Hyperbilirubinemia FAQs

What is changing?

In August 2022, the American Academy of Pediatrics (AAP) published a revision of the previous clinical practice guideline for the management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, which was originally published in 2004 and was last revised in 2009. The most notable differences in this revision are modified thresholds for starting phototherapy and performing exchange transfusion. The revision also has a revised screening process for neonatal isoimmune hemolysis, introduces neurotoxicity risk factors, introduces the concept of escalation of care, introduces changes to timing of rebound bilirubin testing, and provides a framework for follow up for infants with hyperbilirubinemia.

Why are these changes happening?

Since the initial guidance and phototherapy thresholds were published in 2004, there has been emerging evidence that bilirubin-induced neurotoxicity does not occur until levels well above the previous thresholds for initiating phototherapy and exchange transfusion. There has also been emerging evidence that phototherapy is not an entirely benign therapy as there is a small but significant association between receipt of phototherapy and later development of epileptic seizures. Moreover, while exchange transfusion remains the most effective method for rapidly decreasing levels of serum bilirubin, it is an extremely high-risk procedure and should only be performed when absolutely necessary. For these reasons, there was concern for over-treatment with the previous guidelines.

How do I determine the threshold for phototherapy or exchange transfusion for an infant?

Three pieces of information are needed – the gestational age of the infant at birth, the age of the infant in hours, and the presence or absence of neurotoxicity risk factors other than gestational age. The presence of absence of neurotoxicity risk factors will guide the provider to the correct graph (Figures 2, 3, 5, or 6 from the 2022 revision) to determine the threshold for phototherapy or exchange transfusion. The provider then uses the curve on the desired graph that corresponds to the gestational age of the infant in question.

What are neurotoxicity risk factors?

There are 5 risk factors that increase the likelihood of bilirubin induced-neurologic dysfunction:

- Gestational age < 38 weeks (risk increases with degree of prematurity): This risk factor is built into the graphs of thresholds for phototherapy and exchange transfusion, since there is a lower threshold to initiate these interventions at lower gestational ages.
- Albumin < 3.0 g/dL
- Isoimmune hemolytic disease (e.g. positive direct antiglobulin test), G6PD deficiency, or other hemolytic condition(s)
- Sepsis
- Significant clinical instability in the previous 24 hours

Does this mean that every baby needs an albumin checked?

No. There is currently not evidence to recommend routine checking of albumin in infants in the newborn nursery. However, if escalation of care is warranted, checking albumin is recommended since hypoalbuminemia is a neurotoxicity risk factor.

What counts as "significant clinical instability"?

This is left to the discretion of the provider. This catch-all phrase takes the place of the following risk factors initially introduced in the 2004 guidelines: asphyxia, significant lethargy, temperature instability, and acidosis.

When should an infant be screened for hemolysis?

Isoimmune hemolysis remains a major risk factor for hyperbilirubinemia and bilirubin induced neurologic dysfunction. Providers for <u>all</u> infants in the newborn nursery should ensure that there was maternal antibody screening done. If it was either not done or the antibody screen was positive, the infant should have a direct antiglobulin test (DAT or Coombs test) checked as soon as possible. If the infant is positive and it is not attributable to maternal receipt of anti-RhD antibody (Rhogam), this infant is at a markedly increased risk for isoimmune hemolysis and hyperbilirubinemia.

What is the role of testing with transcutaneous bilirubin (TcB)?

Measuring TcB does not directly assess serum bilirubin levels, but it is a reliable and valid non-invasive screening test to identify infants who require measurement of total serum bilirubin (TSB) level. However, the TSB should be the definitive test to guide any and all management decisions for infants with hyperbilirubinemia. If an infant's TcB is within 3 mg/dL of their phototherapy threshold or greater than 15 mg/dL, a TSB should be drawn.

When should IV fluids be considered?

Attempts to optimize hydration and nutrition <u>enterally</u> should be made whenever possible, with expressed maternal breast milk, donor breast milk, or formula supplementation. However, IV fluids for hydration are an important part of escalation of care for severe hyperbilirubinemia. IV fluids are also important for an infant who is clinically dehydrated or is not able to maintain their hydration enterally.

What are the criteria for home phototherapy?

For infants who have already been discharged and then develop a TSB above the phototherapy threshold, treatment with a home LED-based phototherapy device rather than readmission to the hospital is an option if the infant meets <u>ALL</u> the following criteria:

- Gestational age 38 weeks or above
- At least 48 hours old

- Clinically well with adequate feeding
- No known neurotoxicity risk factors
- No previous phototherapy
- TSB is no more than 1 mg/dL above the phototherapy treatment threshold
- An LED-based phototherapy device can be available in the home without delay
- TSB can be measured daily

If at any point any of these criteria are not met, especially if the TSB increases to more than 1 mg/dL above the phototherapy threshold, the infant should be hospitalized for phototherapy.

When should phototherapy be discontinued?

Phototherapy can be discontinued when the TSB has decreased by at least 2 mg/dL below the hour-specific threshold at the initiation of phototherapy. A longer period of phototherapy is an option if there are risk factors for rebound hyperbilirubinemia (gestational age less than 38 weeks, less than 48 hours old, or the presence of hemolytic disease).

When should a rebound bilirubin be checked after stopping phototherapy?

Timing of rebound bilirubin measurement is based on the risk of rebound hyperbilirubinemia.

- **High** risk (infants on phototherapy during birth hospitalization, and infants who had phototherapy started at less than 48 hours of age, positive DAT, or other hemolytic disease): Recheck TSB 6-12 hours after discontinuation and the next day
- **Medium** risk (all other infants receiving phototherapy during birth hospitalization, and infants who previously received phototherapy during birth hospitalization and then later readmitted for phototherapy): Recheck TSB the day after phototherapy discontinuation
- **Low** risk (infants readmitted for phototherapy who did not receive phototherapy during birth hospitalization, and infants treated with home phototherapy who then required admission): Recheck TSB 1-2 days after phototherapy discontinuation

Risk factor for rebound hyperbilirubinemia include younger postnatal age (less than 48 hours of life) at the start of phototherapy, presence of hemolytic disease, gestational age less than 38 weeks, and higher TSB related to the phototherapy threshold at the time of discontinuation. If one or more of these conditions is present, consider checking earlier than what the above guidelines state.

What is "escalation of care"? When should this be done?

Escalation of care refers to intensive care for infants with elevated or rapidly increasing bilirubin concentrations, in order to prevent the need for an exchange transfusion and possible neurologic dysfunction. The threshold at which escalation of care should be initiated is when the bilirubin is within 2 mg/dL of the exchange transfusion threshold, based on the infants gestational age a birth, age in hours, and presence or absence of neurotoxicity risk factors other than gestational age. The following measures should be taken:

- If not at location that is appropriate for exchange transfusion, consult neonatology and initiate an urgent transfer to the NICU
- Continue effective, intensive phototherapy

- Continue enteral hydration and initiate IV hydration
- Obtain labs – total and direct serum bilirubin, CBC, albumin, chemistries, type and screen
- Trend TSB every 2 hours
- If an at location appropriate for exchange transfusion, notify blood bank
- Consider IVIG if isoimmune hemolysis (e.g. positive DAT) is present

Has the role of intravenous immunoglobulin IVIG) in the management of severe hyperbilirubinemia changed?

IVIG remains an adjunct therapy for infants with hemolytic disease. If hemolytic disease is present AND the TSB has reached the escalation of care threshold, 0.5-1 mg/kg of IVIG may be given. Given its unclear effectiveness and a possible association between IVIG and necrotizing enterocolitis, the provider should consider the infant's response to phototherapy, rate of TSB rise, and any challenge(s) to providing a timely exchange transfusion prior to administering IVIG. All other escalation of care measures should be continued if IVIG is given.

When should transfer to a hospital that can provide a higher level of care be considered?

If one is caring for an infant who requires escalation of care and is not at a location with the staffing and resources to perform an exchange transfusion, an urgent transport to a neonatal intensive care unit (NICU) should be expedited.

When should follow up occur following hospitalization for hyperbilirubinemia?

For an infant at least 12 hours old, use the difference between the most recent TSB and the phototherapy threshold at that time based on gestational age, hours of age, and presence or absence of hyperbilirubinemia neurotoxicity risk factors other than gestational age. Use Figure 7 from the clinical practice guideline to determine follow-up timeframe based on the difference between the TSB and the phototherapy threshold, and the age of the infant.

What resources are there to assist with this transition?

BiliTool (www.bilitool.org) has been revamped to include the recommendations from the 2022 clinical practice guideline revision. Some institutions that use the Epic electronic medical record may also have a newly integrated bilirubin view which graphs the individual patient's TSB or TcB compared to their thresholds for phototherapy and exchange transfusion.