

Severe Hyperbilirubinemia Prevention (SHP Toolkit)

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Table of Contents:

- I. Title:
- II. Background:
- III. Recommended Guidelines:
- IV. Quality and Process improvement:
 - a. Benchmarking
 - b. Outcome of use of SHP Toolkit (2007-2012)
- V. Summary of Key Points and implementation

Title:

**Guidelines for the Identification and Follow-Up of Term and Near Term Infants
(≥ 35 weeks gestation) at Risk of Hyperbilirubinemia**

1) Background

Post-natal hyperbilirubinemia is universal and manifests as newborn jaundice in over 80% of all newborns in the United States. Jaundice is one of the commonest clinical sign and is due to elevated total serum/plasma bilirubin levels (TSB) which is unconjugated (indirect) and/or conjugated (direct). Increasing TSB levels are due to imbalances between bilirubin production and elimination. Standard definitions for severity of neonatal hyperbilirubinemia at age >72 hours based on TSB (total serum bilirubin level) are listed in this table.

Adjective	TSB level (at age >72 h)	TSB percentile
Low risk (mild)	<14 mg/dl	<40 th percentile
Significant (moderate)	>17 to ≤20 mg/dl	>95 th percentile
Severe	>20 to ≤25 mg/dl	>98 th percentile
Extreme	>25 to ≤30 mg/dl	>99.9 th percentile
Hazardous	>30 mg/dl	>99.99 th percentile

Confirmation for hyperbilirubinemia is by an assay of TSB or by indirect screening with a transcutaneous bilirubin (TcB). The risk for severe hyperbilirubinemia and the threshold for intervention based upon the hour-specific TSB/TcB value may be determined using Bhutani nomogram (Appendix 1) or free access web-based tool (such as, www.Bilitool.org). Incidence of clinical events and clinical actions are addressed in this table.

Clinical Event	Incidence	Clinical Action
Newborn Jaundice	About 84%	Universal bilirubin screening
Bilirubin >75 th %ile for age in hours	25-30%	Evaluate and treat*
Bilirubin >15 mg/dL	8-12%	Consider use of phototherapy

Use of intensive phototherapy	4-8%	For bilirubin rate of rise >5 mg/dl per 24 h or, 0.2mg/dL/h
Use of exchange transfusion	Rare event	An emergency procedure for onset of any early neurologic signs** or, hazardous bilirubin levels that do not respond to “crash-cart” phototherapy.
Bilirubin level >30 mg/dl	Avoidable event	Intensive monitoring and emergency interventions for possible lifesaving interventions

** Treatment may include increased enteral intake, use of phototherapy and early (<12 hours) repeat testing; ** lethargy, altered mental state, apnea, irritability, muscle tone abnormalities and/or altered cry patterns.*

2) Recommended Guidelines:

Progression of newborn jaundice to severe hyperbilirubinemia is not unusual and usually predictable. Exposure to unexpected trigger(s) that lead to acute hemolysis, as in some infants with G6PD deficiency, are less predictable. Recommended clinical actions commence soon after birthing and are based on evidence reviewed and presented as guidelines.

A. *Clinical Assessment of Jaundice:* Jaundice should be assessed whenever the infant’s vital signs are measured but no less than every 8 to 12 hours. Infants who are jaundiced before 24 hours after birth are at increased risk for severe hyperbilirubinemia (most likely due to hemolysis) and should be considered a newborn emergency. In these infants, TSB or TcB assays are performed urgently. AAP has cautioned against reliance on visual assessment of jaundice as a means to assess the severity of neonatal hyperbilirubinemia.

B. *Hyperbilirubinemia Risk Assessment:* Prior to discharge, every infant should be assessed for the risk of subsequent significant hyperbilirubinemia based on gestational age, hemolysis and bilirubin test.

i) Key clinical risk factors for significant hyperbilirubinemia for earlier follow-up:

Prenatal

- a. Primiparity
- b. Birth trauma
- c. Delivery at <39 weeks' gestation (early term and late preterm)

Postnatal

- a. Jaundice suspected or detected at age < 24 hours
- b. Predischage TSB/ TcB measurements in the high intermediate or high risk zone (>75th percentile for age in hours) of the bilirubin nomogram.
- c. Prematurity, every week of gestational immaturity.
- d. Isoimmune or other hemolytic disease (increased bilirubin production)
- e. Cephalohematoma or significant bruising (increased bilirubin production)
- f. Sub-optimal milk intake or excessive weight loss (>10% over 72 hours; >3.5% per day. This is indicative of either starvation or hypernatremic dehydration)
- g. History of a prior sibling with jaundice or treated with phototherapy
- h. Maternal ethnicity and risk factors for congenital hemolytic disorders, G6PD deficiency and bilirubin elimination disorders

ii) Key risk factors for hyperbilirubinemia that lead to infant's vulnerability to bilirubin neurotoxicity (these guide phototherapy use)

- a. Prematurity (each week GA <39 weeks)
- b. Neonatal hemolysis
- c. G6PD deficiency
- d. Apgar Score <3 at 5 minutes
- e. Perinatal sepsis
- f. Acidosis
- g. Albumin <3 mg/dl

C. Bilirubin Assessment: If jaundice is visible, further testing should be done to evaluate the degree and general etiology of hyperbilirubinemia. Universal bilirubin screening before discharge combined with risk assessment is an easily implemented systems approach that identifies infants at risk for severe hyperbilirubinemia. It can be coordinated and timed with routine metabolic screening in all infants prior to discharge.

1. Urgent Bilirubin Assessment: Visible jaundice at age < 24 hours, requires the nurse caring for the infant to immediately do the following:

- a. Inform attending physician.
- b. Draw TSB by heel stick or venipuncture for STAT results. One may additionally use TcB measurement while TSB results are reported.
- c. Plot TSB/TcB value on the hour-specific, percentile-based bilirubin nomogram, referred to as the Bhutani nomogram (Appendix 2) and use the Bilitool.org website or AAP Phototherapy guidance for immediate initiation of phototherapy or assess for bilirubin rate of rise with a follow up TSB test. The guidance is based on gestational age and presence of neurotoxicity risk factors.

2. Transcutaneous Bilirubin Assessment: Devices that provide a noninvasive TcB measurement can be useful screening tools. TcB screening can reduce the number of blood tests for bilirubin determinations. However, TcB measurements are not reliable in infants undergoing phototherapy; overestimate TSB in infants who have increased skin pigmentation, likely underestimates TSB in light-skinned infants and have diminished accuracy for TSB>12 mg/dL. Under these circumstances if TcB level exceeding the 75th percentile, a confirmatory TSB should be obtained. TcB levels <12 mg/dL may be plotted on the hour-specific bilirubin nomogram Appendix 2 figure or www.bilitool.org.

3. Bilirubin Assessment beyond age 24 hours: When the results of routine pre-discharge bilirubin are obtained, using Appendix 2 figure or www.bilitool.org determines the need for phototherapy beyond age 24 and to schedule follow-up.

D. Phototherapy Techniques: Phototherapy should be initiated in a timely fashion and implemented safely to slow or reverse the rapid rise in bilirubin ($>0.2\text{mg/dL/h}$) in infants at risk for severe hyperbilirubinemia. AAP Guideline 2011 describes the many technical and clinical factors that affect phototherapy efficacy.

- a. Measured irradiance varies widely with the technique used; periodic measurement of phototherapy devices is recommended.
- b. “Effective” phototherapy implies the use of high levels of irradiance (usually 30 to $<45\text{ microW/cm}^2$ per nm) in the blue-green light wave-length of 460 to 490-nm band delivered to as much of the infant’s surface area as possible.
- c. There is a direct relationship (in the dosages recommended) between the irradiance used and the rate at which TSB declines during phototherapy. High irradiance doses should be used with caution in more preterm infants ($<1000\text{g}$) and there are no known indications to use doses $>45\text{ microW/cm}^2$.
- d. Timeliness of implementation is most important either as a prophylaxis or as an urgent intervention (“crash-cart approach”). For urgent intervention, procedures should be conducted while infant is being administered phototherapy. Exposure to therapeutic light may reduce the neurotoxic bilirubin within 15 to 60 minutes due to formation of photobilirubins. Periodic bilirubin levels may assess the rate of response to effective phototherapy.
- e. In most circumstances, it is not necessary to remove the infant’s diaper, but when bilirubin levels approach the exchange transfusion range, a smaller diaper may be used for hygiene until there is clear evidence of a significant decline in the bilirubin level.
- f. Unless there is evidence of dehydration or hypernatremia, routine intravenous fluid or other supplementation (e.g., with dextrose water) is not necessary.
- g. Discontinuation of phototherapy at desired bilirubin threshold is based on clinical judgment on the net rates of bilirubin production and elimination with the awareness of possible rebound hyperbilirubinemia.

E. Additional Evaluation:

Infants who have TSB values \geq 95th percentile or concern of hemolytic disease require subsequent repeat measurement(s) of TSB to assess rate of rise (or, crossing of percentiles to higher risk zones) and further evaluation to determine the specific etiology of jaundice. These investigations may include maternal/infant blood type, assessment for hemolysis, complete blood count and smear, reticulocyte count, G6PD quantitative measurement, if clinically appropriate (either parent is of Mediterranean, African-American, or East-Asian ancestry), direct or conjugated bilirubin (especially in an infant with severe hemolysis). UGT polymorphisms (or variants of Gilbert's syndrome) may need to be considered for prolonged unconjugated hyperbilirubinemia (at age >10 days) especially among Asian infants.

F. Monitoring for need of supplemental intake:

Because TSB values can be marginally higher in adequately breastfed than in formula-fed infants, evaluation of breastfeed support and individualized counseling should be performed. Mothers should ideally have prenatal lactation counseling sessions, be encouraged to breastfeed their infants in the delivery room and be taught to assess for optimal milk transfer with effective sucking. The importance of frequent feedings (at least 8 to 12 times per day for the first several days) is emphasized. Lactation consultants (during and after hospitalization) and home visits by a nurse (after discharge) is often helpful to individualize care and promote breastfeeding. Poor caloric intake and / or dehydration associated with sub-optimal intake (as determined by decreased urine output, delayed meconium transition stool and postnatal weight loss (>3.5% per day) increase the risk for severe neonatal hyperbilirubinemia and even kernicterus. The AAP recommends **against** routine supplementation of non-dehydrated breastfed infants with water or dextrose water. Supplementation with water or dextrose water will not prevent hyperbilirubinemia or decrease TSB levels. There are no contraindications to use of breast milk intake in jaundiced newborns other than proven galactosemia (through routine newborn screening).

G. Predicting Post Discharge Risk of Significant Hyperbilirubinemia.

Infants at risk for significant hyperbilirubinemia will need to have close follow-up after discharge unless risks for neurotoxicity predispose an infant to receive prophylactic

phototherapy. Color coded table below provides recommendation for management and follow up according to pre discharge bilirubin measurements and assigning the bilirubin risk zone, gestation and risk factors for subsequent hyperbilirubinemia. Appropriate post discharge follow up involves a comprehensive clinical examination by a qualified health care professional that includes assessment for hydration and jaundice progression.

Bilirubin Risk Determination for Well Newborns at 36 or more weeks’ gestational age with birth weight 2,000 gm or more or 35 or more weeks’ gestational age and birth weight of 2,500 gm or more* (Modified with permission for post discharge risk assessment, Bhutani et al)

TSB Risk Zones	>38 wks,	35-37 ^{6/7} wks,	35-37 ^{6/7} wks
	No risk factors	>38 wks + risk factors	+ risk factors
>95 th percentile	TSB in 24h	TSB in 4-8h	TSB in 4-8h
>75 th percentile	TSB in 48h	TSB in 24h	TSB 4-24h
40-75 th percentile	TSB in 2-3 days	TSB within 48h	TSB within 24-48h
<40 th percentile	TSB at discretion	TSB in 2-3days	TSB in 2-3days

Risk factors for bilirubin neurotoxicity include Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, albumin <3g/dl.

H. Parent Education: At the time of discharge, appropriate follow-up is arranged, information and written guidelines about jaundice are provided to the parents, and instructions for when to contact medical staff are given to the family. Information is also available on the AAP website, at www.aap.org/family/jaundicefaq.htm. Families at risk for G6PD deficiency, especially those African-American, Asian and Mediterranean backgrounds, should be counseled to take precautions with exposures to chemicals (mothballs, etc), drugs (sulfas, aspirin, etc), dyes (henna, etc) and diet (fava and broad legume beans, herbal teas, high doses of Vitamin C in certain juices, etc) (Kaplan et al, 2016. Journal of Perinatology).

III. Quality and Process improvement:

i) Benchmarking:

Previous CPQCC Toolkits have sought to aid unit benchmarking through reference to available CPQCC/VON datasets or publications citing specific institutional datasets. If you want to benchmark, we offer the following information to aid those seeking to compare their institution's performance with others:

1. Focus on the demographic data such as race/ethnicity, GA of the baby who developed jaundice and required phototherapy by reviewing selective patient charts.
2. Focus on the feeding: Identify the percentage of discontinuation of maternal breast milk or breastfeeding for jaundice and or use of supplemental (bovine) formula use.
3. Focus on use of phototherapy prescription (both inpatient and out-patient).
4. Focus on efficacy of phototherapy, time to initiation and its duration.
5. Focus on access and skills for "crash cart" phototherapy.
6. Survey rates of readmission of phototherapy and exchange transfusion.
7. Survey rate of babies (<1 month of age) with TSB levels > 25mg/dl

ii) Outcome after Implementation of SHP Toolkit 2007-2012

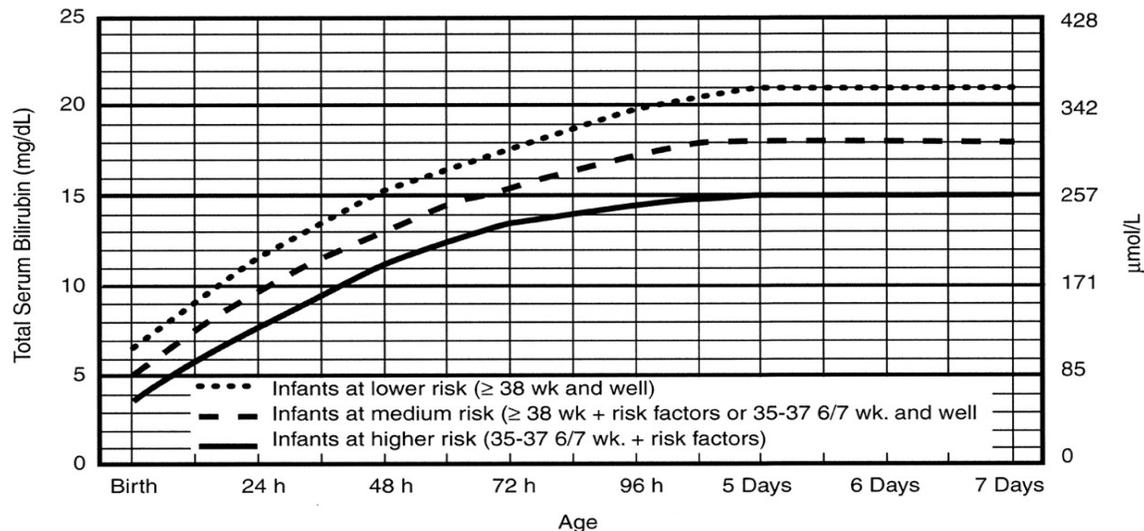
Population risk factors and healthcare services distribution for adverse bilirubin outcomes following the publications national (2004) and statewide learning collaborative (2006) were prospectively studied. Bilirubin outcomes and interventions were retrieved in a standardized manner from the state-wide databases for all re-admissions (infant age <28 days) to neonatal intensive care units (NICUs). Data for all California live births (without congenital abnormalities) born from 2007–2012 were used and included the 128 participating hospitals which represented >90% of all neonates readmitted. The main outcomes were the individual and cumulative frequencies of select adverse outcomes for demographic risk factors. The results demonstrated that risk of extreme hyperbilirubinemia (EHB, TSB >25 mg/dL) at readmission, regardless of birth facility or level of care, was increased among infants for each week <39 wks GA, male gender, and no prenatal care.

Risk was lower among infants born by cesarean-section and to African-American and Hispanic women but was not completely protective. With minor annual variations, estimated EHB and exchange rates decreased from peaks of 27.1 (in 2009) to 14.6 (in 2012) and 5.9 to 1.9

per 100,000 live births ≥ 35 weeks GA, respectively. These data validated that both the use of most recent national guidelines complemented by state-wide learning collaborative decreased adverse outcomes among all birth facilities. To sustain low rates in rescue exchange transfusions among high-risk infants, continued adherence to AAP guidelines and prioritization of clinical training as well as surveillance and tracking of adverse outcomes is needed.

Appendix 2

Figure 1. Guidelines for Phototherapy in Hospitalized Infants of 35 weeks or greater gestation.



- 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 < 3.0g/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 (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

IV) Summary of Key Points and implementation:

Neonatal hyperbilirubinemia, a frequent neonatal condition, is generally benign. When untested or unmonitored, safe and effective interventions may be delayed and place an otherwise healthy newborn infant at risk for bilirubin neurotoxicity. Based on extensive research, clinical experience and use of systems-approach, the need for emergency interventions and clinical diagnosis of acute bilirubin encephalopathy as well as kernicterus have become rare and unusual in USA.

Identifying most frequent clinical contributory risk factors for severe hyperbilirubinemia such as prematurity, maternal obesity, primiparity, and infants large or small for gestational age, increased bilirubin production (polycythemia, iso-immune hemolytic disorders, undiagnosed hemolytic disease, inherited red blood cell diseases (such as Glucose 6-Phosphate Dehydrogenase [G6PD] deficiency, congenital spherocytosis, etc) or due to genetic disorders such as Gilbert's disease (Uridine-diphosphate Glucuronosyl Transferase [UGT]

polymorphisms), galactosemia, Crigler–Najjar syndrome etc) and effective use of phototherapy treatment will prevent acute bilirubin encephalopathy. In addition, concurrent complications of dehydration, sepsis, or acidosis, hypoalbuminemia, low Apgar scores or poor feeding confound the degree of infant’s neurologic vulnerability. Adequate evidence supports combined screening using risk factors (specifically, gestational age) and hour specific bilirubin measurements for the identification of infants at risk for developing severe hyperbilirubinemia. We provided with some clinical guidelines, benchmarking tools with this toolkit. Using the supplemental problem identification worksheets, you can analyze your practice focusing PDCA.

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