

Clinical Performance Guideline
Neonatal Resource Services
Neonatal Hyperbilirubinemia

Medical Necessity Guideline

Purpose: To provide guidelines on the identification and optimal management of infants with neonatal hyperbilirubinemia.

Target Client Population: This guideline applies to both term and preterm infants in the NICU who have an elevated serum bilirubin concentration.

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| <p>Background</p> | <p>Bilirubin is a byproduct of the normal breakdown of heme, a component of hemoglobin and other tissues. After production in the reticuloendothelial cells it is processed by the liver for elimination from the body and the serum bilirubin level is determined by a combination of the rate of production and the rate of clearance of bilirubin. Any condition that increases production of bilirubin (e.g., hemolysis, polycythemia), decreases hepatic conjugation and excretion (e.g., cholestasis), and/or increases the enterohepatic reabsorption of bilirubin (e.g., ileus, poor feeding) or any combination of these processes will increase the blood concentration of bilirubin. Clinical jaundice is the yellowish discoloration of the skin and/or conjunctiva resulting from bilirubin deposition.</p> <p>In the United States, more than 80% of healthy newborns \geq 35 weeks' gestation exhibit benign physiologic jaundice in the first few days of life. It is estimated that 1-2% of the 4,000,000 infants born yearly in the U.S. have bilirubin levels which are \geq 20 mg/dl. This level can be defined as "severe hyperbilirubinemia". An infant's bilirubin level usually peaks at 72-120 hours of age and resolves by 2-3 weeks following birth. (FDA, 2012)</p> <p>According to the United States Preventive Services Task Force (USPSTF), risk factors for hyperbilirubinemia include bruising, exclusive breastfeeding, male gender, gestational age $<$36 weeks, cephalohematoma, G6PD deficiency, ethnicity (Asian, black) and family history of neonatal jaundice. (2009) Rh and ABO isoimmune hemolytic disease and sepsis are also associated with hyperbilirubinemia.</p> <p>Testing includes serum bilirubin or transcutaneous bilirubin measurement. All infants should have at least one evaluation prior to discharge. Higher risk infants should be followed up within 24-48 hours.</p> <p>Acute bilirubin induced neurological dysfunction (BIND) describes the acute neurological symptoms of bilirubin toxicity. These include alterations in mental status, muscle tone, cry and gaze. The term "kernicterus" is used for the chronic bilirubin encephalopathy causing permanent neurologic sequelae. (AAP, 2004)</p> <p>Treatment is undertaken to prevent neurological damage. Phototherapy devices are classified according to their light source: fluorescent-tube devices, metal halide bulbs, light-emitting diodes (LEDs) or high-intensity LEDs. The efficacy of phototherapy is determined by the spectrum of light being delivered to the infant, the irradiance (radiant power incident on a surface per unit area of the surface), and the surface area of the infant exposed to phototherapy. (Maisels, 2012) Turning of the infant under a phototherapy device does not improve the efficacy of phototherapy. (Maisels, 2012) It is clinically more important to maximize the body surface area treated than it is to increase the number of devices. (Bhutani, 2011)</p> <p>Factors associated with successful use of phototherapy include the spectrum of light,</p> |
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| | <p>the distance from the infant, the irradiance and the skins surface exposed.</p> <p>IVIG infusion (500-1000mg/kg) has been utilized to prevent exchange transfusion in infants with acute immune mediated hemolytic crises, approaching or passing exchange levels.</p> <p>Double volume exchange transfusion is utilized for infants with high TSB levels based on risk factor analysis and hour of age. (AAP, 2004; USPSTF, 2009)</p> |
| <p>Treatment Criteria</p> | <p>Clinical evidence in the medical literature supports the following:</p> <p><u>Infants ≥ 35 weeks' gestation</u></p> <ul style="list-style-type: none"> • Screening for hyperbilirubinemia in infants ≥35 weeks' gestation may consist of a risk-factor assessment, serum measurement of bilirubin (TSB), transcutaneous estimation of bilirubin (TcB) or a combination of these methods. (USPSTF, 2009) • Combining a TSB or TcB with the infant's gestation provides a prediction of the risk of severe hyperbilirubinemia that is as accurate as an evaluation of all of the known risk factors (other than confirmed iso-immune or other known hemolytic disease). (Maisels, 2012) • Most experts currently recommend that a TSB or TcB should be obtained on every infant prior to discharge from the nursery. (Maisels, 2009) • TcB may be imprecise in estimating the TSB so TcB should be confirmed with a comparison TSB measurement prior to treatment initiation. (NICE, 2016; Olusanya, 2016; Maisels, 2009) • Transcutaneous bilirubin measurements are measurements of the yellow color of the blanched skin and subcutaneous tissues and are not a measurement of the serum bilirubin. They are very useful, however when used as a screening tool to help determine whether the TSB should be measured. TcB measurements can significantly reduce the number of TSB measurements needed in both the term nursery and the NICU. They help to estimate the risk of subsequent hyperbilirubinemia and they are invaluable in the outpatient setting. Because they are noninvasive, TcB measurements can be repeated several times during the birth hospitalization and provide useful information about the rate of rise of the bilirubin. When plotted on a nomogram, TcB levels that are crossing percentiles indicate the need for additional observation and evaluation. (Maisels 2012) • The recommended treatment for hyperbilirubinemia is phototherapy. Exchange transfusion is recommended for the treatment of extreme hyperbilirubinemia. (USPSTF, 2009; AAP, 2004) • The initiation of phototherapy should be based on the AAP guidelines, taking into account the infant's postnatal age in hours and the risk for bilirubin neurotoxicity. (AAP, 2004) Neurotoxic risk factors include isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis and serum albumin <3 g/dL. • One clinical tool for hyperbilirubinemia management based on the 2004 AAP guidelines can be accessed at: http://bilitool.org . The BiliTool™ provides the cutoff by age (in hours) for initiating phototherapy. • Another tool is the Bhutani curve which is utilized to establish infants at high risk for hyperbilirubinemia. • The efficacy of phototherapy is demonstrated by a decrease of >2 mg/dL total serum bilirubin (TSB) within 4-6 hours of initiation. Serial TSB measurements |

are necessary to monitor continued effectiveness. (Bhutani, 2011)

- There are no well documented or established guidelines for discontinuing phototherapy. Infants who require phototherapy prior to discharge from the nursery are more likely to have a rebound than those who are readmitted with hyperbilirubinemia. In the latter group, the risk of significant rebound is very low (<1%).
- The risk of rebound hyperbilirubinemia following discontinuation may be quantified based infant's gestational age, age at phototherapy initiation, and TSB relative to the treatment threshold at phototherapy termination. (Chang, 2017)
- For acute hemolytic crisis the administration of IVIG may avert the need for double volume exchange.

Infants < 35 weeks' gestation

- The range of bilirubin threshold levels that are utilized to initiate treatment at various birth weights and gestational ages is diverse due to the lack of clinical evidence to support a consistent approach. (Maisels, 2012)
- Consensus-based recommended treatment levels by Maisels et al (2012) include:

| | Initiate Phototherapy | Exchange Transfusion |
|--------------------------|---------------------------------|---------------------------------|
| Gestational Age in Weeks | TSB level (mgdl ⁻¹) | TSB level (mgdl ⁻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 |

- Effective phototherapy and the prevention of Rh hemolytic disease by utilizing Rh (D) immunoglobulin have decreased the need for exchange transfusions in preterm NICU infants. (Maisels, 2012)
- If the TSB continues to rise while the infant is receiving phototherapy, increase the body surface area that is exposed and/or increase the irradiance by moving the phototherapy lamp closer to the infant if feasible. (Maisels, 2012) This cannot be done with halogen and tungsten lamps which are hot and can cause a severe burn.
- Phototherapy may be discontinued when TSB is 1-2 mg/dL below the initiation level for the infant's postmenstrual age (PMA). (Maisels, 2012)
- Exchange transfusion is recommended for infants whose TSB levels reach those shown in the table above in spite of receiving maximal intensive phototherapy and for any infant who shows signs of acute bilirubin encephalopathy. (Maisels, 2012)
- When the use of phototherapy or exchange transfusion is being contemplated, utilize the TSB level without subtracting the direct (conjugated) bilirubin level.

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| | <p>However, individual attention should be given to those infants whose direct bilirubin level is >50% of the TSB. (Maisels, 2012)</p> <ul style="list-style-type: none"> • Metalloporphyrins can prevent and treat hyperbilirubinemia but they are not FDA approved. (FDA, 2012; Bhutani & Wong, 2013) |
| <p>Clinical Evidence</p> | <p><u>Infants ≥ 35 weeks gestation</u></p> <ul style="list-style-type: none"> • A technical report from the Committee on Fetus and Newborn authored by Bhutani (2011) sought to provide consistency in phototherapy utilization in accordance with the AAP clinical practice guideline for the management of hyperbilirubinemia. This document provides several Grade B recommendations (moderate certainty that the net benefit is moderate to substantial) on phototherapy administration. The maximum body surface area should be exposed to the light source and the clinical effectiveness of the phototherapy device should be known prior to administration with continued monitoring during the application. The output of the phototherapy devices can also be useful in predicting the potential effectiveness in reducing the infant's bilirubin level. • A clinical summary on the screening of infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy from the USPSTF (2009) did not provide any recommendations on this topic. This summary was applicable to healthy newborn infants' ≥35 weeks' gestation. The committee was unable to determine the offset of benefits and harms when screening newborn infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy due to the lack of clinical evidence. • The American Academy of Pediatrics Subcommittee on Hyperbilirubinemia has not updated their 2004 guideline on the management of hyperbilirubinemia in newborn infants' ≥35 weeks' gestation. This document included recommendations for the prevention and management of hyperbilirubinemia in this patient population: 1) breastfeeding should be supported and encouraged; 2) a systemic assessment for the risk of hyperbilirubinemia should be performed prior to discharge; 3) follow-up (early and focused) should be performed based on the risk assessment; and 4) treatment should include phototherapy or exchange transfusion, as indicated, to prevent the development of severe hyperbilirubinemia and bilirubin encephalopathy. Assessment of jaundice in the first 24 hours after birth or in an infant whose jaundice appears excessive for their age should include a TSB and/or TcB. In most infants with TSB levels <15 mg/dL, TcB levels can provide a valid estimate of the TSB level. A repeat TSB may be repeated in 4-24 hours for an infant who is receiving phototherapy or has a rapidly rising TSB. When TSB is <13-14 mg/dL, phototherapy can be discontinued. Specific evaluations and interventions for the management of infants with hyperbilirubinemia are provided. • A retrospective review by Taylor et al (2015) compared TSB levels with TcB levels performed on 8,319 infants in 27 newborn nurseries. In a multivariate analysis, the discrepancy between the serum and transcutaneous levels was larger in African-American newborns than in infants of other races. The difference also varied based on the brand of TcB meter that was used. Overall, the mean TcB-TSB difference was found to be 0.84 ± 1.78 mg/dL. The authors concluded that TcB measurement provided a reasonable alternative to TSB levels in healthy newborn infants. • A population-based study by Lain et al (2015) evaluated the association |

between early hospital discharge and readmission for jaundice in term infants. 781,074 term infants that were discharged from the hospital in the first 14 days following birth were followed. 33.5% were discharged in the first two days after birth, 43.2% were discharged on days 3 or 4 and 23.3% remained in the hospital for ≥ 5 days. The data demonstrated that the number of infants readmitted for the diagnosis of jaundice declined as their gestational age and length of hospital stay increased. The infants that were discharged within two days of birth were found to be twice as likely to be readmitted with jaundice when compared to the infants discharged on the third or fourth day. In the cohort of infants discharged in the first two days after birth, important risk factors for readmissions included births at 37-38 weeks' gestation, vaginal deliveries, breastfed infants and Southeast Asian ethnicity.

Transcutaneous Bilirubin Measurement

- Olusanya et al (2016) performed a retrospective study of 2,107 TcB/TSB measurements from 1,553 black African infants in order to ascertain any differences between these two bilirubin measurement techniques. BiliChek and JM-103 bilirubinometers were utilized for TcB assessment and were found to significantly overestimate TSB in this cohort of infants. This overestimation by TcB could result in excessive or unnecessary treatment.
- Maisels et al (2009) provided consensus recommendations on hyperbilirubinemia in infants ≥ 35 weeks' gestation including clarification of some items in the 2004 AAP guideline on this topic. The authors recommended that a predischarge TSB or TcB be performed and the infant's risk for hyperbilirubinemia be assessed based on the infant's age in hours and this measurement. If an infant is discharged when they are less than 72 hours of age, a follow-up within two days should be performed and earlier follow-up may be necessary for infants at higher risk for hyperbilirubinemia.
- A 2010 NICE guideline was updated in May 2016 and provides guidance in the management and treatment of jaundiced newborn infants < 28 days old. This guideline includes a consensus-based bilirubin threshold table for phototherapy and exchange transfusion intervention. A 2016 recommendation was added indicating that a serum bilirubin measurement should be used if the bilirubin level is at or above the treatment threshold.

Phototherapy Termination

- A retrospective cohort study by Chang et al (2017) attempted to create a prediction tool which would estimate the probability of rebound hyperbilirubinemia following phototherapy. The three variables that best predicted rebound hyperbilirubinemia were gestational age <38 weeks, younger age at phototherapy initiation and TSB relative to treatment threshold at phototherapy termination. The equation for calculating the prediction score was developed as follows: $Score = 15$ (if gestational age <38 weeks) $- 7 \times$ (age in days at phototherapy initiation) $- 4 \times$ (AAP phototherapy threshold $-$ TSB at phototherapy termination) $+ 50$. A score <20 corresponded to a <4% probability of rebound hyperbilirubinemia. Out of 7,048 infants treated with inpatient phototherapy, 4.6% (324 infants) met their definition of rebound hyperbilirubinemia (return to phototherapy treatment threshold within 72 hours of termination of infant's first inpatient phototherapy). The authors indicate implementation of this prediction tool can help guide decisions regarding discontinuation of phototherapy.

Subthreshold Phototherapy

- A retrospective cohort study by Wickremasinghe et al (2018) evaluated the use of subthreshold phototherapy utilized in the birth hospitalization as a possible means of preventing hospital readmissions for phototherapy. A cohort of 25,895 infants born at ≥ 35 weeks' gestation who had a qualifying first TSB level from 0.1 to 3.0 mg/dL below the AAP phototherapy were included in the study. A total of 4,956 infants received subthreshold phototherapy during the birth hospitalization with 2,931 infants readmitted for phototherapy. The authors identified 72% lower adjusted odds of readmission for phototherapy in the infants who had received subthreshold phototherapy. They concluded that although subthreshold phototherapy during birth hospitalization may prevent readmissions for phototherapy, it results in unwarranted treatment of many infants.

Preterm Infants < 35 weeks gestation

- A meta-analysis by Shabuj et al (2017) evaluated the efficacy of TcB measurements in the preterm infant population. Twenty-eight studies met the authors' inclusion criteria and compared TcB values (via Bilicheck and JM103 devices) to TSB levels when measured at the forehead and sternum sites prior to phototherapy. The TcB measurements were found to be comparable with the TSB values using the two measurement sites and the two investigated devices. The authors concluded TcB measurement can be a reliable approach in the assessment of preterm infants with possible hyperbilirubinemia.
- Bhutani et al (2016) reviewed the evolving evidence on bilirubin-associated brain injury in preterm infants. They advise the degree of jaundice does not accurately predict the degree of hyperbilirubinemia and bilirubin neurotoxicity. Although the incidence of kernicterus in preterm infants has declined over the past 30 years, there are still a small number of cases. The presence of early-onset hyperbilirubinemia at < 24 hours of age is a medical emergency and total bilirubin levels assessed between 24 and 60 hours of age can predict the development of severe hyperbilirubinemia and the need for phototherapy. There is little evidence to support a consistent management strategy. Interventions should be focused on prevention rather than rescue.
- Palma & Arain (2016) discuss the development of electronic clinical decision support (CDS) tools which can be used to standardize clinical practice. For optimized management of hyperbilirubinemia in preterm infants < 35 weeks' gestational age, the web-based CDS tool Premie BiliRecs was developed. This tool was adapted from the consensus-based recommendations of Maisels et al (2012) and provides the bilirubin thresholds for phototherapy and exchange transfusion in the moderately preterm infant population. The authors indicate the most significant limitation to the use of the Premie BiliRecs tool is the lack of available evidence to guide management of hyperbilirubinemia in preterm infants rather than to the tool itself. This tool does not provide recommendations for infants < 27 weeks gestational age or for moderately preterm infants < 48 hours of age. After validation, this tool will be made publically available for manual data entry and electronic medical record integration.
- Maisels et al (2012) provided consensus-based guidelines for preterm infants < 35 weeks' gestation. Recent studies had suggested that even modest increases in TSB can lead to neurodevelopmental impairment in ELBW infants

but other studies suggested there was no risk of neurotoxicity resulting from moderate hyperbilirubinemia. In an attempt to resolve these conflicting results, a prospective randomized controlled trial by the Neonatal Research Network was performed. Prophylactic versus therapeutic phototherapy is generally used in infants \leq 35 weeks' gestation. There is a paucity of good data to guide practitioners in the management of an infant with an elevated direct-reacting or conjugated bilirubin level and generally speaking, the direct or conjugated bilirubin level should not be subtracted from the total when considering the initiation of phototherapy. In infants with hemolytic disease, exchange transfusion is recommended at a lower bilirubin level due to increased risk of bilirubin encephalopathy.

- A prospective randomized controlled trial by Morris et al (2008) for the NICHD the Neonatal Research Network evaluated the efficacy of aggressive versus conservative phototherapy in ELBW infants. No difference in primary outcome of death or neurodevelopmental impairment (NDI) was identified between the two cohorts at 18 to 20 months of corrected age. However, when evaluating the survivors, aggressive phototherapy was found to significantly reduce the incidence of NDI, hearing loss, profound impairment and athetosis. Aggressive phototherapy, however, was found to increase the mortality in infants with birth weights of 501-750 g so the risk must be balanced with the benefit of this therapy.

Alternative Treatments

- In 2012, an FDA advisory committee met to evaluate the evidence on potential drug therapies for the management of neonatal hyperbilirubinemia. At the current time, intensive phototherapy and exchange transfusions are two interventions utilized to treat neonatal hyperbilirubinemia. Metalloporphyrins were assessed as a potential alternative for treatment of neonatal hyperbilirubinemia. There is limited data on the long-term neurodevelopmental outcomes of infants that have been treated with metalloporphyrins. Future evaluation of this topic needs to include observational trials that identify reliable risk factors, trials that focus on important clinical outcomes and the study of high-risk infants.
- Bhutani & Wong (2013) reported on the risk and prevention of bilirubin neurotoxicity in preterm infants. Included in these recommendations is mention on the use of stannic porphyrins to inhibit the enzyme heme oxygenase and block transformation of heme to biliverdin and bilirubin. Although this treatment has been investigated, the FDA still has not approved its use in the United States.
- A Cochrane review by Mishra et al (2015) reviewed the evidence on the use of oral zinc salt supplementation as a preventative strategy for hyperbilirubinemia. One randomized controlled trial met their inclusion criteria. This study compared oral zinc salt to placebo in 286 infants. The incidence of the need for phototherapy was identified as comparable between the two groups but the zinc therapy cohort was found to have a significantly shorter duration of phototherapy when compared to the placebo group. The authors concluded that based on the limited evidence, the use of oral zinc supplementation administered to infants up to one week of age does not reduce the incidence of hyperbilirubinemia or necessity for phototherapy.

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Revision History

The following are approved changes incorporated into the revision numbers indicated below.



| Revision | Date | Description of Change |
|-----------------|-------------|--|
| 1.0 | 05/17/2017 | New clinical guideline developed. Approved by MTAC 07/06/2017. (CE) |
| 2.0 | 05/16/2018 | Annual review by AJ. Double volume exchange information revised. Approved by MTAC 06/07/2018. (CE) |