PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

Evaluation and Management of Hyperbilirubinemia in the Newborn Nursery and NICU

Clinical Guideline Name	Evaluation and Management of Hyperbilirubinemia in the Newborn Nursery and NICU
Implementation Date	March 1, 2016
Due for CPC Review	
Contact Person	Medical Director, NICU
Approved By	Department of Pediatric Newborn Medicine Clinical Practice Council _1/14/16_____ CWN PPG 1/13/16_____ BWH SPP Steering 2/17/16_____ Nurse Executive Board/CNO_2/22/16____

I. Purpose

The purpose of this clinical practice guideline is to ensure that all infants receive optimal and consistent care for hyperbilirubinemia by establishing standard practices for the evaluation and management of hyperbilirubinemia in preterm and term infants.

II. All CPGs will rely on the **NICU Nursing Standards of Care.** All relevant nursing PPGs are listed below (all underlined text is hyperlinks):

WNH P.1 Phototherapy for Infants
WNH B.8 Infant Bilirubin Screening
WNH B.2 Infant Heelstick Blood Sampling
WNH ---- Care of the Late Preterm Infant
IVIG DAG

III. Scope

These guidelines apply to all infants in the care of the Department of Pediatric Newborn Medicine. The guidelines include recommendations for evaluation, diagnosis and monitoring of hyperbilirubinemia, as well as indications for administration of phototherapy, intravenous immunoglobulin (IVIG) and exchange transfusion.

IV. Etiology and Evaluation

- Every infant with jaundice should be evaluated for etiology and severity of hyperbilirubinemia to guide appropriate therapy
- For jaundice appearing on
  - Day 1: consider isoimmunization (ex. Rh, ABO incompatibility) and congenital infection
    - If mother is blood type O+, obtain infant blood type and direct antiglobulin test (DAT)

- Days 2-6: consider bacterial infection (including urinary tract infection), resorption jaundice (ex. cephalohematoma), metabolic disease (ex. galactosemia), isoimmunization, congenital infection, breastfeeding jaundice/dehydration, physiologic jaundice, RBC membrane defects (ex. spherocytosis), RBC enzyme defects (ex. G6PD deficiency, pyruvate kinase deficiency)
  - Obtain blood type, DAT, hematocrit, reticulocyte count, and blood smear
  - If hemolysis is present with negative DAT, check RBC enzymes
  - If elevation of direct bilirubin, obtain urinalysis and urine culture and evaluate causes of cholestasis
- Days 7+:
  - Indirect (unconjugated) hyperbilirubinemia: consider breast milk jaundice, hypothyroidism, sepsis
  - Direct (conjugated) hyperbilirubinemia: evaluate causes of cholestasis

- Jaundice appearing within 24 hours of life is pathologic until proven otherwise
- It is crucial to determine presence or absence of hemolysis
- The total serum bilirubin (TSB) level is used when determining levels for phototherapy or exchange transfusion
- Physiologic hyperbilirubinemia is a diagnosis of exclusion. Persistent hyperbilirubinemia in an non-breast fed infant should be considered abnormal, and warrants further investigation

V. Assessing risk

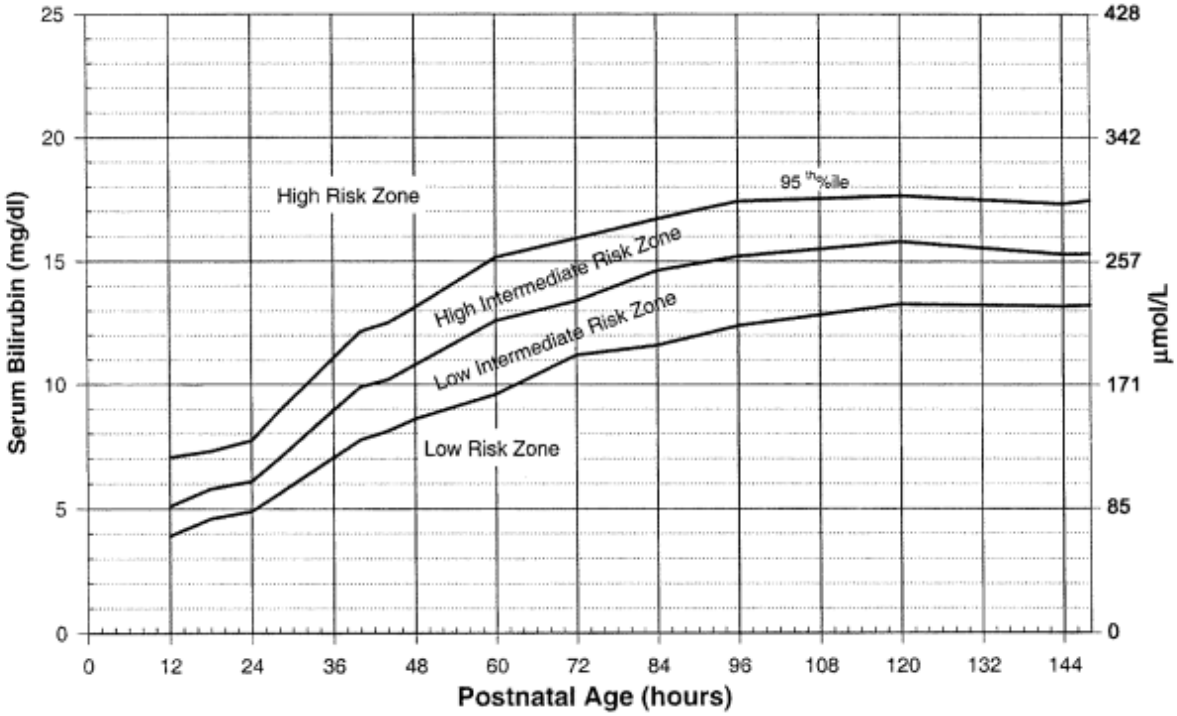
a. Major risk factors for developing severe hyperbilirubinemia:

- TSB in the high risk zone of the Bhutani nomogram
- Jaundice observed in first 24 hours of life
- Blood group incompatibility (Rh or ABO) or known hemolytic disease
  - If mother is blood type O+, obtain infant blood type and DAT
- Prematurity
- Cephalohematoma, subgaleal hemorrhage, or other significant bruising
- Previous sibling with hyperbilirubinemia requiring phototherapy
- Exclusive breastfeeding, particularly in setting of excessive weight loss
- East Asian race

b. Use of nomograms:

- Nomograms help assess risk for developing hyperbilirubinemia and assist in determining the timing of appropriate follow-up
- Bhutani curve (below) is the accepted nomogram for assessing hyperbilirubinemia risk for infants ≥ 35 weeks gestation, based on bilirubin level and postnatal age

Bhutani nomogram (≥ 35 weeks gestation):



Bhutani et al. nomogram for well newborns at >36 weeks' gestational age with birth weight of >2000 g or more or >35 weeks' gestational age and birth weight of >2500 g based on hour-specific serum bilirubin values.

c. Bilitool:

- Bilitool (www.bilitool.org) is a web site that provides a free, user-friendly, interactive way to match infant bilirubin levels with the Bhutani nomogram and established phototherapy guidelines (for infants ≥35 weeks)

VI. Light source and irradiance

- Blue fluorescent lamps or LED systems (ex. neoBLUE®) provide irradiance in the 430 – 490 nm band and are determined to be the most effective light source for phototherapy
    - LED lights provide the greatest TSB decrease during first 24 hours, followed by spotlights, bank of lights, and blankets
- If TSB continues to rise despite phototherapy, consider increasing irradiance by bringing phototherapy lamp closer to infant or increasing body surface area exposed to phototherapy (ex. place additional light source beneath infant and reflecting material around incubator or radiant warmer)
- Use radiometer recommended by manufacturer of phototherapy system to measure irradiance (Biomed)

- Due to increased mortality associated with phototherapy use in ELBW infants, if BW < 750g, consider initiating phototherapy at lower irradiance level (i.e. "low" setting) and only increase irradiance (or surface area exposed) if TSB continues to rise

VII. Infants ≥ 35 weeks gestation

a. Key points:

- TSB levels progressively increase during the first 96-120 hours after birth and usually decline depending on the maturation of the infant's liver, initiation of enteral feeds, motility of the GI tract, and infant's ability to clear the bilirubin load
    i. Note: TSB levels in late preterm infants may peak later (as compared with term infants), and rate of rise may be steeper
- Jaundice should resolve by 2 weeks of life in most infants; persistent jaundice beyond age 2 weeks warrants further investigation

Device	Irradiance ($uW/cm^2/nm$)	Location	Notes
Giraffe Spot PT Lite (GE)	6-35	NICU	Output depends on distance from lens to infant Utilizes white light To be discontinued by GE and replaced with blue LED spotlights
NeoBlue (Natus)	12-15 (low) 30-35 (high)	NICU, Newborn Nursery	Both low and high settings assume distance of 12" from light to infant Utilizes blue LED
BiliSoft Blanket (GE)	70 (small pad) 49 (large pad)	NICU	Utilizes blue LED
NeoBlue Cozy Bed (Natus)	30-35	Newborn Nursery	Utilizes blue LED
BiliBed (Medela)	40-60	Newborn Nursery	Utilizes blue fluorescent tube
BiliBlanket Plus (Datex-Ohmeda)	15 (low) 25 (medium) 35 (high)	NICU, Newborn Nursery	Used rarely in NICU

b. Bilirubin measurement:

- Initial transcutaneous bilirubin (TcB) measurement should be obtained around the time of the initial newborn screen (between 24-48 hours of life)
    - Note, if mother is blood type O+ and **Coombs is positive**, TcB should be obtained at 12 hours of life and further close follow-up recommended
- If TcB level is above the threshold (use table below), obtain a serum bilirubin (TSB)

Postnatal age (hours)	Threshold transcutaneous bilirubin level (mg/dL)
24-36 h	7
37-48 h	8
49-72 h	10
72-96 h	12
96+ h	14

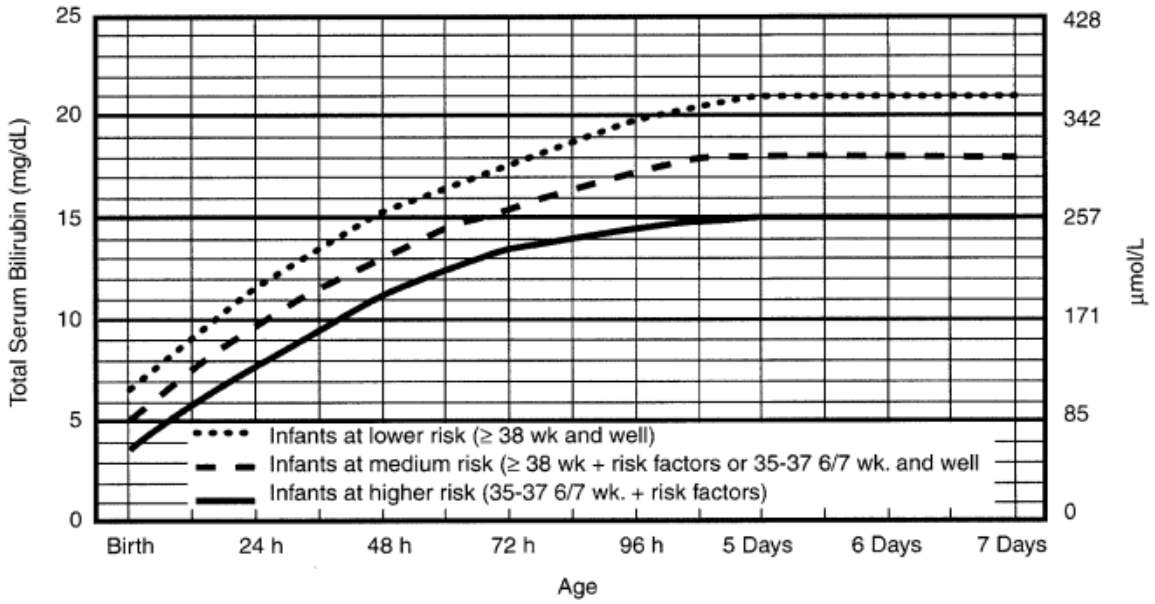
- If major risk factors are present (see below), or if infant appears jaundiced, consider obtaining initial TcB at earlier time point
- Note: in NICU setting, consider obtaining TSB (instead of TcB) to coincide with scheduled blood draw
- Note: TcB measurement may be used on infants of any race or ethnic background but results may be mildly affected by skin pigmentation
    - TcB typically overestimates TSB in infants who are dark-skinned, and likely underestimates TSB in light-skinned infants

c. Risk factors for bilirubin toxicity:

- Hemolysis
- G6PD deficiency
- Asphyxia
- Neurological signs including significant lethargy or irritability
- Temperature instability
- Confirmed or suspected sepsis
- Acidosis
- Hypoalbuminemia (< 3 g/dL in near term and term infants)

d. Phototherapy:

Guideline for initiating phototherapy (≥ 35 weeks gestation)



e. Ongoing monitoring:

- Obtain daily morning (04:00) TcB until downtrending
- If TcB level is above the threshold (use table in section VII. b above), obtain TSB
- Once phototherapy has been initiated:
    - Follow serial TSB levels (TcB levels will no longer be accurate)
    - Repeat TSB in 12-24 hours after starting phototherapy
    - For bilirubin levels approaching exchange level or rapid rate of rise more frequent bilirubin measurements are recommended
    - Use bilitool.org for specific recommendations regarding timing of serial TSB measurements
- Decisions regarding when to discontinue phototherapy should be based on the infant's individual risk factors and clinical situation
- Measure bilirubin within 12-24 hours after phototherapy is discontinued, then as clinically indicated (i.e. in setting of ongoing hemolysis)
- Consult with neonatologist if TSB is within 2 mg/dL of exchange transfusion threshold, or earlier as clinically indicated (ex. presence of hemolysis or other major risk factors)

f. Fluids, electrolytes and nutrition:

- Encourage breastfeeding or bottle feeding up to 20 minutes duration every 2-3 hours, using expressed maternal milk for supplemental feeds when available
- Give enteral feeds but do not interrupt phototherapy for patients nearing exchange transfusion threshold or rapidly rising TSB
- Do not routinely supplement with IV fluids
    - Consider IV fluids if within 2 mg/dL of exchange transfusion threshold

g. Follow-up after discharge:

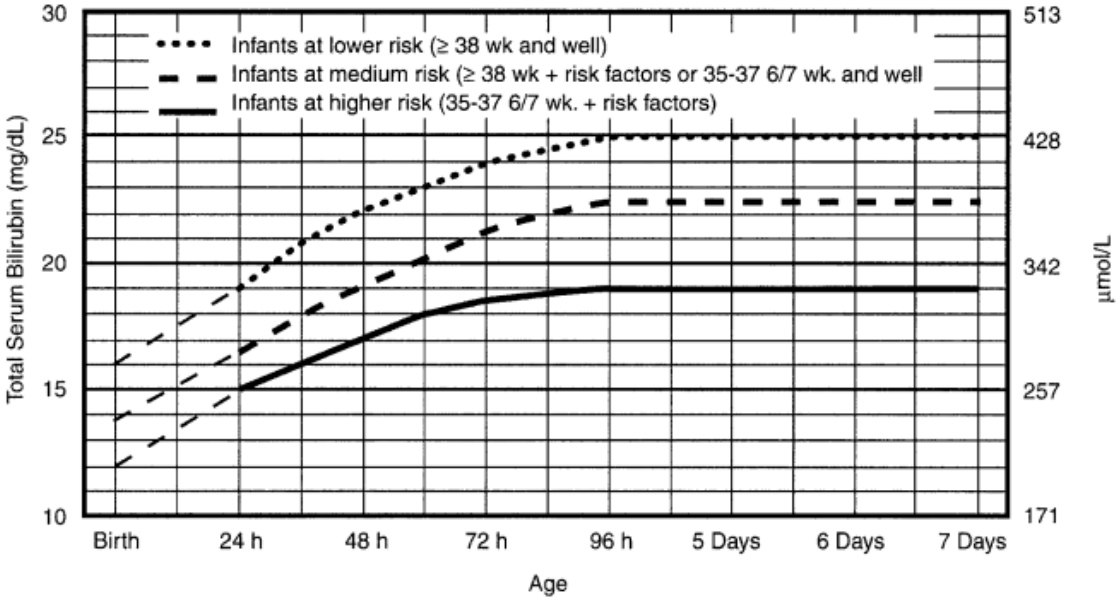
- Appropriate follow-up after hospital discharge is essential, particularly with the advent of earlier mother-infant discharge
- Timing of follow-up depends on the age of the infant at discharge and whether risk factors for hyperbilirubinemia are present
- Use bilitool.org for specific recommendations based on infant risk category
- Ensure the following occur at the time of hospital discharge:
    - Follow-up appointment with PCP is arranged
        i. Note: direct communication with PCP should occur if infant needs to have bilirubin level checked the next day
    - Parents are provided with information about jaundice
    - Family is given instructions on when and whom to contact for medical issues (ex. jaundice and adequacy of feeding) prior to their appointment
- Infants with TSB levels that approach exchange transfusion threshold should be monitored until school age
    - Follow-up should include brainstem auditory evoked response (BAER) hearing test, neurologic and neurodevelopmental evaluation, and MRI
    - BAER recommended for all infants with bilirubin ≥ 20mg/dl. Performed at 3 months of age as outpatient.

h. Intravenous immunoglobulin (IVIG):

- IVIG will only be administered in the NICU
- Several studies have shown an overall decreased need for exchange transfusions in isoimmune hemolytic disease (Rh or ABO incompatibility) with use of higher dose IVIG (1g/kg) compared with phototherapy alone.[4, 5]

- In setting of isoimmune hemolytic disease, consider administration of IVIG (1 g/kg IV infused over 6 hours) if:
    - TSB is rising despite intensive phototherapy for at least 6 hours, or
    - TSB is within 2-3 mg/dL of the exchange transfusion level
- Dose may be repeated in 12-24 hours
- Rare but serious adverse effects include hypotension, tachycardia, and potentially NEC
- See medication DAG for IVIG infusion details: Link to IVIG DAGExchange transfusion:
- Exchange transfusion should be considered after 6 hours of intensive phototherapy unless there is evidence of acute bilirubin encephalopathy (significant lethargy, hypertonia, neck hyperextension, opisthotonus, high pitched cry) OR the total serum bilirubin is ≥ 5mg/dl above exchange level in infants >35 weeks

Guideline for exchange transfusion (≥ 35 weeks gestation)



- Note that it may take several hours to prepare blood for double volume exchange transfusion; therefore, contact blood bank ASAP if exchange transfusion is anticipated. Ensure intensive phototherapy is administered in the meantime.
- See Exchange Transfusion CPG for more details

VIII. Infants < 35 weeks gestation

a. Key points:

- Hyperbilirubinemia is more prevalent, severe, and protracted in preterm infants because of immature RBCs, liver, and GI tract
- Preterm brain is more vulnerable to bilirubin toxicity (increased oxidative stress, immature neurons more susceptible to bilirubin, increased disruption of blood-brain barrier)
- Bilirubin-related neurotoxicity can result in death or acute multisystem impairment and long-term neurodevelopmental impairment
- Even moderate or low TSB levels can lead to brain damage in sick preterm infants; risk increases both as GA decreases and TSB concentration rises
- Acute findings of bilirubin-induced neurologic dysfunction are often absent in preterm infants
- Phototherapy can prevent bilirubin neurotoxicity, but not without risk – especially in sickest premature infants < 750g BW (greater transmission of light through thin/gelatinous skin leads to increased photo-oxidative cell injury, phototherapy affects mesenteric and cerebral blood flow, bilirubin serves as a "natural" antioxidant)

b. Bilirubin measurement:

- Routine use of transcutaneous bilirubin (TcB) devices are not recommended in preterm infants based on currently available information[6]
- Infants > 1000g: obtain TSB at 24 hours of life (sooner if clinically jaundiced)
- Infants < 1000g: obtain TSB at 12 and 24 hours of life
- Frequency of monitoring serial bilirubin levels should be individualized based upon infant's clinical condition and risk factors (see below)
    - Consider monitoring every 12 hours if TSB is within 90% of phototherapy level
    - Consider monitoring every 4-6 hours if:
        - Evidence of hemolysis (ex. high reticulocyte count, rapidly rising bilirubin level (>0.5 mg/dL/hr))
        - Rising TSB despite phototherapy
        - TSB nearing exchange level

c. Risk factors for bilirubin toxicity:

- Hemolysis
- G6PD deficiency
- Asphyxia
- Neurological signs including significant lethargy or irritability
- Temperature instability
- Confirmed or suspected sepsis
- Acidosis

- Hypoalbuminemia (< 2.5 g/dL in preterm infants)

d. Phototherapy:

Guideline for initiating phototherapy (< 35 weeks gestation):

Gestational age	Initiate phototherapy Total serum bilirubin (mg/dL)
<28 0/7	5
28 0/7–29 6/7	6
30 0/7–31 6/7	8
32 0/7–33 6/7	10
34 0/7–34 6/7	12

Maisels et al.2012

- Note: use POSTMENSTRUAL AGE for phototherapy levels. For example, when a 29 0/7 week neonate is 7 days old, use the TSB level for 30 0/7 weeks
- Consider discontinuing phototherapy when TSB is at least 1-2 mg/dL below the phototherapy level for the infant's postmenstrual age

e. Ongoing monitoring:

- Measure bilirubin within 12-24 hours after phototherapy is discontinued
- Continue measuring bilirubin every 12-24 hours until TSB starts declining

f. Direct (conjugated) hyperbilirubinemia

- Some evidence suggests that direct hyperbilirubinemia may decrease albumin-binding capacity, and infants with bronze baby syndrome may be at increased risk of developing bilirubin encephalopathy[10,11]
- If direct bilirubin is $\geq$ 2 mg/dL and the infant is receiving parenteral nutrition, lipids should be restricted to 1 g/kg/day and the trace elements should be adjusted to reduce and/or omit manganese. Consider initiating/advancing enteral nutrition, as medically feasible
- Once the infant is fully enterally–fed, consider supplementing with fat soluble vitamin supplementation (i.e. AquADEK)
- Consider ursodiol for infants with biliary atresia or PN-associated cholestasis
- Consider subspecialist consultation if direct bilirubin level >50% of TSB

g. Follow-up after discharge:

- Infants with TSB levels that approach exchange transfusion threshold should be monitored until school age
- Follow-up should include neurologic and neurodevelopmental evaluation, MRI, and auditory brainstem response

h. Intravenous immunoglobulin (IVIG):

- IVIG will only be administered in the NICU
- Data is less established for the use of IVIG in preterm infants with antibody-mediated hemolysis
- In setting of isoimmune hemolytic disease (ex. Rh disease, ABO incompatibility, or minor blood group incompatibility), consider administration of IVIG (0.5 g/kg IV infused over 6 hours) if:
  - TSB is rising despite intensive phototherapy for at least 6 hours, or
  - TSB is within 2-3 mg/dL of the exchange transfusion level
- See medication DAG for IVIG infusion details: Link to IVIG DAG

i. Exchange transfusion:

- Sick preterm infants are more likely than term infants to experience serious complications (including death) from exchange transfusion

Guideline for exchange transfusion (< 35 weeks gestation):

Gestational age	Initiate Exchange transfusion Total serum bilirubin (mg/dL)
<28 0/7	11–14
28 0/7–29 6/7	12–14
30 0/7–31 6/7	13–16
32 0/7–33 6/7	15–18
34 0/7–34 6/7	17–19

Maisels et al.2012

- Use lower levels for infants with any of the following risk factors:
  - Hemolysis
  - Asphyxia
  - Neurological signs including significant lethargy or irritability
  - Temperature instability
  - Confirmed or suspected sepsis
  - Acidosis
  - Hypoalbuminemia (< 2.5 g/dL in prematures)
- Note that it may take several hours to prepare blood for double volume exchange transfusion. Therefore contact blood bank ASAP if exchange transfusion is anticipated. Ensure intensive phototherapy is administered in the meantime.
- See Exchange Transfusion CPG for more details

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