JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Neonatal Hyperbilirubinemia Clinical Pathway

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Table of Contents

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Neonatal Hyperbilirubinemia Clinical Pathway for Infants ≥ 35 Weeks Gestational Age

Rationale

This clinical pathway was developed by a consensus group to standardize the management of infants being evaluated and treated for neonatal hyperbilirubinemia for patients greater than or equal to 35 weeks gestational age. It addresses the following clinical questions or problems:

1. How to evaluate for neonatal hyperbilirubinemia
2. When to consider hospital admission
3. When to initiate treatment (ie phototherapy, IVIG, Exchange Transfusion)
4. When to initiate IV fluids
5. How to optimize breastfeeding and when to intitiate supplementation
6. When to end phototherapy and when to obtain rebound TsB
7. When to discharge infants ≥ 35 weeks gestational age
8. Management of hyperbilirubinemia in premature infants < 35 weeks gestional age

Background

Neonatal hyperbilirubinemia is the most commonly encountered clinical issue in newborn babies. A number of risk factors contribute to severe hyperbilirubinemia in newborn infants with gestational age ≥ 35 weeks. Evaluation for and management of hyperbilirubinemia is variable among clinical providers despite publication of AAP clinical practice guideline (6). In some instances, phototherapy is initiated earlier than the recommended total serum bilirubin (TsB) threshold based on the risk factors and postnatal age. More importantly, significant variation exists regarding TsB value at which phototherapy is discontinued and regarding the collection of a rebound bilirubin level, leading to increased length of hospitalization, interruption in breastfeeding, family dissatisfaction, and denials by the insurance companies.

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EC Management: Neonatal Hyperbilirubinemia Clinical Pathway
Infants ≥ 35 weeks Gestational Age

Obtain history, pattern and quality of stooling and voiding, mode of feeding (mother's own milk and/or formula), volume of feeding, physical exam, vital signs & growth parameters (based on EC protocol),

↓

Obtain STAT **CMP, CBC, Retic Count** *and* **Neonatal Type & Screen-Dat IgG** (if infant blood type and DAT status unknown),

Assess for Significant Hyperbilirubinemia Risk Factors, Neurotoxicity Risk Factors and Signs of Acute Bilirubin Encephalopathy,

Plot total serum bilirubin on Phototherapy Thresholds Nomogram (www.bilitool.org or www.peditools.org/bili2022),

↓

Is infant showing signs/symptoms of ACUTE BILIRUBIN ENCEPHALOPATHY[2], irrespective of bilirubin level?
or
Is TsB ***at/above*** PHOTOTHERAPY THRESHOLD*?
or
Is TsB ***less than 3 mg/dL below*** PHOTOTHERAPY THRESHOLD **but** with signs/symptoms of ACUTE HEMOLYSIS?

Provider discrection to start phototherapy if TsB < 3 mg/dL below threshold in order to prevent readmission.

↓ no

Is TsB ***below*** PHOTOTHERAPY THRESHOLD
and
meets following criteria?:

1) without any risk factors for neurotoxicity,
2) demonstrating adequate oral intake / hydration status,
3) without signs/symptoms of acute hemolysis,
4) close follow-up assured with PCP within 24 hrs of EC discharge

↓ yes

Discharge Home

yes →

no →

Admit to Hospital & refer to Inpatient Management Pathway
(For JHACH patients, contact NICU first regarding unit assignment (ie NICU vs PICU vs Pediatric Medicine).

Obtain **U/A & urine culture** via catheter specimen to evaluate for UTI, if hx & lab data not suggestive of dehydration/poor oral intake or hemolysis & without clear etiology for jaundice.

Start phototherapy STAT in the EC.

Significant Hyperbilirubinemia Risk Factors

*Lower gestational age (ie, risk increases with each additional week less than 40 wk)
*Jaundice in the first 24 h after birth
*Predischarge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) concentration close to the phototherapy threshold
*Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB or TcB of >0.3 mg/dL per hour in the first 24 h or >0.2 mg/dL per hour thereafter.
*Phototherapy before discharge
*Parent or sibling requiring phototherapy or exchange transfusion
*Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate dehydrogenase (G6PD) deficiency
*Exclusive breastfeeding with suboptimal intake
*Scalp hematoma or significant bruising
*Down syndrome
*Macrosomic infant of a diabetic mother

Neurotoxicity Risk Factors:

*Gestational age
*Albumin < 3.0 g/dL
*Isoimmune hemolytic disease (ie, positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
*Sepsis
*Significant clinical instability in the past 24h

Signs of Acute Bilirubin Encephalopathy:

*Hypertonia
*Arching
*Retrocollis
*Opisthotonos
*High-pitched cry
*Recurrent apnea

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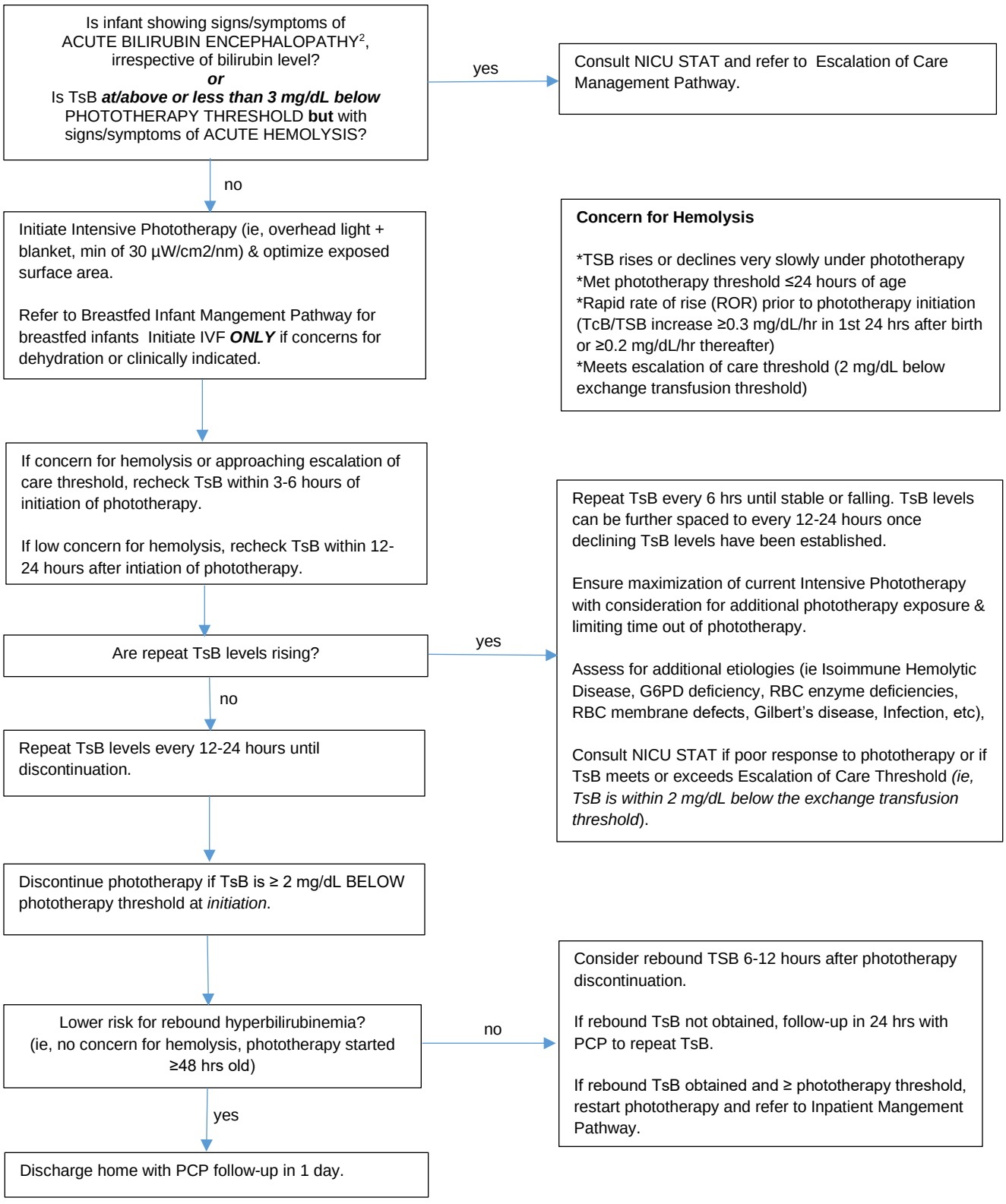
Inpatient Management: Neonatal Hyperbilirubinemia Clinical Pathway
Infants ≥ 35 weeks Gestational Age



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Escalation of Care Management: Neonatal Hyperbilirubinemia Clinical Pathway
Infants ≥ 35 weeks Gestational Age

TSB ≥ Escalation of Care threshold *(within 2 mg/dL below the exchange transfusion threshold)*
Consult Neonatology & admit to NICU STAT

Signs of Acute Bilirubin Encephalopathy?

yes

no

Start Intensive Phototherapy STAT:
* Overhead lights + pad/blanket LED devices, if available)
* Ensure maximization of current Intensive Phototherapy with optimized surface exposure & allowing NO time out of phototherapy for anything that is not medically necessary (Roll down diaper, etc)
* Position infant under center of device
* Decrease distance between device and infant
* Ensure irradiance >30 µW/cm2 /nm

Obtain STAT Labs (if not already done):
* CBC, Reticulocyte Count, CMP, Neonatal Type & Screen-Dat IgG, UA & Urine Culture
* Consider Sepsis evaluation (Blood Culture, CSF studies, & UA/Urine Cx if not already done), G6PD deficiency test, Blood Smear and/or Haptoglobin
* STAT TsB at least every 2 hours

Obtain STAT Vascular Access:
* Place peripheral IV
* Consider umbilical lines (Double Lumen UVC) with XR to confirm placement

Ensure Hydration:
* Total fluids 80-120 mL/kg/day (PO+IV)
* IV fluids with D10% +/- Electrolytes based on age and serum chemistry results
* Enteral feeds PO+NG/OG at 80 mL/kg/day

Consider IVIG administration:
* For infants with isoimmune hemolytic disease if TsB reaches or exceeds escalation of care threshold
* IVIG dose is 1 gram/kg over 2 hours and may be repeated in 12 hours if needed

Is TSB ≥ Exchange Transfusion Threshold?

yes

no

Continue Intensive Phototherapy

Continue phototherapy, hydration, and other interventions as above:
* Make NPO, Obtain Consent & Prepare for Urgent Exchange Transfusion (ET)
* Notify blood bank & place central line (if not yet placed)
* If, while preparing for the ET but before starting the procedure, a TsB concentration is < ET threshold and the infant does not show signs of acute bilirubin encephalopathy, then the ET may be deferred while continuing intensive PT & following the TsB every 2 hours until the TSB is below the escalation of care threshold.
* **Do not delay performing the ET while awaiting lab results**

Perform Exchange Transfusion* (ET)1, 2:
* Double volume ET: 160 mL/kg total blood
* Packed RBC & FFP to reconstitute HCT of 40-50%
* Cross-matched, < 48 hrs old, irradiated blood
* Aliquots by patient weight (3+ kg: 20 mL/aliquot; 2 kg: 15 mL/aliquot; 1 kg: 5-10 mL/aliquot)
* Lab monitoring before, during, and after ET (ie, Platelets, Glucose, Ca/iCa, Albumin, Serum Chemistries, TsB)
* Continuous cardiac and pulse oximetry
* Refer to hospital protocol for procedure detail

The bilirubin to albumin ratio (B/A) in relation to GA and risk can be used in conjunction with the TsB in determining the need for ET:
* ≥ 8.0 if the GA ≥ 38 wks & no neurotoxicity risk factors
* ≥ 7.2 if the GA ≥ 38 wks & at least 1 neurotoxicity risk factor
* ≥ 7.2 if the GA 35 – 37 wks & no neurotoxicity risk factors
* ≥ 6.8 if the GA 35 – 37 wks & at least 1 neurotoxicity risk factor

Neurotoxicity Risk Factors:
* GA < 38 wks & it increases with degree of prematurity
* albumin < 3.0 g/dL
* Isoimmune hemolytic disease
* sepsis
* significant clinical instability in the previous 24 hours

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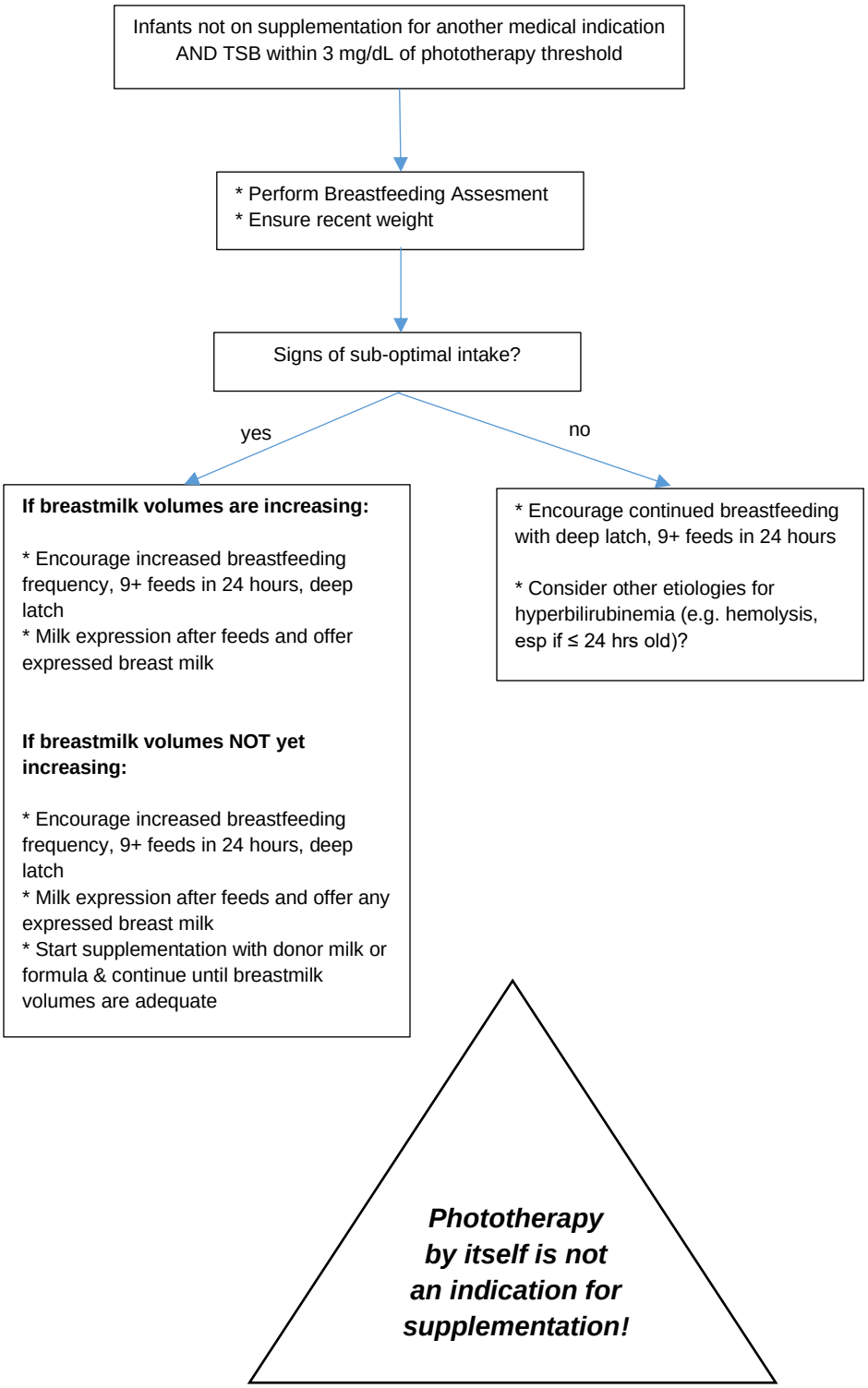
Breastfed Infant Management: Neonatal Hyperbilirubinemia Clinical Pathway
Infants ≥ 35 weeks Gestational Age



Breastfeeding Assessment:

* Consult Lactation, if available
* Risk factors for delayed lactogenesis
* Lactation History
* Maternal breast shape, breast changes
* LATCH scores & Latch depth
* Feeding frequency
* Infant transfer at the breast

Signs of Suboptimal Intake:

* Ineffective latch and/or suck
* Sleepy and difficult to wake for feedings
* Delayed colostrum or milk supply
* Weight loss > 10% from birth weight
* Laboratory abnormalities (e.g. hypoglycemia, hypernatremia)
* Ineffective milk transfer
* Uric acid crystals in urine
* < 4 stools on day 4 or meconium stools on day 5

Suggested supplementation volumes by ABM1,2:

Time (hrs)	mL/feed
0-24	2-10
24-48	5-15
48-72	15-30
72-96	30-60

*with expressed breast milk, donor breast milk (if available), or formula

Phototherapy Management:

In order to optimize intensive phototherapy, recommend keeping biliblanket under infant during breastfeeding sessions and to limit breastfeeding sessions to no more than 20 minutes.

1 Kellams A, Harrel C, Omage S, Gregory C, Rosen-Carole C. ABM clinical protocol #3: supplementary feedings in the healthy term breastfed neonate, revised 2017. Breastfeed Med. 2017;12:188-198. doi:10.1089/bfm.2017.29038.ajk

2 Flaherman VJ, Maisels MJ; Academy of Breastfeeding Medicine. ABM clinical protocol #22: guidelines for management of jaundice in the breastfeeding infant 35 weeks or more of gestation—revised. Breastfeed Med. 2017;12(5): 250–257

Algorithm developed with assistance from E. Hayes Bakken, MD, IBCLC, FAAP and Julie Gallois, MD, FAAP

Evaluation

- *Initial Assessment*
    a. EC Patients
        - Obtain history (including prenatal, birth and post-natal), pattern and quality of stooling and voiding, mode of feeding (mother's own milk and/or formula), volume of feeding, physical exam (including neurologic, hydration status, and jaundice), vital signs, growth parameters (ie weight).

- *Initial Evaluation*
    a. Obtain baseline laboratory tests: CBC, Reticulocyte Count, CMP and Neonatal Type & Screen-Dat IgG (if infant blood type and DAT status unknown). If labs abnormal and/or suggestive of infection and/or infant with clinical signs/symptoms of sepsis, a full sepsis work up including CSF culture, blood culture and urine culture (via catheter specimen) should be obtained before initiation of broad spectrum antibiotics in order to assess for neonatal sepsis. Refer to Febrile Neonate and UTI clinical pathways for additional recommendations and guidance.
    b. If history and laboratory data ***are not*** suggestive of dehydration / poor oral intake, hemolysis and without clear etiology for jaundice, obtain catheter urinalysis and urine culture, as data reveals significant number of neonates with jaundice as presenting sign of UTI. Of note, if U/A is suspicious for UTI via catheter specimen, a blood culture and lumbar puncture should be obtained before initiation of broad spectrum antibiotics in order to assess for neonatal sepsis. Refer to Febrile Neonate and UTI clinical pathways for additional recommendations and guidance. Consider consultation with Infectious Disease regarding appropriate antibiotic choice and length of treatment in cases of confirmed neonatal UTI obtained via catheter specimen.
    c. If history and laboratory data ***are not*** suggestive of dehydration / poor oral intake ***and*** suggestive of hemolysis, and particularly if bilirubin levels do not respond to or require additional phototherapy, assess further for:
        - Isoimmune Hemolytic Disease
        - G6PD deficiency
        - RBC enzymes deficiencies
        - RBC membrane defects
        - Gilbert disease
        - Infection
    d. Assess Significant Hyperbilirubinemia Risk Factors:
        - Lower gestational age (ie, risk increases with each additional week less than 40 wk)
        - Jaundice in the first 24 h after birth
        - Predischarge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) concentration close to the phototherapy threshold
        - Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB or TcB of >0.3 mg/dL per hour in the first 24 h or >0.2 mg/dL per hour thereafter
        - Phototherapy before discharge

- Parent or sibling requiring phototherapy or exchange transfusion
- Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Exclusive breastfeeding with suboptimal intake
- Scalp hematoma or significant bruising
- Down syndrome
- Macrosomic infant of a diabetic mother

e. Assess Neurotoxicity Risk Factors:
   - Gestational age
   - Albumin < 3.0 g/dL
   - Isoimmune hemolytic disease (ie, positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
   - Sepsis
   - Significant clinical instability in the past 24h

f. Assess Signs of Acute Bilirubin Encephalopathy:
   - Hypertonia
   - Arching
   - Retrocollis
   - Opisthotonos
   - High-pitched cry
   - Recurrent apnea

g. Plot total serum bilirubin on Hour-Specific Nomogram, Phototherapy Nomogram and Exchange Nomogram (www.bilitool.org or www.peditools.org/bili2022).

h. Hospital Admission / EC Discharge Criteria:
   - Admit to Hospital. *For JHACH patients, NICU to be first point of contact for ALL infants that require hospital admission, including discussions surrounding unit assignment (ie NICU vs PICU vs Pediatric Medicine) as well as need for NICU consults in cases where infants are admitted to units outside of NICU.* Possible scenarios for hospital admission include:
     - Infant with signs /symptoms of ACUTE BILIRUBIN ENCEPHALOPATHY, irrespective of bilirubin level
     - TsB ***at/above*** PHOTOTHERAPY THRESHOLD
     - TsB ***less than 3 mg/dL below*** PHOTOTHERAPY THRESHOLD *and* with signs/symptoms of ACUTE HEMOLYSIS?
     - Provider discrection to start phototherapy if TsB < 3 mg/dL below threshold in order to prevent readmission
     - Start phototherapy STAT in the EC
   - Consider discharge to home from EC if TsB is ***below*** PHOTOTHERAPY THRESHOLD and provided meets following criteria:
     - without any risk factors for neurotoxicity,
     - demonstrating adequate oral intake / hydration status,
     - without signs/symptoms of acute hemolysis,
     - close follow-up assured with PCP within 24 hrs of EC discharge

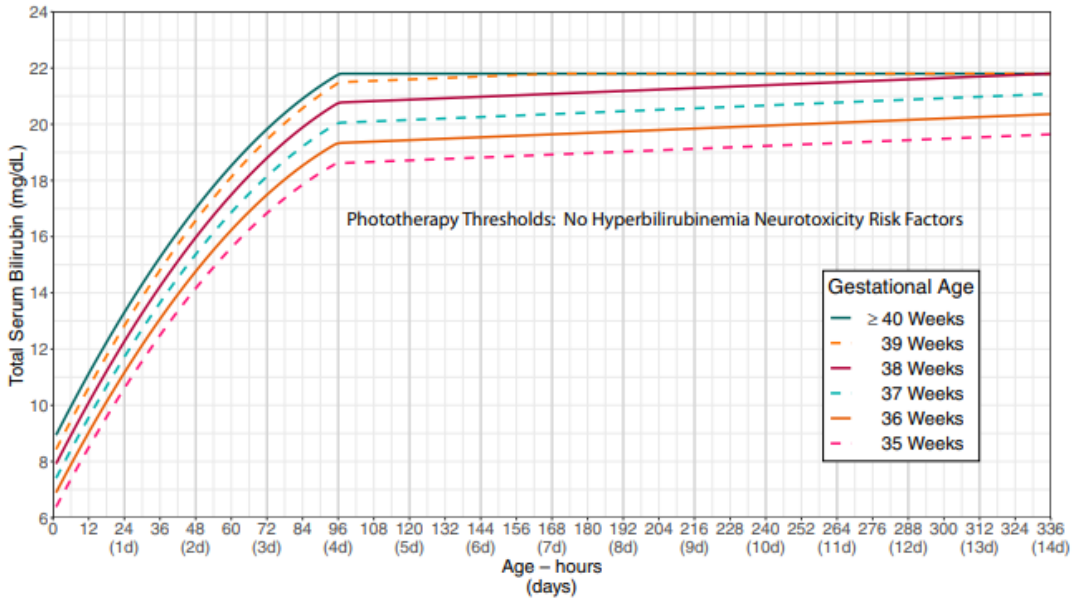


FIGURE 2

Phototherapy thresholds by gestational age and age in hours for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Note that infants <24 hours old with a TSB at or above the phototherapy threshold are likely to have a hemolytic process and should be evaluated for hemolytic disease as described in recommendation 14. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. See Supplemental Fig 1.

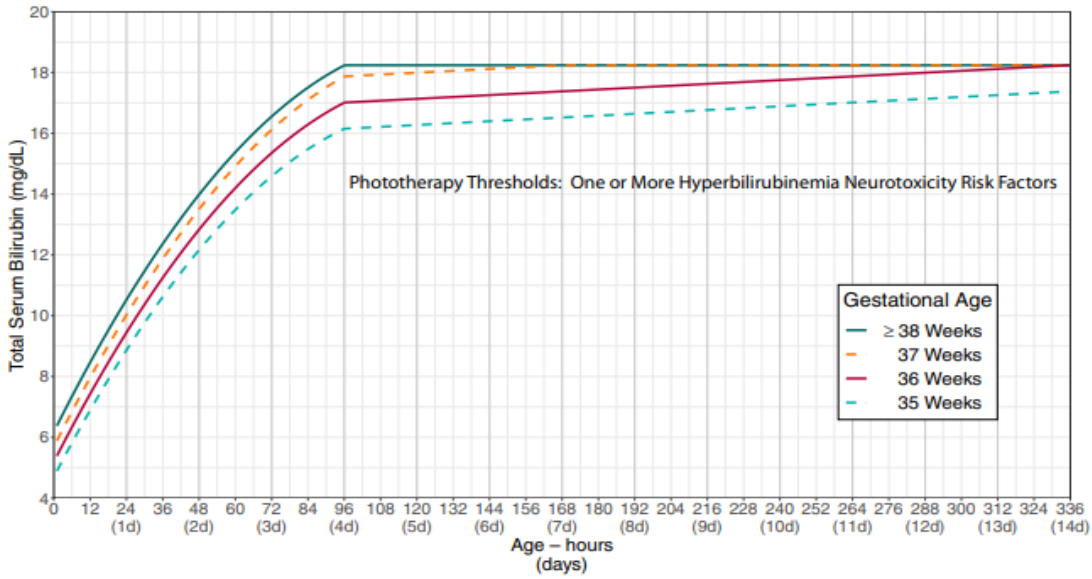


FIGURE 3

Phototherapy thresholds by gestational age and age in hours for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract the direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. See Supplemental Fig 2.

Treatment

- *Guidelines for Administration of Phototherapy*
    a. Recommend initiation of intensive phototherapy= 30 µW/cm2/nm (ie overhead light and biliblanket) and optimize exposed surface area.
    b. Measure the irradiance level with bilimeter upon initiation of phototherapy, upon addition of another phototherapy device, and at least every 12 hours.
    c. If concern for hemolysis or approaching escalation of care threshold (ie within 2 mg/dL below exchange transfusion threshold), recheck TsB within 3-6 hours of initiation of phototherapy. If low concern for hemolysis, recheck TsB within 12-24 hours after intiation of phototherapy.
        - If repeat TsB's are not rising with administration of phototherapy, repeat TsB levels every 12-24 hours until discontinuation,
        - If repeat TsB's are rising in spite of administration of phototherapy:
            - Repeat TsB every 6 hrs until stable or falling. TsB levels can be further spaced to every 12-24 hours once declining TsB levels have been established.
            - Ensure maximization of current Intensive Phototherapy with consideration for additional phototherapy exposure & limiting time out of phototherapy.
            - Assess for additional etiologies (ie Isoimmune Hemolytic Disease, G6PD deficiency, RBC enzyme deficiencies, RBC membrane defects, Gilbert's disease, Infection, etc).
            - Consult NICU STAT if poor response to phototherapy or if TsB meets or exceeds Escalation of Care Threshold.

- *Guidelines for Discontinuation of Phototherapy and Obtaining Rebound Bilirubin Levels*
    a. Discontinue phototherapy if TsB is ≥ 2 mg/dL BELOW phototherapy threshold at initiation.
    b. If infant is at lower risk for rebound hyperbilirubinemia? (ie, no concern for hemolysis, phototherapy started ≥48 hrs old), discharge home with PCP follow-up in 1 day.
    c. If infant is at risk for rebound hyperbilirubinemia (ie, concern for hemolysis, phototherapy started ≤48 hrs old), consider rebound TSB 6-12 hours after phototherapy discontinuation.
        - If rebound TsB not obtained, follow-up in 24 hrs with PCP to repeat TsB.
        - If rebound TsB obtained and ≥ phototherapy threshold, restart phototherapy and refer to Inpatient Mangement Pathway.

- *Breastfed Infant Management*
    a. For infants not on supplementation for another medical indication AND TSB within 3 mg/dL of phototherapy threshold, document recent weight and perform a Breastfeeding Assessment:
        - Consult Lactation, if available
        - Risk factors for delayed lactogenesis
        - Lactation History

- Maternal breast shape, breast change
- LATCH scores & Latch depth
- Feeding frequency
- Infant transfer at the breast

b. Assess for signs of suboptimal intake:
   - Ineffective latch and/or suck
   - Sleepy and difficult to wake for feedings
   - Delayed colostrum or milk supply
   - Weight loss > 10% from birth weight)
   - Laboratory abnormalities (e.g. hypoglycemia, hypernatremia)
   - Ineffective milk transfer
   - Uric acid crystals in urine
   - < 4 stools on day 4 or meconium stools on day 5

c. If there are NO signs of suboptimal intake, continue to encourage breastfeeding with deep latch, 9+ feeds in 24 hours, and consider other etiologies for hyperbilirubinemia (e.g. hemolysis, esp if ≤ 24 hrs old).

d. If there ARE signs of suboptimal intake:
   - and breastmilk volumes ARE increasing:
     - Encourage increased breastfeeding frequency, 9+ feeds in 24 hours, deep latch.
     - Milk expression after feeds and offer expressed breast milk.
   - and breastmilk volumes are NOT increasing:
     - Encourage increased breastfeeding frequency, 9+ feeds in 24 hours, deep latch.
     - Milk expression after feeds and offer any expressed breast milk.
     - Start supplementation with donor milk or formula and continue until breastmilk volumes are adequate.

e. Suggested supplementation volumes (of note, phototherapy by itself is not an indication for supplementation):
   - 0-24 hours of life – supplement 2-10 ml each feed
   - 24-48 hours of life – supplement 5-15 ml each feed
   - 48-72 hours of life – supplement 15-30 ml each feed
   - 72-96 hours of life – supplement 30-60 ml each feed

f. In order to optimize intensive phototherapy, recommend keeping biliblanket under infant during breastfeeding sessions and to limit breastfeeding sessions to no more than 20 minutes.

- *<u>Intravenous Fluids (IVF) Administration Management</u>*

a. IV fluids and/or supplemental formula is routinely NOT indicated unless clinical signs of dehydration are suspected. It is important to underscore that enteral feeds hasten elimination of bilirubin.

b. Encourage frequent feedings every 2-3 hours and for breastfed infants, engage lactation specialist for additional breastfeeding support.

c. Consider initiating IVF based on the following clinical factors:
   - Weight loss disproportionate for postnatal age
   - Hypernatremia

- Increased urine specific gravity
- Poor oral intake
- Decreased urine output
- Signs of poor perfusion
- TsB above or within 3 mg/dL of exchange level

- *<u>Escalation of Care Management (defined as within 2 mg/dL below exchange transfusion level)</u>*
    a. Consult Neonatalogy and Admit to NICU STAT.
    b. If there ARE signs of acute bilirubin encephalopathy, then, proceed to "Is TsB ≥ Exchange Transfusion Threshold" subset below.
    c. If there are NO signs of acute bilirubin encephalopathy:
        - Start Intensive Phototherapy STAT:
            - Overhead lights + pad/blanket LED devices, if available)
            - Ensure maximization of current Intensive Phototherapy with optimized surface exposure and allowing no time out of phototherapy for anything that is not medically necessary (Roll down diaper, etc)
            - Position infant under center of device
            - Decrease distance between device and infant
            - Ensure irradiance >30 μW/cm2 /nm
        - Obtain STAT Labs, if not already done:
            - CBC, Reticulocyte Count, CMP, Neonatal Type & Screen-Dat IgG, UA and Urine Culture
            - Consider Sepsis evaluation (Blood Culture, CSF studies, as well as UA and Urine Culture if not already obtained), G6PD deficiency test, Blood Smear and Haptoglobin
            - STAT TsB at least every 2 hours
        - Obtain STAT Vascular Access:
            - Place peripheral IV
            - Consider umbilical lines (Double Lumen UVC) with XR to confirm placement
        - Ensure Hydration:
            - Total fluids 80-120 mL/kg/day (PO+IV)
            - IV fluids with D10% +/- Electrolytes based on age and serum chemistry results
            - Enteral feeds PO+NG/OG at 80 mL/kg/day
        - Consider IVIG Administration
            - For infants with isoimmune hemolytic disease if TsB reaches or exceeds escalation of care threshold
            - IVIG dose is 1 g/kg over 2 hours and may be repeated in 12 hours, if needed
        - If TsB ≥ Exchange Transfusion Threshold:
            - Continue phototherapy, hydration, and other interventions as above:

a. Make NPO, Obtain Consent & Prepare for Urgent Exchange Transfusion
b. Notify blood bank and place central line (if not yet placed)
c. If, while preparing for the Exchange Transufsion but before starting the procedure, a TsB concentration is < Exchange Transfusion threshold and the infant does not show signs of acute bilirubin encephalopathy, then the Exchange Transfusion may be deferred while continuing intensive Phototherapy & following the TsB every 2 hours until the TsB is below the escalation of care threshold
d. Do not delay performing the ET while awaiting lab results

- Perform Exchange Transfusion:
  a. Double volume ET: 160 mL/kg total blood
  b. Packed RBC & FFP to reconstitute HCT of 40-50%
  c. Cross-matched, < 48 hrs old, irradiated blood
  d. Aliquots by patient weight (3+ kg: 20 mL/aliquot; 2 kg: 15 mL/aliquot; 1 kg: 5-10 mL/aliquot)
  e. Lab monitoring before, during, and after ET (ie, Platelets, Glucose, Ca/iCa, Albumin, Serum Chemistries, TsB
  f. Continuous cardiac and pulse oximetry
  g. Refer to hospital protocol for procedure detail
- The bilirubin to albumin ratio (B/A) in relation to GA and risk can be used in conjunction with the TsB in determining the need for Exchange Transfusion:
  a. ≥ 8.0 if the GA ≥ 38 wks & no neurotoxicity risk factors
  b. ≥ 7.2 if the GA ≥ 38 wks & at least 1 neurotoxicity risk factor
  c. ≥ 7.2 if the GA 35 – 37 wks & no neurotoxicity risk factors
  d. ≥ 6.8 if the GA 35 – 37 wks & at least 1 neurotoxicity risk factor

- If TsB < Exchange Transfusion Threshold, then continue Intensive Phototherapy

Criteria for Hospital Discharge

- All other hospital discharge criteria have been met.
- Close follow-up with PCP within 24-48 hrs (based on risk for rebound hyperbilirubinemia) of discharge has been assured.
- Verbal and written information regarding signs/symptoms of jaundice warranting immediate medical attention distributed to caregivers.

Patient Status:

All patients with neonatal indirect hyperbilirubinemia should be placed in “inpatient” status if admitted for phototherapy.

Outcomes

1) Rate of readmissions for jaundice/hyperbili
2) Rate of administration of IV fluids
3) Rate of obtaining rebound bilirubin levels prior to discharge
4) Length of stay for patients in the ER
5) Total length of stay for patients in the hospital
6) Length of phototherapy (time initiated to time discontinued)

Care Management: Neonatal Hyperbilirubinemia Clinical Pathway
Infants < 35 weeks Gestational Age

Hyperbilirubinemia in premature infants less than 35 weeks gestational age (GA) is more prevalent and protracted than in term infants and carries a higher risk for the development of bilirubin-induced neurologic dysfunction (BIND) at lower TsB values. This is thought to be due to the immaturity of the central nervous system and the associated co-morbdities that may potentiate bilirubin toxicity.(9)

Risks factors:

Inherent to premature infants include:
- Increased red blood cells breakdown causing a higher bilirubin load
- Immature liver function leading to decreased bilirubin clearance and conjugation
- Increased enterohepatic circulation due in part to the delay in initiating and advancing enteral feeds

Clinical presentations:

Are most often limited to mild and protracted jaundice. Premature infants are at higher risk for BIND and unfortunately, the acute signs and symptoms of BIND in premature infants are subtle and non-specific and may present primarily as recurrent apneic episodes.

It has been reported that the increased maximum total bilirubin level in premature infants is independently associated with hearing screen failure. Further prospective studies are needed to understand whether this increased risk of hearing screen failure translates to increased risk of hearing loss (10)(Singh 2021)

In unstable VLBW preterm infants, increasing levels of total plasma bilirubin were also found to be directly associated with increasing risk of death or adverse neurodevelopmental outcomes at 18-22 months of age (11) (Ohs, 2010).

Bilirubin measurements:

Even though the accuracy of transcutaneous bilirubin (TcB) measurements has been validated in infants 28-34 6/7 weeks GA (12-Maisels 2015; 13-Nagar 2013), the tool is not uniformly used in the premature baby population and a 2018 study found that only 28% of NICUs in California actually use TcB measurement in this patient population (14) (Bhatt 2018).

Management Approach:

Unlike in term infants, evidence-based guidelines to the initiation of phototherapy and performing an exchange transfusion in infants < 35 weeks GA are lacking. This is due in part due to the absence of reliable and predictive measures of bilirubin neurotoxicity as well as

uncertainties about the risk / benefit ratio of the interventions in this at risk patient poplation.

Initiation of Phototherapy:

The expert opinion concensus on initiating phototherapy in infants < 35 weeks was proposed by Maisels in 2012 (17). It has since been routinely followed by the majority of NICUs in the U.S.

Postmenstrual age is to be used to compute need for phototherapy as follows:

- GA <28 weeks – TB 5 to 6 mg/dL (86 to 103 micromol/L)
- GA 28 to 29 weeks – TB 6 to 8 mg/dL (103 to 137 micromol/L)
- GA 30 to 31 weeks – TB 8 to 10 mg/dL (137 to 171 micromol/L)
- GA 32 to 33 weeks – TB 10 to 12 mg/dL (171 to 205 micromol/L)
- GA 34 to <35 weeks – TB 12 to 14 mg/dL (205 to 239 micromol/L)

Given the concerns of increased mortality in infants < 1000 grams exposed to aggressive phototherapy, it is recommended to start with an irradiance of 15 microW/cm per nm. If TB continues to rise, increase the surface area of exposure. Only if a poor response is still observed, increase the irradiance in increments as needed up to a max of 30 microW/cm per nm.

Indications for Exchange Transfusions:

Exchange transfusion carries a significant risk of complications that include cardio-respiratory arrest, arrhythmias, thrombosis, thrombocytopenia, hypothermia, necrotizing enterocolitis and infection.(18) (Patra, 2004)

Assessment of the risk/benefit ratio of an exchange transfusion needs to be taken into consideration. Candidates for such an intervention would be infants who have neurologic signs suggestive of BIND or those who fail to respond to aggressive phototherapy with persistently rising TsB levels.

The expert opinion concensus on initiating exchange transfusion in infants 25 weeks to 35 weeks GA was proposed by Maisels in 2012.(16)

Postmenstrual age is to be used to compute need for exchange transfusion as follows:

- GA <28 weeks – TB 11 to 14 mg/dL (188 to 239 micromol/L)
- GA 28 to 29 weeks – TB 12 to 14 mg/dL (205 to 239 micromol/L)
- GA 30 to 31 weeks – TB 13 to 16 mg/dL (222 to 274 micromol/L)
- GA 32 to 33 weeks – TB 15 to 18 mg/dL (257 to 308 micromol/L)
- GA >34 weeks – TB 17 to 19 mg/dL (291 to 325 micromol/L)

Per the authors, “The wider ranges and overlapping of values in the exchange transfusion column reflect the degree of uncertainty in making these recommendations. They recommend to use the lower range of the listed TSB levels for infants at greater risk for bilirubin toxicity – such as (1) lower gestational age, (2) lower serum albumin levels < 2.5 g/dL, (3) rapidly rising TB and (4) clinically unstable infants such as those with severe metabolic acidosis, sepsis, significant apnea or hypotension, among other conditions”

Special Considerations for Infants 24 – 28 weeks GA and/or ELBW infants:

Is Bilirubin harmful?

Uncertainties remain as to the safe levels of TsB in this very premature patient population. Some observational studies have raised concerns about very low levels of TSB (≤ 5 mg/dL) as potentially causing long-term neurodevelopmental deficits. Others suggested that moderate TsB levels may actually be of benefit given the antioxidant properties of bilirubin.

Is Phototherapy (PT) Safe?

A. A multicenter, randomized NICHD Neonatal Research Network study published in 2008 (17), compared aggressive to conservative PT among 1974 ELBW infants. Infants were stratified in 2 groups: BW 501 - 750 g and BW 751 - 1000 g. Conservative PT was initiated, continued, or restarted for TSB ≥ 8 mg/dL for infants with BW 501 to 750 g and for TsB ≥ 10 mg/dL for infants with BW 751 to 1000 g. Aggressive phototherapy was initiated, continued, or restarted for TSB ≥ 5 mg/dL for infants in either group.

They found: 1) no significant difference in the rate of death or neurodevelopmental impairment (the primary outcome) at 18 to 22 months of CGA age between neonates randomized to either conservative of aggressive PT; 2) a significant reduction in the rate of neurodevelopmental impairment among the aggressive PT group; and 3) the rate of death among infants with BW 501 to 750 g was higher with aggressive PT. The difference was not statistically significant (p=0.15) but a post hoc, Bayesian analysis, estimated an 89% probability that aggressive phototherapy increased the rate of deaths in this subgroup. This finding was considered worrisome and needing to be taken seriously given an older trial (18) that raised similar concerns and the limited power of the study. The etiology for such a correlation is postulated to be secondary to oxidative injury to cell membranes and DNA.

B. Because of the reported increased mortality in infants with BW 501 to 750 g, prudence has been advocated, at least in infants with BW <750 g, to initiate phototherapy at lower irradiance levels and only to increase these levels, or to increase the surface area of the infant exposed to phototherapy, if the TSB continues to rise (Maisels, 2012)(15)

C. A substudy of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network PT trial was performed to evaluate the efficacy of phototherapy (PT) devices and the outcomes of ELBW infants treated with those devices. It included 1404 infants treated with a single type of PT device during the first 24±12 h of treatment. Their standard of care included the following guidelines to intensify PT for TSB values of: 11 mg/dL in 501 to 750 g infants and 13 mg/dL in 751 to 1000 g infants. The definition of 'high TSB' was predefined as a TSB within 2 mg/dl of the predetermined exchange transfusion criterion (≥11 mg dl^{-1} for 501 to 750 g infants and ≥13 mg/dl for 751 to 1000 g infants). An exchange transfusion was indicated if the TSB exceeded the threshold values after 8 h of intensified treatment (Morris, 2013)(19)

D. In a UpToDate review (20), Bhutani suggested the following guidelines for increasing the irradiance level in infants 24 to 26 weeks GA when TSB continues to rise despite adequate phototherapy:

- >26 to 28 weeks GA:
  - Start with 25 to 30 microW/cm^2/nm to one (dorsal/ventral) body surface.
  - Increase to 25 to 30 microW/cm^2/nm to both ventral and dorsal body surfaces.
  - Pre-exchange – 30 microW/cm^2/nm to both ventral and dorsal body surfaces.

- 24 to <26 weeks GA:
  - Start with 15 to 25 microW/cm^2/nm to one (dorsal/ventral) body surface.
  - Increase to 15 to 25 microW/cm^2/nm to both ventral and dorsal body surfaces.
  - Pre-exchange – 25 microW/cm^2/nm to both ventral and dorsal body surfaces.

E. Information about hyperbilirubinemia management in infants < 501 grams is currently lacking. PT initiation threshold may be lower than what is reported in the tables above and provider discretion is advised.

Clinical Management:

Infants born at < 35 weeks gestation are to have their TsB regularly checked in the first week of life per the NICU standard of care. Indications for the initiation of PT or performing an exchange transfusion will be based on the expert opinion concensus proposed by Maisels in 2012 as follows.

	Phototherapy	*Exchange transfusion*
Gestational age (week)	*Initiate phototherapy total serum bilirubin (mg dl^{-1})*	*Total serum bilirubin (mg dl^{-1})*
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

Reproduced from Maisels, 2012

Important Information:

* Use PMA for Phototherapy

* Consider discontinuation of Phototherapy when TsB is 1–2 mg/dL below the initiation level for the infant's PMA.

* Prophylactic phototherapy in case of skin bruising is not routinely recommended. For infants at higher risk, it is suggested to follow TsB every 12 hours until phototherapy is started, then proceed per guidelines

* For infants > 28 wks or >1000 gms, using TcB or bilirubin measurement via blood gas analyzer could be an option as to minimize blood draws in stable patients with significant skin bruising.

* For infants < 28 wks or <1000 gms, using bilirubin measurement via blood gas analyzer could be an option as to minimize blood draws in stable patients with significant skin bruising.

* Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin from the total.

* Given the high risk and complications of exchange transfusion in infants < 35 weeks, it is recommended for exchange transfusion to be performed if TsB value is at exchange level after 8 hours of intensive and optimized Phototherapy. Exceptions would be at the discretion of the physician.

* Information about hyperbiliruinemia management in infants < 25 weeks is currently lacking. Phototherapy and exchange transfusion initiation threshold may be lower than what is reported in the tables above and provider discretion is advised

* Measure irradiance at regular intervals per NICU protocol.

* For infants <1000 g BW, start phototherapy at lower irradiance levels (15-20 Mwatts). If the TsB continues to rise, increase the surface area exposed.
Increase the irradiance only if the TsB continues to rise.

* Increases of irradiance ought to be done in a stepwise fashion based on Bhutani's recommendations:

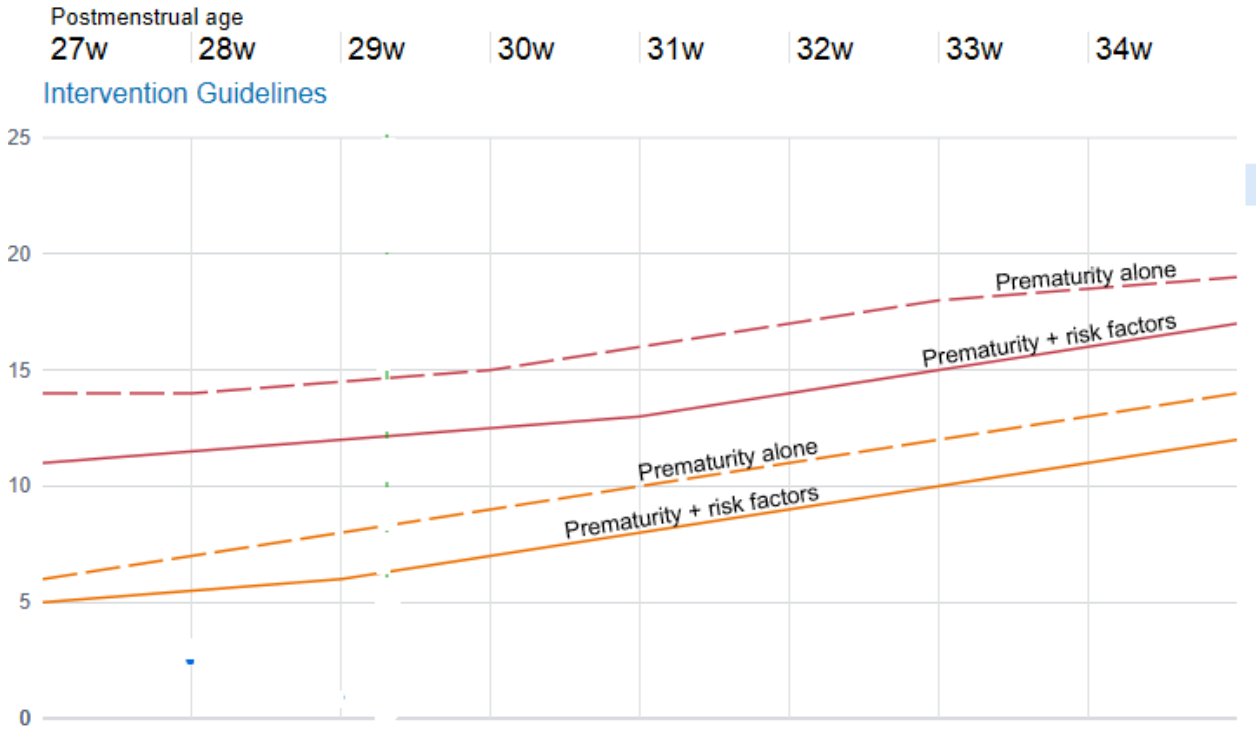
>26 to 28 weeks GA:

- •Start with 25 to 30 microW/cm^2/nm to one (dorsal/ventral) body surface.
- •Increase to 25 to 30 microW/cm^2/nm to both ventral and dorsal body surfaces.
- •Pre-exchange – 30 microW/cm^2/nm to both ventral and dorsal body surfaces.

24 to <26 weeks GA:

- •Start with 15 to 25 microW/cm^2/nm to one (dorsal/ventral) body surface.
- •Increase to 15 to 25 microW/cm^2/nm to both ventral and dorsal body surfaces.
- •Pre-exchange – 25 microW/cm^2/nm to both ventral and dorsal body surfaces.

The below information is currently in Epic, under bilirubin activity as follows:



Stanford Children's Health Premie BiliRecs
Use the lower range of the listed TSB levels for infants at greater risk for bilirubin toxicity:
1. Serum albumin levels < 2.5 g/dL
2. Rapidly rising TSB levels suggesting hemolytic disease
3. Those who are clinically unstable, as described below:

When a decision is being made about the initiation of phototherapy or exchange transfusion, infants are considered to be clinically unstable if they have one or more of the following conditions:
A. Blood pH < 7.15
B. Blood culture positive sepsis in the prior 24 hours
C. Apnea and bradycardia requiring cardio-respiratory resuscitation (bagging and/or intubation) during the previous 24 hours
D. Hypotension requiring pressor treatment during the previous 24 hours
E. Mechanical ventilation at the time of blood sampling

Stanford Children's Health Premie BiliRecs, a free, publicly available clinical decision support tool found at https://pbr.stanfordchildrens.org/, which notes that its "[r]esults are based on An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation by Maisels et al. (J Perinatol 2012)." Used with permission.

Transfusion Guidelines Legend
- Prematurity alone
- Prematurity + additional neurotoxicity risk factors

Phototherapy Guidelines Legend
- Prematurity alone
- Prematurity + additional neurotoxicity risk factors

Glossary:
g – grams
B/A: bilirubin to albumin
BIND: bilirubin induced neurologic dysfunction
BW – birth weight
ELBW – extremely low birth weight
ET- exchange transfusion
GA – gestational age
mg/dL – millirgram per deciliter
PMA – post menstrucal age
PT – phototherpy
TcB – transcutaneous bilirubin
TsB – total serum bilirubin

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Appendix A: Neonatal Phototherapy Nursing Checklist

- ☐ Phototherapy source ordered in the patient's EMR (bili-blanket, spot, etc.)
- ☐ Bilimeter to test irradiance level (as per phototherapy order – generally 30-35 μW/cm^2/nm
- ☐ Infant should be in diaper only, no clothes
- ☐ Position phototherapy device at bedside with lights set at recommended distance from the infant. For fluorescent and LED lights, this is as close as possible to the infant's skin, typically less than 10 cm. If using a halogen spot light, the light should be kept at the manufacturer recommended distance to avoid overheating.
- ☐ Isolette (Giraffe Omnibed) – please see attached neonatal quick reference
    - Isolette is needed for most phototherapy. If infant is on bili-blanket only, may be in open crib if swaddled
- ☐ Temperature probe and temperature probe cover for use in isolette
- ☐ Thermometer to measure axillary temperature
- ☐ Eye protection
- ☐ Bili-blanket: obtain bili-blanket cover and ensure that illuminated side is facing patient
- ☐ TsB order present with frequency listed

<u>Further information may be found in:</u>

MyLearning:

ACH-Giraffe Bed video

Mosby's Nursing Skills:

Phototherapy (Maternal-Newborn)

Phototherapy Blanket (Maternal-Newborn)

NICU Education Specialists: x72116 and x72881

Appendix B: Neonatal Thermoregulation Quick Reference

- **Giraffe**
  - Infants should remain in servo (baby) mode and their body temperature should be maintained at 36.5C-37.5C.
    - Keep top down as much as possible and work through portholes
  - Temperature probe over the liver (not over bone) while supine or on the flank while prone
    - When using phototherapy lights, the **probe must be directly in the path of the radiant heat of the light**; do not place the probe in an area shielded from the phototherapy light
    - Cover probe with reflective temp probe cover
    - Probe must be visible
  - No clothing or swaddling

- **Thermoregulation**
  - Infant's axillary temperature should be 36.5-37.5.
  - Keep top of isolette down whenever possible
  - Use "Air boost" button when working through portholes
  - Check axillary temperature every 3 hours
    - If there is more than a 0.5 degree difference between the axillary temperature and isolette temp probe temperature, the two are not correlating.
      - Check temperature probe position and adjust if needed
      - Replace temperature probe if necessary