Newborn Critical Care Center (NCCC) Clinical Guidelines

Management of Non-Hemolytic Hyperbilirubinemia

GOALS

- Prevent bilirubin-induced neurological dysfunction, including bilirubin encephalopathy or kernicterus
- Avoid exchange transfusion
- Minimize the risk of harms associated with management of hyperbilirubinemia

This clinical guideline includes recommendations from the 2022 American Academy of Pediatrics (AAP) Clinical Practice Guideline on management of hyperbilirubinemia in infants ≥35 weeks gestation.[1] For ease of reference, we have noted when content in this clinical guideline is directly relevant to a pertinent key action statement (KAS) from the 2022 AAP Guideline. While the AAP Guideline addresses management of hyperbilirubinemia regardless of its cause, our guideline is specifically for neonates with *non-hemolytic* hyperbilirubinemia.

When a neonate's bilirubin approaches exchange level, the AAP Guideline recommends management of hyperbilirubinemia in the ICU setting (Section II. e.). Our guideline aligns with all AAP Guideline recommendations directly relevant to escalation of care.

Recommendations for management of hyperbilirubinemia *prior to escalation of care* in the AAP Guideline are written for newborns who are typically not cared for in an ICU setting. With this in mind, we have listed these recommendations as considerations (Sections II. b-d.). Providers should consider the recommendation in the context of their patient, and use their clinical judgement regarding its implementation.

Given the paucity of data on management of hyperbilirubinemia in neonates <35 weeks gestation, our guideline focuses on the management of non-hemolytic hyperbilirubinemia in neonates ≥35 weeks gestation. When there is data to support a recommendation for neonates <35 weeks gestation, we have noted this by underlining the recommendation. Of note, our clinical guideline includes phototherapy and exchange transfusion thresholds for neonates <35 weeks gestation (see Appendix C).

ASSESSMENT AND MONITORING FOR HYPERBILIRUBINEMIA

A. Identifying Risk Factors for Hyperbilirubinemia

1. The following factors increase the risk of hyperbilirubinemia:
    a. Prematurity
    b. Clinically apparent jaundice within 24 hours of birth
    c. Known or suspected hemolysis, indicated by one or more of the following:
    d. Positive DAT
    e. Rate of rise of bilirubin >0.3mg/dL/h in the first 24 hours
        i. This rapid rate of increase is exceptional and suggests hemolysis; perform a DAT if not previously done (KAS 7[1])
    f. Rate of rise of bilirubin >0.2mg/dL/h after the first 24 hours
    g. Family history of red blood cell disorders, including G6PD

h. History of phototherapy or exchange transfusion in a parent or sibling
i. Exclusive breastfeeding with insufficient intake
j. Trisomy 21
k. Macrosomic neonates of diabetic mothers
l. Cephalohematoma, subgaleal hemorrhage, or other significant bruising

B. Identifying the Need for Treatment

1. Visually assess all newborns for jaundice at least every 12 hours from birth to discharge.
   a. If jaundice is noted within 24 hours of birth, measure a transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) immediately (KAS 4 & 5[1]).
   b. Otherwise, collect a TcB or TSB between 24 and 48 hours after birth or before discharge.
2. *TcB is an appropriate screening tool for all neonates, regardless of gestational age, to determine the need for TSB measurement.*[1,3]
   a. If the TcB measurement is above phototherapy threshold, within 3 mg/dL of threshold, or exceeds 15 mg/dL, measure a TSB.
   b. Decisions to initiate phototherapy, to escalate care for hyperbilirubinemia, or to discontinue phototherapy must be based on the TSB (KAS 3 & 6[1]).

TSB levels at which phototherapy or double volume exchange transfusion should be initiated are based on age in hours, gestational age, and the presence of neurotoxicity risk factors.

TSB thresholds may be found in the following appendices:

Appendix A: Phototherapy thresholds for neonates ≥35 weeks gestation

Appendix B: Exchange transfusion thresholds for neonates ≥35 weeks gestation

Appendix C: Phototherapy and exchange transfusion thresholds for neonates <35 weeks gestation

Appendix D: Epic tools for phototherapy and exchange transfusion thresholds

TREATMENT OF NON-HEMOLYTIC HYPERBILIRUBINEMIA

A. Providing Phototherapy

1. If a neonate is above the hour-specific threshold for phototherapy, initiate intensive phototherapy (KAS 10[1]).
   a. Intensive phototherapy is defined as narrow-spectrum LED blue light with irradiance ≥30 μW/cm^2 per nm at a wavelength of 460-490nm.[1,2]
   b. Of note, treatment with a bili blanket is not considered intensive phototherapy;[2] however, inpatient use due to family preference is reasonable if TSB is within 2 mg/dL of the phototherapy threshold.

2. Support the neonate's own physiologic clearance of bilirubin with full enteral feeds when clinically appropriate (KAS 2[1]).

B. Monitoring Neonates Receiving Phototherapy

1. Once phototherapy is initiated, determine timing of TSB measurements based on the neonate's age, neurotoxicity risk factors, and rate of rise of TSB; consider a maximum of 24 hours between measurements (KAS 12[1]).
2. For neonates requiring phototherapy:
    a. Consider checking a hemoglobin, hematocrit, or CBC to assess for anemia and to have a baseline (KAS 14[1])
    b. Obtain a DAT in neonates of mothers with a positive antibody screen, blood type O, or Rh(D)
    c. Consider evaluating for G6PD if bilirubin is unresponsive or rising on intensive phototherapy (KAS 14[1])

C. Discontinuing Phototherapy

1. Consider discontinuing phototherapy once TSB is at least 2mg/dL below *the hour-specific threshold at which phototherapy was initiated*
    a. Providers may consider continuing phototherapy longer if risk factors exist (KAS 15[1])

D. Follow-up After Phototherapy

1. Obtain a follow-up TSB after phototherapy cessation based on the risk of rebound, generally 24 hours after discontinuation (KAS 16[1])
    a. Consider obtaining a rebound earlier (e.g., at 6-12 hours after discontinuation) for neonates who had phototherapy prior to 48 hours after birth (KAS 16[1])
2. Once more than 24 hours have transpired since phototherapy discontinuation, TcB may be used in neonates ≥35 weeks gestation (KAS 16[1])
    a. *For neonates <35 weeks gestation, data is insufficient to support the use of TcB after phototherapy*
    b. If appropriate follow-up cannot be arranged for an infant recommended to have an outpatient follow-up bilirubin measure, discharge may be delayed (KAS 8[1])

E. Escalation of Care

1. Neonates approaching exchange level (defined as within 2mg/dL of the exchange threshold) require an escalation of care and management in the NCCC (KAS 17[1])
2. Obtain the following labs STAT at the time of escalation of care:
    a. Total and direct serum bilirubin
    b. CBC
    c. Albumin
    d. Chem 10 panel
    e. Type and Screen and ABO/Rh
    f. DAT (if not already obtained)
    g. Reticulocyte count

3. Monitor TSB every 2 hours until below *the level at which escalation of care was initiated* (KAS 18, 20[1])

4. Provide intensive phototherapy, PO and IV hydration (KAS 19[1])

F. Providing Exchange Transfusion

1. Exchange transfusions are rarely required for non-hemolytic hyperbilirubinemia. See Exchange Transfusion Guidelines for further details.

2. An urgent exchange transfusion should be performed for infants if the TSB is at or above the exchange transfusion threshold. If, while preparing for the exchange transfusion but before starting the exchange transfusion, a TSB concentration is below the exchange transfusion threshold and the infant does not show signs of intermediate or advanced stages of acute bilirubin encephalopathy, then the exchange transfusion may be deferred while continuing intensive phototherapy and following the TSB every 2 hours until the TSB is below the escalation of care threshold (KAS 23[1])

G. Prolonged jaundice (KAS 9[1])

1. This can be defined as jaundice that persists *beyond 3-4 weeks for breastfed* infants or *beyond 2 weeks for formula fed* infants

2. The clinician should evaluate total and direct serum bilirubin as well as the newborn screening results and consider consultation of GI

References:

1. Kemper AR, Newman TB, Slaughter JL, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics*. 2022;150(3).
2. American Academy of Pediatrics. (2011). Phototherapy to Prevent Severe Neonatal Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics, 128(4):e1046-e1052).
3. Nagar G, Vandermeer B, Campbell S, Kumar M. Reliability of transcutaneous bilirubin devices in preterm infants: a systematic review. Pediatrics. 2013;132(5):871-881.
4. Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol*. 2012; 32: 660-664.
5. Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *N Engl J Med*. 2008 Oct 30; 359 (18).

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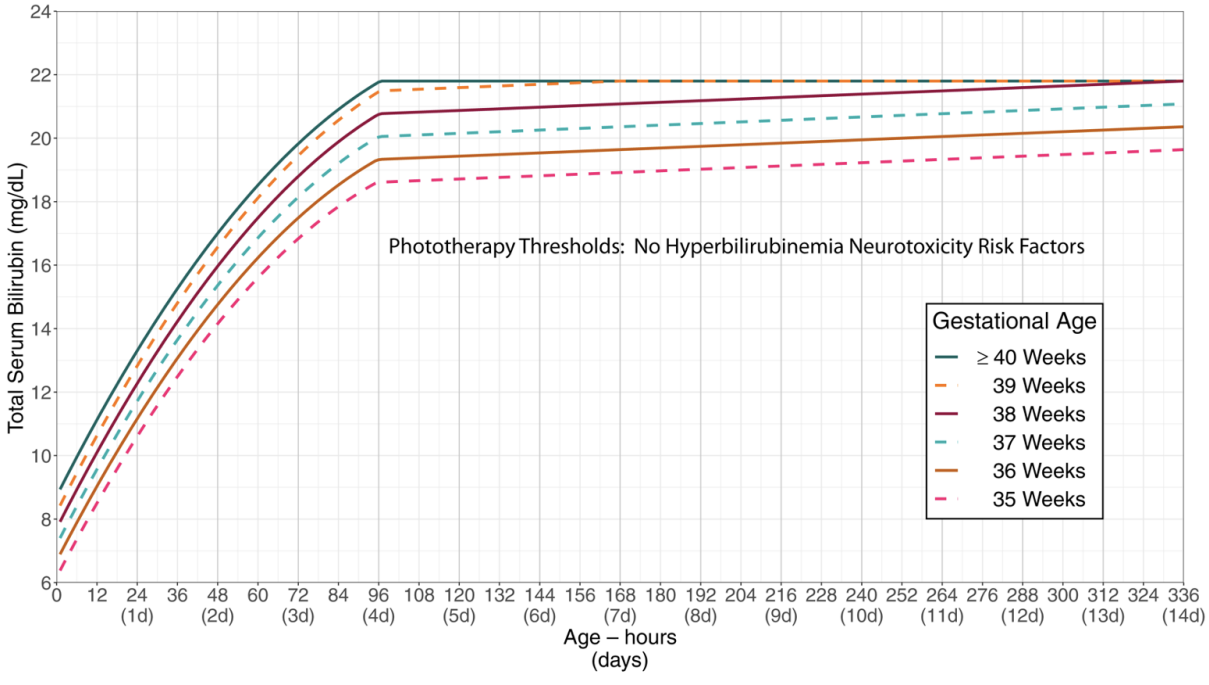
APPENDIX A: Phototherapy thresholds for neonates ≥ 35 weeks gestation

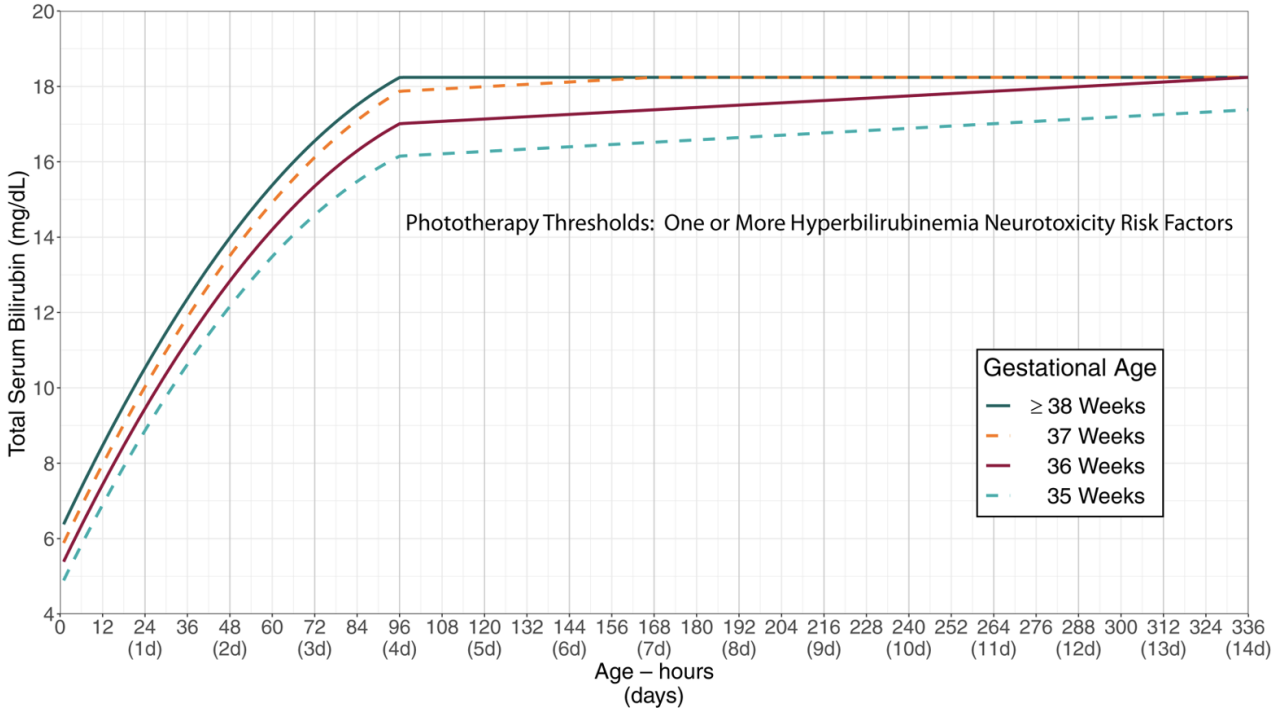
For neonates ≥ 35 weeks gestation, use the following phototherapy nomograms. Both nomograms are based on the 2022 AAP Clinical Practice Guideline on management of hyperbilirubinemia in infants ≥ 35 weeks gestation.[1]

Phototherapy Thresholds for Infants ≥ 35 Weeks Gestation without Neurotoxicity Risk Factors



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. 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.

Phototherapy Thresholds for Infants ≥ 35 Weeks Gestation with 1 or more Neurotoxicity Risk Factors

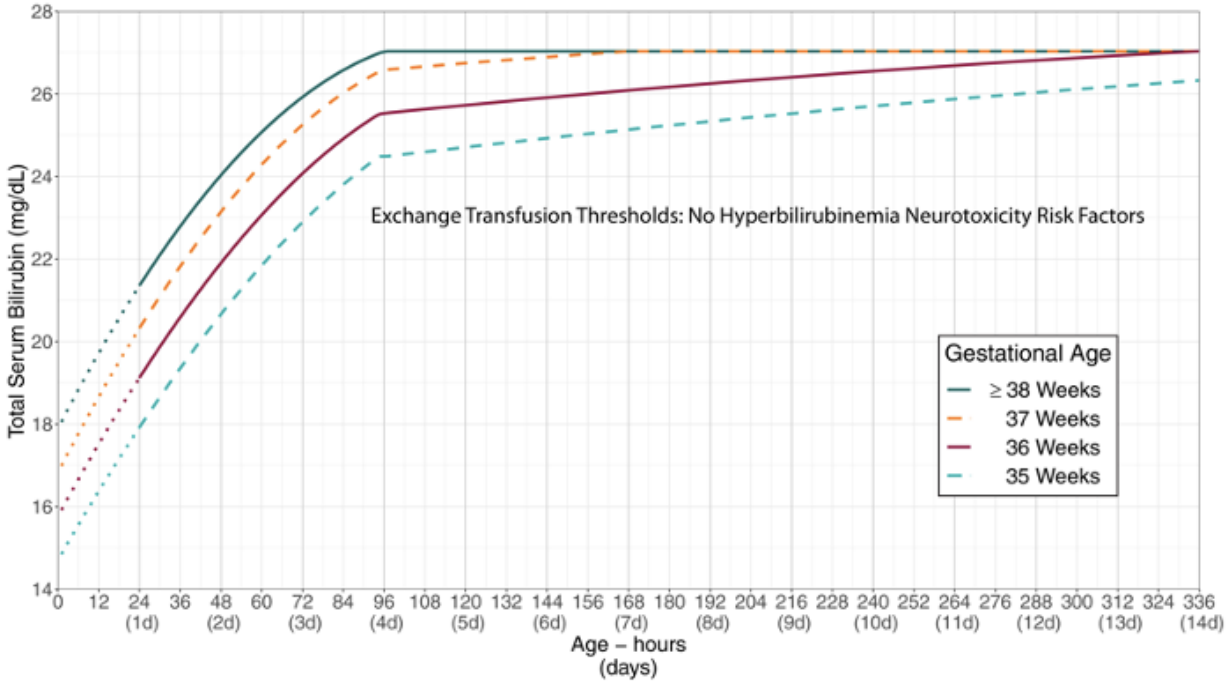


Phototherapy thresholds by gestational age and age in hours for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract 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. 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.

APPENDIX B: Exchange transfusion thresholds for neonates ≥ 35 weeks gestation

For neonates ≥ 35 weeks gestation, use the following exchange transfusion nomograms. Both nomograms are based on the 2022 AAP Clinical Practice Guideline on management of hyperbilirubinemia in infants ≥ 35 weeks gestation.[1]

Exchange Transfusion Thresholds for Infants ≥ 35 Weeks Gestation without Neurotoxicity Risk Factors



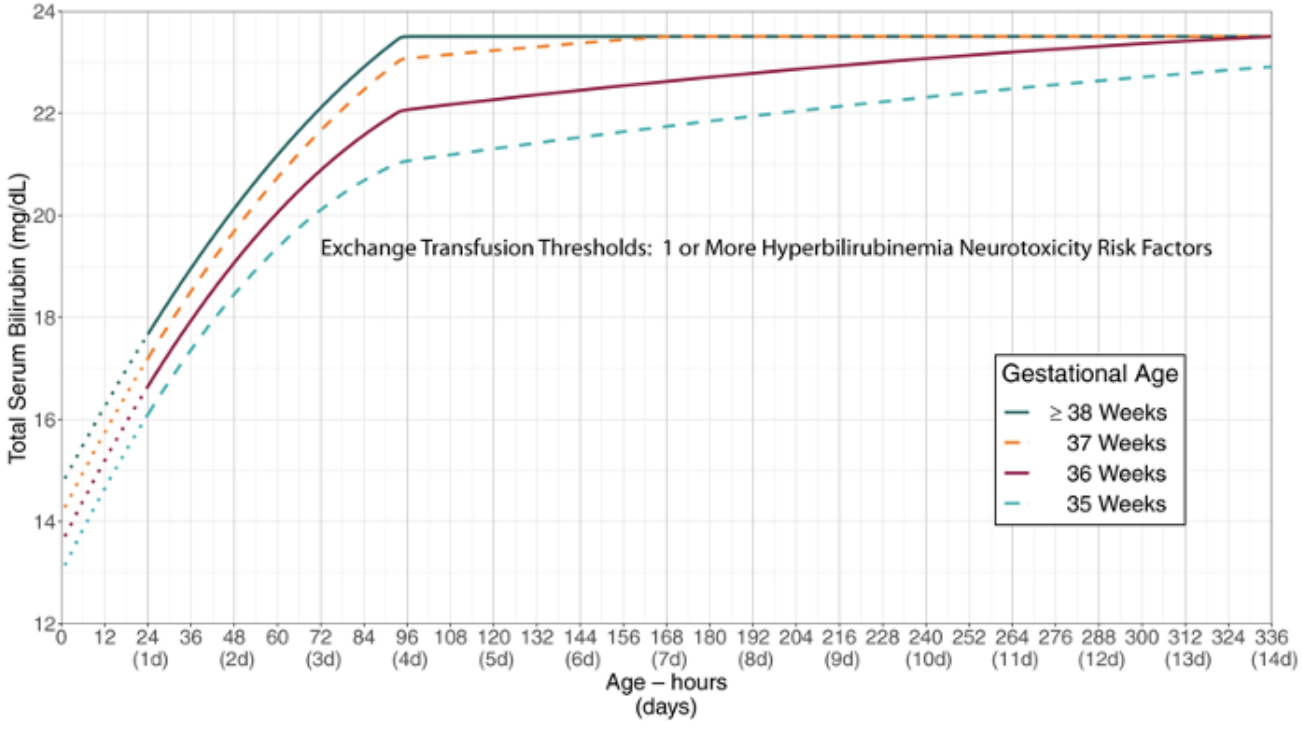
Exchange transfusion thresholds by gestational age for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct 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 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.

Escalate care if bilirubin is within 2 mg/dL of the exchange transfusion threshold

IF ESCALATING CARE, OBTAIN THE FOLLOWING:

1. Total and direct bilirubin
2. CBC
3. Chem10
4. Albumin
5. Type and screen
6. ABO/Rh
7. DAT
8. Reticulocyte count
9. Repeat TSB every 2 hours until below escalation of care threshold

Exchange Transfusion Thresholds for Infants ≥ 35 Weeks Gestation with 1 or more Neurotoxicity Risk Factors



Exchange transfusion thresholds by gestational age 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 escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct 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 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.

Escalate care if bilirubin is within 2mg/dL of the exchange transfusion threshold

IF ESCALATING CARE, OBTAIN THE FOLLOWING:

1. Total and direct bilirubin
2. CBC
3. Chem10
4. Albumin
5. Type and screen
6. ABO/Rh
7. DAT
8. Reticulocyte count
9. Repeat TSB every 2 hours until below escalation of care threshold

APPENDIX C: Phototherapy and exchange transfusion thresholds for neonates < 35 weeks gestation

For neonates < 35 gestation at birth, use the following phototherapy and exchange transfusion guidelines. These guidelines are based on the Maisels et al. consensus-based recommendations for phototherapy and exchange transfusion levels for neonates < 35 weeks gestation.[4] ***Of note, when a preterm infant exceeds 35 weeks postmenstrual age, they remain at the highest phototherapy and exchange thresholds in the following table, rather than progressing to the AAP thresholds.***

Table 1: Guidelines for treatment of hyperbilirubinemia in neonates < 35 weeks gestation

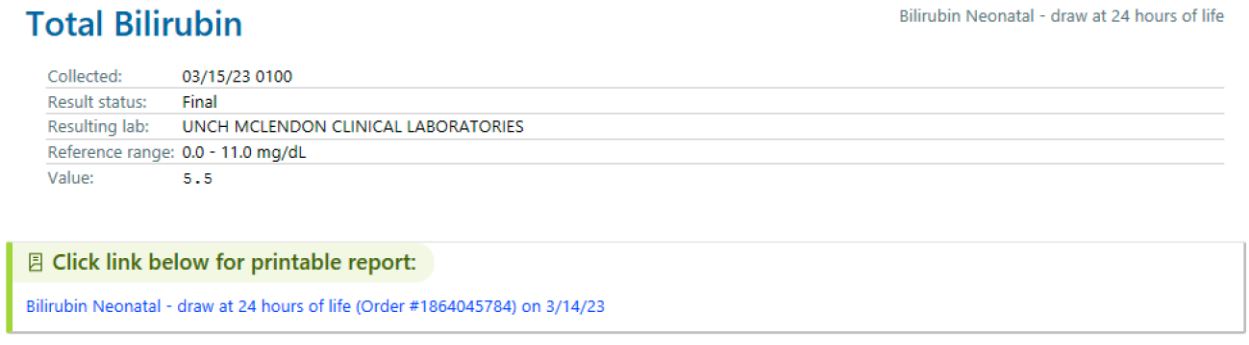
Post-Menstrual Age	PHOTOTHERAPY THRESHOLD (TSB in mg/dL)	EXCHANGE THRESHOLD (TSB in mg/dL)
<28 weeks PMA	5-6	11-14
28-29 weeks PMA	6-8	12-14
30-31 weeks PMA	8-10	13-16
32-33 weeks PMA	10-12	15-18
34-35 weeks PMA	12-14	17-19

Note: We reviewed the Morris et al. RCT that examined the effect of aggressive versus conservative phototherapy in extremely low birthweight neonates. While this trial demonstrated a reduction in profound NDI with aggressive phototherapy, Bayesian analysis estimated an 89% probability of increased risk of death in neonates < 750g in the same arm.[5] Given these inconclusive results, we have elected to align our guideline with the Maisels et al. consensus-based recommendations which fall between the aggressive and conservative thresholds used in the Morris trial.

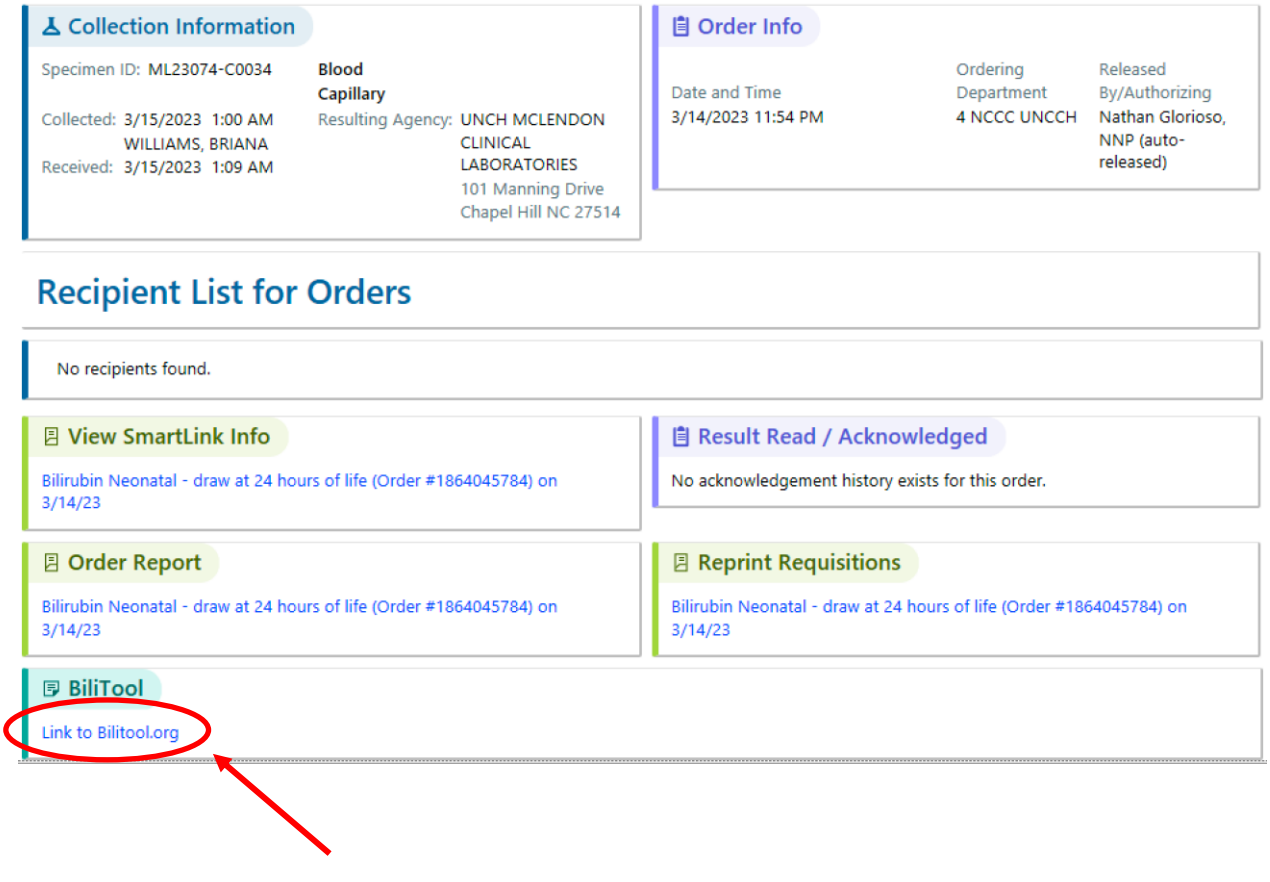
APPENDIX D: Epic tools for phototherapy and exchange transfusion thresholds

To access Bilitool via EPIC:

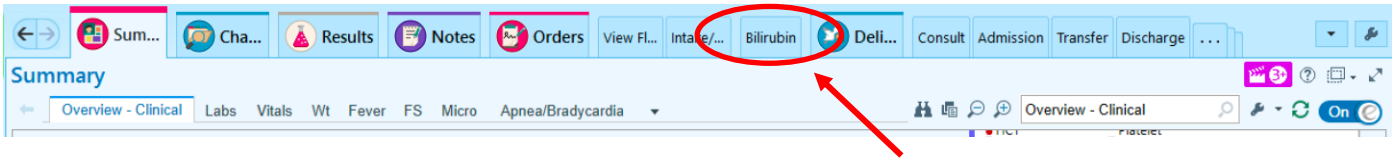
1. Open Results Review tab, double click on current bilirubin level and window will appear as below:



2. Scroll all the way to the bottom of the results window to find link for Bilitool:



Alternatively, the AAP Recommendations are integrated in EPIC via the Bilirubin tab. To add this tab, use the wrench in the top right corner of the patient chart.



The bilirubin tab will then track all TcB and TSB measurements and plot them along the AAP Nomogram for phototherapy or exchange transfusion. Gestational age will be automatically selected by Epic, but you may access the different curves along the top of the graph.

The Premie BiliRecs tool is found in the same locations. It is based on the Maisels et al. recommendation and may be used for infants born at 27-35 weeks gestation. ***Preterm infants remain on this curve even when PMA exceeds 35 weeks.*** For infants with a younger gestational age, use the table in Appendix C.