period of time. Interruption of breast-feeding is not recommended unless TSB level exceeds 20 mg/dl.

6. Clinical examination of jaundice

Originally described by Kramer¹⁴, dermal staining of bilirubin may be used as a clinical guide to the level of jaundice. Dermal staining in newborn progresses in a cephalo-caudal direction. The newborn should be examined in good daylight. The skin should be blanched with digital pressure and the underlying color of skin and subcutaneous tissue should be noted. A rough guide for level of dermal staining with level of bilirubin is included in Table 1.

Newborns detected to have yellow discoloration of the skin beyond the legs should have an urgent laboratory confirmation for levels of TSB. Clinical assessment is not very reliable if a newborn has been receiving phototherapy and if the baby has dark skin.

7. Measurement of TSB levels

7.1. Biochemical: Laboratory estimation of TSB based on High Performance Liquid Chromatography (HPLC) remains the gold standard for TSB estimation. However this test is not universally available and laboratory estimation of TSB usually done in labs is based on Vanden Bergh reaction. It usually have marked interlaboratory variability with coefficient of variation up to 10 to 12 percent for TSB and over 20 percent for conjugated fraction.¹⁵

7.2 Micro method for bilirubin estimation: It is based on spectro-photometry and estimates TSB on a micro blood sample. It is useful in neonates, as bilirubin is predominantly unconjugated.

7.3. **Transcutaneous bilirubinometer:** This method is non invasive and based based on reflectance data of multiple wavelengths from the bilirubin stained skin. It averages the spectra of five replicate measurements at one site to give bilirubin estimation in mmol/l (or mg/dl). Transcutaneous bilimeter (TcB) has a linear correlation to TSB and may be useful as a screening device to detect clinically significant jaundice and decrease the need for frequent TSB determinations.¹⁶

8. Clinical approach to jaundice

8.1 Is the newborn term or preterm?

Basic pathophysiology of jaundice is same in term and preterm neonates but at lower gestation babies are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring. TSB values for intervention also vary in term, near-term, and preterm neonates less than 35 weeks period of gestation.

Management of hyperbilirubinemia in preterm infants is still in grey zone for lack of enough objective evidences. Clinical practice guidelines from American Academy of Pediatrics (AAP) applies to the newborn infants of 35 or more weeks of gestation.¹⁷

8.2 Is there evidence of hemolysis?

Setting of Rh or less frequently ABO incompatibility, onset of jaundice within 24 hours, presence of pallor and hydrops, presence of hepato-splenomegaly, presence of hemolysis on the peripheral blood smear, raised reticulocyte count (>8%), rapid rise of bilirubin (>5 mg/dl in 24 hours or >0.5 mg/dl/hr) or a suggestive family history of significant jaundice should raise a suspicion of hemolytic jaundice. However, end-tidal carbon monoxide corrected for ambient carbon monoxide (ETCO_c) levels can confirm the presence or

absence of hemolysis, and measurement of ETCO_c is the only clinical test that provides a direct measurement of the rate of heme catabolism and the rate of bilirubin production.¹⁷

8.3 Does the infant have an underlying serious disease? (sepsis, galactosemia)

Presence of lethargy, poor feeding, failure to thrive, hepato-splenomegaly, temperature instability or apnea may be a marker of an underlying serious disease.

8.4 Does the infant have cholestatic jaundice?

Presence of jaundice (>10 mg/dl) beyond 3 weeks, presence of dark urine (staining the clothes) or pale colored stools would suggest cholestatic jaundice.

9. Jaundice in a term healthy baby

9.1. Advise for physiological jaundice:

The parents should be explained about the benign nature of jaundice. The mother should be encouraged to breast-feed frequently. The newborn should be exclusively breast-fed with no top feeds, water or dextrose water. Mother should be told to bring the baby to the hospital if the baby looks too yellow or yellow discoloration of the skin beyond the legs .

Any newborn discharged prior to 72 hours of life should be evaluated again in the next 48 hours for adequacy of breast-feeding and progression of jaundice.

Clinical judgment should be used in determining follow-up. Earlier or more frequent follow-up should be provided for those who have risk factors for hyperbilirubinemia (table 4).¹⁷

9.2 Management of pathological Jaundice

Any term or near-term newborn noted to have yellow staining of the skin beyond the legs / estimated clinical or TcB in the high risk zone of nomogram should have a confirmatory serum bilirubin level. The American Academy of Pediatrics (AAP)¹⁷ has laid down criteria

for managing babies with bilirubin in the pathological range (Figure 2). Jaundice appearing within 24 hours should be managed as hemolytic jaundice.

All infants with bilirubin levels in the phototherapy range should have the following investigations: blood type and Coombs' test, if not obtained with cord blood (if mother is Rh negative or O group); complete blood count and smear for hemolysis and red blood cell morphology; reticulocyte count and G6PD estimation. These investigations are done to exclude any hemolytic cause of jaundice. Repeat TSB in 4–24 h depending on infant's age and TSB level.

We usually do repeat TSB within 4 to 6 hrs if initial was TSB in or near the exchange transfusion range meanwhile blood is arranged for the exchange transfusion, so that exchange can be done if there is no significant fall in the TSB. In a healthy neonates without setting for hemolytic jaundice and TSB not near exchange range we repeat TSB after 12 to 24 hrs. In Rh isoimmunization we do repeat TSB at 8 to 12 hr interval for first 48 hrs and 12 to 24 hourly afterwards when probability of unexpected rise in TSB usually decreased.

We in neonatal division of AIIMS follows American Academy of Pediatrics (AAP)'s guidelines for initiating phototherapy in term and near term infants (fig 2).¹⁷ For preterm and VLBW infants guidelines for phototherapy are not so clear for lack of data. We follow the ranges given in table 3.

For paucity of evidence these phototherapy guidelines are given only for first week of life.

We follows the same guidelines for neonates with hyperbilirubinemia post first week of life, however these babies are probably less prone for bilirubin induced brain damage with similar TSB.

10. Hemolytic jaundice

The common causes of hemolytic jaundice include Rh hemolytic disease, ABO incompatibility, G-6-PD deficiency and minor blood group incompatibility.

10.1 Rh hemolytic disease:

A baby born to an Rh-negative mother (and Rh-positive father) should have Rh typing and a Direct Coomb's test (DCT) on cord blood. Newborns suspected to have Rh isoimmunization should have a blood group and Rh typing, DCT, PCV and serum bilirubin on cord blood to facilitate early treatment. A reticulocyte count should be sent prior to the first exchange transfusion (ET). Intensive phototherapy (section 15.1) should be started at birth and continued till two consecutive readings are below phototherapy range. Indications for exchange transfusion at birth and subsequently at a later age are mentioned in Table 2. Intervention for Rh hemolytic disease in preterm babies is indicated at lower values. A level greater than 0.5% and 1% birth weight (kg) can be used as a rough guide for phototherapy and exchange blood transfusion respectively.

Intravenous immunoglobulin (IVIG) is an alternative therapy which may be effective in treating isoimmune haemolytic jaundice. In isoimmune haemolysis red blood cells are probably destroyed by an antibody-dependent cytotoxic mechanism mediated by Fc receptor bearing cells of the neonatal reticuloendothelial system. The putative mechanism of IVIG action is non-specific blockade of Fc receptors. IVIG may be used in a dose of 0.5g to 1g/kg (single dose) after the first ET / as early as possible if ET not indicated. Phenobarbitone 5 mg/kg/day x 5 days may be started after the first ET / with in 12 hrs if ET not indicated

10.2 ABO Incompatibility:

Babies born to women with O blood group should be closely monitored for jaundice and discharged after 72 hours. If the maternal blood is group O, Rh-positive, it is an option to test the cord blood for the infant's blood type and direct antibody test, but it is not required provided that there is appropriate surveillance, risk assessment before discharge, and follow-up. Jaundice due to ABO incompatibility usually appears in the first 24 hours. In the presence of significant jaundice or jaundice appearing within 24 hours, the work up for pathological jaundice as given in section 10.1 should be done. An approach to phototherapy and ET has been outlined in section 15.

10.3 Other hemolytic states:

G6PD deficiency, hereditary spherocytosis, minor group incompatibilities should be managed similar to ABO incompatibility. Investigations for G-6-PD deficiency should be considered in all term and near-term infants with jaundice requiring phototherapy, with a family history of significant jaundice or a geographic origin associated with G-6-PD deficiency.

11. Jaundice in preterm babies

In premature infants, the term '*physiologic jaundice*' is of little value. In VLBW infants, TSB levels well within the "physiologic range" might be hazardous and sometimes need to be treated with phototherapy.¹⁸

Clinicians should ensure that all premature infants are routinely monitored for the development of jaundice. Serum bilirubin should be measured at 24 hours of age with follow up estimations every 12-24 hours until the levels stabilize. Recommendations for starting phototherapy in VLBW infants have been mentioned in Table 3. Bilirubin should

be repeated within 24-48 hours of stopping phototherapy or sooner if clinical jaundice reappears. Direct bilirubin should be measured weekly in infants on parenteral nutrition.

As a rough guide in healthy low birth weight infants phototherapy should be started at a bilirubin level of 1% of the birth weight (in grams) e.g. a baby weighing 1000 grams should receive phototherapy if the bilirubin levels exceed 10 mg/dl. An exchange transfusion should be considered at a value of 5mg/dl higher than that for phototherapy (1% of birth weight + 5 mg/dl). A sick VLBW baby requires intervention at lower levels.

12. *Small for gestational age (SGA) babies:*

Bilirubin handling in newborn is related to maturity of liver, which is dependent upon gestational age. Gestational age and corresponding appropriate weight may be a better guide for intervention as compared to actual birth weight in SGA infants.

13. Jaundice in a sick newborn

At high bilirubin levels sick neonates are more prone for bilirubin induces brain damage than the healthy neonate of similar gestation and weight. Intervention for jaundice in this group should start at lower levels of TSB (at a centile line below the expected for that gestation in figure 2 & 3).

Additional investigations in a sick newborn include direct bilirubin, septic screen, blood and urine culture and urine for reducing substances

14. Prolonged jaundice beyond 3 weeks:

This is defined as persistence of significant jaundice (10 mg/dl) beyond three weeks in a term baby. The common causes include breast milk jaundice, extravasated blood (cephalhematoma), ongoing hemolytic disease, G-6PD deficiency and hypothyroidism.

One should rule out cholestasis by noting the urine and stool color and checking the level of direct bilirubin. The diagnostic work up in such a newborn includes:

- Investigations to rule out cholestasis (stool color, urine color, direct and indirect bilirubin levels)
- Investigations to rule out ongoing hemolysis, G-6PD screen
- Investigations to rule out hypothyroidism
- Investigations to rule out urinary tract infection.

15. Treatment options:

15.1 Phototherapy

Factors That Affect the Dose and Efficacy of phototherapy

(a) *Spectrum of light emitted:* Blue-green spectrum is most effective. At these wavelengths, light penetrates skin well and is absorbed maximally by bilirubin. Use special blue tubes or LED light source with output in blue-green spectrum for intensive PT.

(b) *Spectral irradiance (irradiance in certain wavelength band) delivered to surface of infant:* If special blue fluorescent tubes are used, bring tubes as close to infant as possible to increase irradiance. Special blue tubes 10–15 cm above the infant will produce an irradiance of at least 35 $\mu\text{W}/\text{cm}^2$ per nm.

(c) *Spectral power (average spectral irradiance across surface area)* For intensive PT, expose maximum surface area of infant to PT. Double surface phototherapy may be more effective than single surface phototherapy

(d) *Cause of jaundice* PT is likely to be less effective if jaundice is due to hemolysis or if cholestasis is present. When hemolysis is present, start PT at lower TSB levels. Use intensive PT. Failure of PT suggests that hemolysis is the cause of jaundice.

(e) *TSB level at start of PT* The higher the TSB, the more rapid the decline in TSB with PT. Use intensive PT for higher TSB levels. Anticipate a more rapid decrease in TSB when TSB >20 mg/dL (342 µmol/L).

Continuous phototherapy is better than intermittent phototherapy. Phototherapy should be interrupted in a newborn only during breast-feeding and nappy changes.

Conventional phototherapy: If jaundice is non-hemolytic or rate of rise of jaundice is slow then one can use either conventional or fibre-optic phototherapy units.

Intensive phototherapy: In case of hemolytic or rapidly rising bilirubin or when a conventional unit is not effective, use of intensive phototherapy is warranted. This can be achieved by placing the infant on bili-blanket and using additional overhead phototherapy units with special blue lights and lowering the phototherapy units to within a distance of 15-20 cm. "Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 µW/cm² per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system¹⁷.

Hydration: Maintaining adequate hydration and good urine output should help to improve the efficacy of phototherapy.

Failure of phototherapy: Failure of phototherapy has been defined as an inability to observe a decline in bilirubin of 1-2 mg/dl after 4-6 hours and/ or to keep the bilirubin below the exchange transfusion level. Exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider

exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours. The recommended levels for exchange transfusion have been given in Figure 3. However, an exchange transfusion (ET) may be performed at the slightest suspicion of bilirubin encephalopathy irrespective of the bilirubin value.

When Should Phototherapy Be Stopped? : There is no standard for discontinuing phototherapy. For infants who are readmitted after their birth hospitalization (usually for TSB levels of 18 mg/dL or higher), phototherapy may be discontinued when the serum bilirubin level falls below 13 to 14 mg/dL. Discharge from the hospital need not be delayed to observe the infant for rebound. If phototherapy is used for infants with hemolytic diseases or is initiated early and discontinued before the infant is 3 to 4 days old, a follow-up bilirubin measurement within 24 hours after discharge is recommended. For infants who are readmitted with hyperbilirubinemia and then discharged, significant rebound is rare, but a repeat TSB measurement or clinical follow-up 24 hours after discharge is a clinical option.

Sunlight Exposure: Although sunlight provides sufficient irradiance in the 425- to 475-nm band to provide phototherapy, the practical difficulties involved in safely exposing a naked newborn to the sun either inside or outside (and avoiding sunburn) preclude the use of sunlight as a reliable therapeutic tool, and it therefore is not recommended.

15.2 Exchange transfusion

Rh isoimmunization: Blood used for exchange transfusion in neonates with Rh isoimmunization should always have Rh negative blood group. The best choice would be O (Rh) negative packed cells suspended in AB plasma. O (Rh) negative whole blood or cross-matched baby's blood group (Rh negative) may also be used in an emergency.

ABO incompatibility: Only O group blood should be used for exchange transfusion in neonates with ABO incompatibility. The best choice would be O group (Rh compatible) packed cells suspended in AB plasma or O group whole blood (Rh compatible with baby).

Other situations: Cross-matched with baby's blood group.

Blood volume used:

- Partial exchange done at birth in Rh hemolytic disease with severe anemia / hydrops (aims at increasing the oxygen carrying capacity of blood): 50 ml/ kg of packed cells
- Double volume exchange: 2 x (80-100 ml/kg) x birth weight in Kg (arrange 70% PRBC and 30% FFP, so that PCV of whole arranged blood ~ 50-55)

15.3 Pharmacological treatment:

Phenobarbitone: It improves hepatic uptake, conjugation and excretion of bilirubin thus helps in lowering of bilirubin. However its effect takes time. When used prophylactically in a dose of 5 mg/kg for 3-5 days after birth, it has shown to effective in babies with hemolytic disease, extravasated blood and in preterms without any significant side effects.

Intravenous Immunoglobulins (IVIG): High dose intravenous γ -globulin (IVIG) (0.5 to 1 gm/kg) has been shown to reduce the need for exchange transfusions in Rh and ABO hemolytic disease.¹⁷

Pharmacologic Therapy: There is now evidence that hyperbilirubinemia can be effectively prevented or treated with tin-mesoporphyrin, a drug that inhibits the production of heme oxygenase. Tin-mesoporphyrin is not approved by the US Food and Drug Administration. If approved, tin-mesoporphyrin could find immediate application in preventing the need for exchange transfusion in infants who are not responding to phototherapy.

16. Follow-up:

Babies with serum bilirubin ≥ 20 mg/dl and those who require exchange transfusion should be kept under follow-up in the high- risk clinic for neuro-developmental outcome. Hearing assessment (BERA) should be done at 0-3 months of corrected age. With prompt treatment, even very elevated serum bilirubin levels within the range of 25 to 29 mg/dl are not likely to result in long-term adverse effects on neurodevelopment.¹⁹

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Annexure:

Table 1. **Guide to dermal staining with level of bilirubin (Modified from Kramer's original article)¹⁴**

Area of body	Level of bilirubin
Face	4-6 mg/ dl
Chest, upper abdomen	8-10 mg/dl
Lower abdomen, thighs	12-14 mg/dl
Arms, lower legs	15-18 mg/dl
Palms, soles	15-20 mg/dl

Table 2. **Indications for exchange transfusion in Rh Isoimmunization.⁶**

An exchange transfusion soon after birth is indicated if:
Cord bilirubin is ≥ 5 mg/dl Cord Hb is ≤ 10 mg/dl, PCV < 30 Previous sibling history and positive DCT.
Subsequent exchange transfusions are indicated if:
<ol style="list-style-type: none"> 1. Bilirubin ≥ 10 mg/dl within 24 hours of age 2. Bilirubin ≥ 15 mg/dl between 25-48 hours of age 3. Bilirubin ≥ 20 mg/dl after 48 hours of age. 4. Rate of rise of bilirubin is ≥ 0.5 mg/dl/hr.

Table3. Management of neonatal hyperbilirubinemia in low birth weight babies based on bilirubin levels (mg/dl)⁵

Weight (gm)	Phototherapy	Consider exchange transfusion
500-750	5-8	12-15
750-1000	6-10	>15
1000-1250	8-10	15-18
1250-1500	10-12	17-20
1500-2500	15-18	20-25

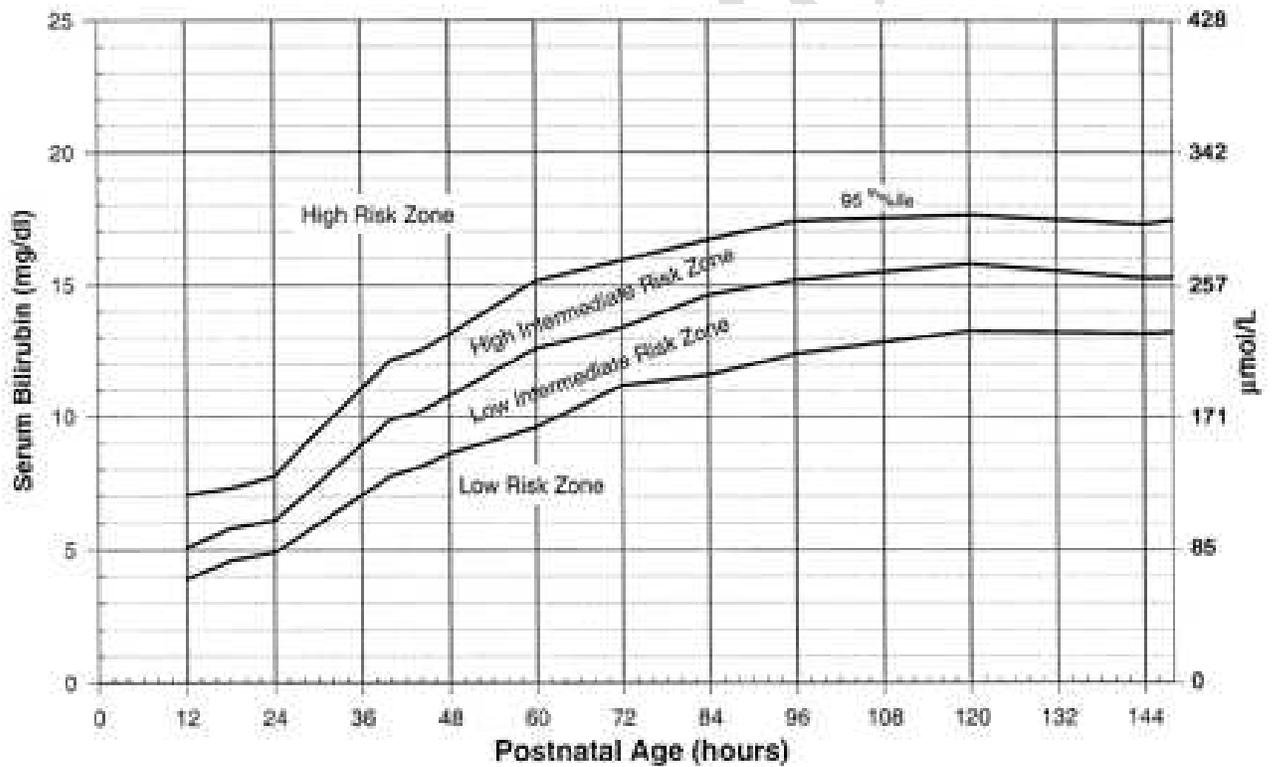


Figure 1. Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values⁸

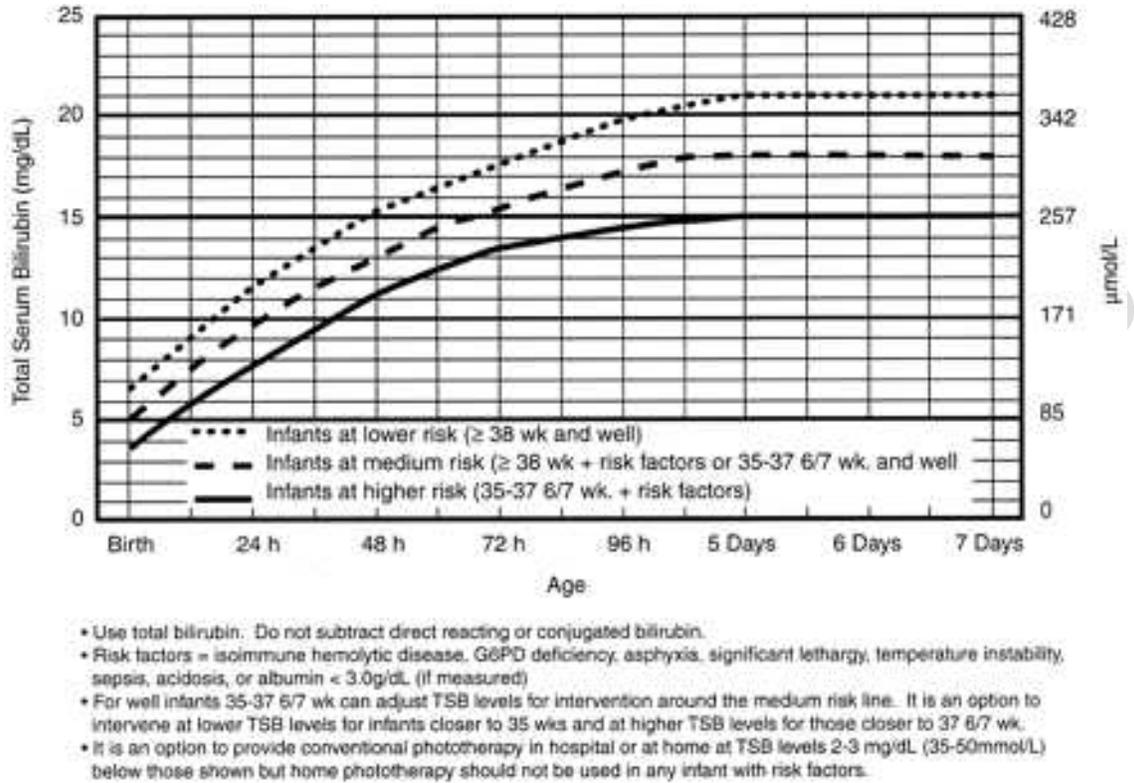
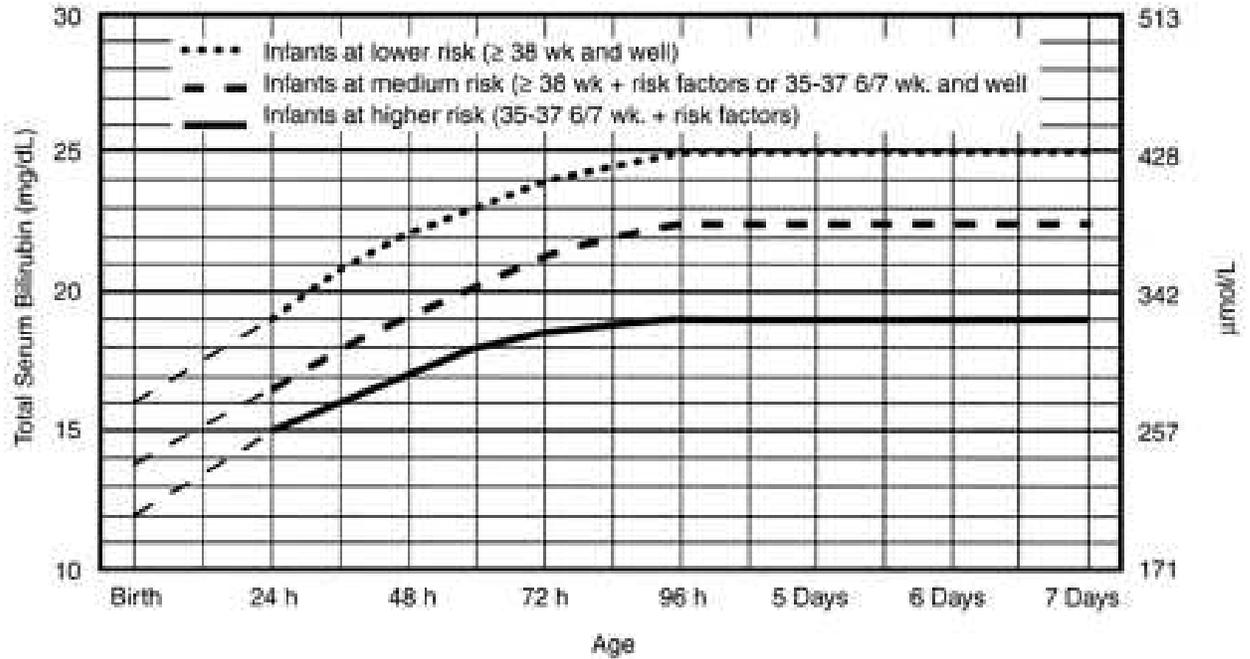


Figure 2. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.¹⁷



- The dashed lines for the first 24 hours 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 $\mu\text{mol/L}$) 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
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Figure 3. Guidelines for exchange transfusion in infants 35 or more weeks' gestation.¹⁷

TABLE 4. Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance)¹⁷

Major risk factors

Predischarge TSB or TcB level in the high-risk zone (Fig 2)
 Jaundice observed in the first 24 h
 Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency)
 Gestational age 35–36 wk
 Previous sibling received phototherapy
 Cephalohematoma or significant bruising
 If breastfeeding is not going well and weight loss is excessive

Minor risk factors

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

Male gender

Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)

TSB or TcB level in the low-risk zone (Fig 2)
 Gestational age ≥ 41 wk

Discharge from hospital after 72 h