Hyperbilirubinemia Guideline

(Note: Pediatric Gastroenterology (GI) should be consulted for persistent jaundice or direct hyperbilirubinemia)

Definition:
Hyperbilirubinemia is an elevation in total bilirubin beyond the level considered normal for age. Neonatal hyperbilirubinemia is a common problem which can cause neurotoxicity, kernicterus, and long-term disability if left untreated. Phototherapy is an effective treatment for hyperbilirubinemia.

Incidence:
Hyperbilirubinemia, more commonly known as newborn jaundice, is a fairly common presentation in the neonatal period. Reportedly anywhere from 60-84% of infants born at 35 weeks or greater will be diagnosed as having hyperbilirubinemia. An even larger percent of infants born preterm will be affected.

Etiology:
In infants, although there are a variety of syndromes and medical issues such as sepsis that can lead to elevated bilirubin, in the typical healthy infant there are 3 general known causes: 1) physiologic jaundice 2) breastfeeding or breast milk jaundice 3) hemolytic jaundice. The physiologic causes can be found in the pathogenesis section below.

Physiological jaundice is most commonly seen within 24 hours to 5 days following birth and is a result of increased bilirubin in combination with an immature hepatic system to break down the increased load. Breastfeeding jaundice typically occurs in those infants that are exclusively breastfed and is a result of decreased caloric intake while the mother's milk is still in the process of coming in. The cause of breast milk jaundice remains unknown however is thought to be due to increased enterohepatic circulation of bilirubin and b-glucoronidase resulting in deconjugation of bilirubin. Hemolytic jaundice is a result of destruction of blood products through ABO incompatibility, rhesus factor hemolysis, or minor heme antibody led hemolysis. This leads to increased bilirubin production which may result in jaundice.

Lastly, there is pathological jaundice which will be excluded from this guideline as those diagnoses may require other interventions and work up.

Epidemiology:
All infants may be at risk of developing jaundice, however certain risk factors can be useful for identifying which infants may be more likely to develop jaundice. Risk factors include:

- prematurity
- history of maternal diabetes
- Asian and Native American race
- male sex
- trisomy 21
- cephalohematoma at birth
- exclusive breastfeeding
- delayed passage of meconium
- history of siblings who had neonatal jaundice

Other components of the history which may reveal additional risk factors include family history of neonatal jaundice, chronic liver disease, and history of hematologic or metabolic conditions.

Table: Factors contributing to risk of hyperbilirubinemia

Major risk factors	• Predischarge total bilirubin is in the high-risk zone • Jaundice observed within first 24 hours of life • Blood group incompatibility with positive Coomb's, other known hemolytic disease, elevated ETCO • Gestational age 35-36 weeks • Cephalohematoma or significant bruising • Exclusive breastfeeding • Excessive weight loss • East Asian race
Minor risk factors	• Predischarge total bilirubin is in the high-intermediate risk zone • Gestational 37-38 weeks • Jaundice noticed before discharge • Macrosomic infant of a diabetic mother • Maternal age is greater than or equal to 25 years of age • Male gender
Decreased risk factor	• Total bilirubin in the low-risk zone • Gestational age greater than or equal to 41 weeks • Exclusive bottle feeding • Black race • Discharge from the hospital after 72 hours of life

Pathogenesis:

Bilirubin is a breakdown product of heme derived from hemoglobin and other heme proteins. When it is initially broken down, it is released into the blood in its unconjugated form. Unconjugated bilirubin from all over the body is transported through the blood to the liver bound to albumin. It cannot be excreted from the body until it is changed into conjugated bilirubin. In the liver, an enzyme called uridine 5'-diphospho-glucuronosyltransferase (B-UGT) converts bilirubin into the conjugated form, allowing it to be easily excreted in urine and feces. Conjugated bilirubin is also known as direct bilirubin.

Anything that causes increased bilirubin products in the blood (i.e. RBC breakdown), decreases enterohepatic circulation, or interferes with B-UGT can cause levels of bilirubin to rise in the blood. Newborns often have multiple such factors that increase their overall risk of severe hyperbilirubinemia.

If bilirubin is not excreted and levels increase above a certain threshold in the blood, it will deposit in extravascular tissue and cross the blood-brain barrier. Deposition in the skin causes jaundice, and deposition in

the basal ganglia and substantia nigra in the brain can cause acute bilirubin encephalopathy (short-term sequelae) and kernicterus (long-term sequelae).

Phototherapy treatment involves using a specific wavelength of light that converts unconjugated bilirubin to a water soluble form in which it can be excreted.

Differential Diagnosis:

Unconjugated Hyperbilirubinemia

Increased production of bilirubin:

- Hemolysis
  - Isoimmune: ABO incompatibility, Rh, or minor blood group antigen incompatibility.
  - Erythrocyte membrane defects: spherocytosis, elliptocytosis.
  - Enzyme defects: G6PD deficiency, pyruvate kinase deficiency, etc.
  - Hemoglobinopathies
  - Disseminated intravascular coagulopathy.
- Cephalohematoma or extensive bruising
- Polycythemia - Infant of diabetic mother, delayed cord clamping.

Impaired conjugation or decreased hepatocellular uptake

- Gilbert syndrome - decreased B-UGT
- Crigler-Najjar syndrome, types I and II - decreased or absent B-UGT function.
- Medications: aspirin, cephalosporins, sulfonamides (interfere with bilirubin to albumin binding), rifampin (competes with bilirubin for hepatocellular uptake).
- Congenital hypothyroidism - decreased B-UGT enzyme activity

Increased enterohepatic circulation - poor feeding, infrequent stooling, or bowel obstruction.

Mixed etiology:

- Physiologic jaundice and prematurity related jaundice
- Breastfeeding/breast milk jaundice

Conjugated Hyperbilirubinemia

- Obstruction of biliary system
  - Biliary atresia
  - Choledochal cyst
  - Alagille syndrome
- Metabolic liver diseases and systemic conditions:
  - Infection: TORCH infections, sepsis, or UTI
  - Acute liver injury related to ischemia, hypoxia, or acidosis
  - Parenteral nutrition-associated cholestasis

    - Gestational alloimmune liver disease
- Bile acid synthesis, storage, or transport defect
    - Progressive familial intrahepatic cholestasis
    - Dubin Johnson syndrome
    - Rotor syndrome

Guideline Inclusion Criteria:

- Previously healthy infants
- Age >24 hours and <21 days
- > 35 weeks gestational age

Guideline Exclusion Criteria:

- Conjugated hyperbilirubinemia defined as > 2 mg/dL or greater than 20% of the TSB concentration
- Meeting NICU direct admission criteria for exchange transfusion
- Suspected acute bilirubin encephalopathy or displaying clinical findings associated with acute bilirubin encephalopathy such as hypotonia, weak suck or high pitched cry; and
- Suspected sepsis, history of fever or ill-appearing on assessment

Diagnostic Evaluation:

TABLE 1. Laboratory Evaluation of the Jaundiced Infant of 35 or More Weeks' Gestation

Indications	Labs to consider
Jaundice in first 24 hours of life	• Transcutaneous total bilirubin (TcB) or total serum bilirubin (TSB)
Jaundice appears excessive for infant's age	• TcB or TSB
Infant receiving phototherapy or TSB rising rapidly and unexplained by history or exam	• Blood type • Coomb's test if not previously obtained • Complete blood count • Peripheral smear • Direct bilirubin • Repeat TSB within 4 to 24 hours depending on hour of life and prior TSB level
TSB approaching exchange levels or not improving with phototherapy	• Reticulocyte count, G6PD, ETCO
Elevated direct (or conjugated) bilirubin level (exclusion criteria)	• Urinalysis • Urine culture • Consider sepsis evaluation (CBC, blood culture, UA, urine culture, lumbar puncture) • Consider for work-up of biliary atresia
Jaundice present beyond 3 weeks of age	• Total and direct bilirubin

(exclusion criteria)	• Evaluate for cholestasis if elevated direct bilirubin • Check newborn screen for thyroid, galactosemia • Consider evaluating for hypothyroidism especially if concerning on exam • Consider work up of biliary atresia

Critical Points of Evidence

Fluids/Nutrition:

Evidence Supports

- Promoting oral feeding during phototherapy to make up for insensible losses that are increased by the treatment.

Evidence Lacking/Inconclusive

- There is low-moderate quality evidence showing that infants who have fluid supplementation have faster decline in bilirubin compared to control groups at some time points but not others. The clinical significance in the variability found in the one to two groups is not clear.
- There is no clear evidence demonstrating that IV fluid supplementation contributes to preventing infants from having acute bilirubin encephalopathy, kernicterus, or cerebral palsy in otherwise healthy full term newborns.

Treatment/Equipment:

Evidence Supports

- Putting LED lights within 10cm of the infant to improve irradiance levels. (LED lights and fluorescent lights may be placed as close as possible to an infant whereas halogen lights cannot.) Use of an open bassinet may be preferred due to difficulty in placing an LED light within 10cm of a baby while in an incubator. (Management of Hyperbili)
- Use of LED lights in the blue-green light spectrum 430 to 490 nm exposed to greatest body surface area
- LED lights are to be used instead of fluorescent or halogen lights due to lower heat emission leading to potentially less side effects, and improved cost effectiveness
- Keep irradiance measurement > 30 microwatts/cm2/nm up to max of 55 microwatts/cm2/nm
- Use of biliblanket in combination with overhead conventional light improves the rate of decrease compared to conventional or biliblanket alone
- Use of phototherapy is contraindicated in congenital porphyria or in patients being treated with photosensitizing drugs
- The use of reflective materials to line the sides of the crib has a meaningful reduction in bilirubin and decreases length of hospital stay and should be considered if bilirubin is approaching exchange transfusion level.
- Infusion of IVIg 0.5 -1g/kg over 2 hours for infants with isoimmune hemolytic disease AND either 1) a total bilirubin within 2-3mg/dL of exchange transfusion threshold OR 2) rapidly rising total bilirubin despite intensive phototherapy. May repeat dose in 12 hours if necessary (Management of Hyperbili)
- High-risk indicator for hearing loss (red flag) - Hearing check for infants with hyperbilirubinemia at levels requiring exchange transfusion.[6]

Evidence Lacking/Inconclusive

- Use of eye masks to prevent retinal damage was drawn from research in newborn monkeys without any evidence seen in humans.

Evidence Against

- No evidence that biliblanket is more favorable on parent-child bonding or nurse satisfaction than conventional overhead phototherapy

Laboratory Testing:

Evidence Supports

- If an infant has direct hyperbilirubinemia, further work up for cholestasis should be evaluated.
- Infants with direct bilirubinemia should have a urinalysis and urine culture. Clinicians should also consider an evaluation for sepsis if warranted.
- Glucose-6-phosphate dehydrogenase (G6PD) level should be obtained for a jaundiced infant receiving phototherapy with a family history or genetic factor increasing the likelihood of G6PD deficiency and/or for an infant with poor response to phototherapy.

Evidence Lacking/Inconclusive

- There are no good studies in which laboratory timing is examined. Frequencies recommended in various guidelines span a wide range. Per AAP guidelines, if TSB > 25 mg/dL (428 mol/L), repeat TSB within 2–3 hours. If TSB 20–25 mg/dL (342–428 mol/L), repeat within 3–4 h. If TSB < 20 mg/dL (342 mol/L), repeat in 4–6 hours. If TSB continues to fall, repeat in 8–12 hours.
- Infants jaundiced past 3 weeks or sick should have a measurement of total and direct or conjugated bilirubin to identify cholestasis as well as thyroid and galactosemia screening.

Evidence Against

- Evidence shows it is not necessary to keep infants in the hospital to check for rebound. For infants who require phototherapy during their birth hospitalization and for those with significant hemolytic disease, it was recommended to obtain a follow-up bilirubin level 24 hours after discharge.

Risk Factors for Neurotoxicity:

High Risk Curve: Gestational Age Less than 38 weeks AND one of the following (ABO isoimmune hemolytic disease, sepsis, acidosis, significant lethargy, temperature instability, albumin < 3 g/dL, G6PD deficiency)

Medium Risk Curve: Gestational Age Less than 38 weeks with no risk factors OR more than or equal to 38 weeks plus one of the following (ABO isoimmune hemolytic disease, sepsis, acidosis, significant lethargy, temperature instability, albumin < 3 g/dL, G6PD deficiency)

Low Risk Curve: 38 weeks or older AND well

Consults/Referrals:

- Consider Neonatology consult if patient is 2-3 mg/dl from exchange transfusion threshold
- Consider Gastroenterology consult if Direct Bilirubin is persistently elevated
- Lactation Consultation for all breastfeeding mothers

Admission Criteria:

- Meets criteria for needing phototherapy (use the following phototherapy guidelines from the AAP: https://pediatrics.aappublications.org/content/pediatrics/114/1/297/F3.large.jpg?width=800&height=600&carousel=1 or BiliTools.com)

- Persistently elevated total bilirubin with evidence of dehydration (>10% loss from birth weight, sunken fontanel, lethargic, poor feeding, decreased urine output or stool output)

Discharge Criteria:

1. Discontinue phototherapy when TSB is 2-3mg/dL below phototherapy threshold or 13-14mg/dL.
2. Follow up within 24 hours at PCP office for babies with isoimmune hemolytic disease (may need rebound TSB drawn at PCP office.) Do not draw a rebound TSB In the hospital.

Follow-Up Care:

- Follow up with a primary care doctor within 24 to 48 hours. At that time, the provider can assess whether a repeat lab is indicated with history and physical exam.
- Weight and percent change from birth weight should be recorded.
- Infants should be assessed for adequate intake, stooling patterns and urine output.
- If a provider is unsure about the degree of jaundice, a total serum bilirubin should be obtained. Visual diagnosing jaundice can be prone to error, especially in dark skinned infants.

Prevention:[1]

- Promote and support breastfeeding
- Establish nursery protocols for identifying and evaluating hyperbilirubinemia
- Measure bilirubin levels in all infants with jaundice in the first 24 hours after delivery
- Recognize that visual estimation of bilirubin levels is inaccurate
- Interpret all bilirubin levels according to the infant's age in hours
- Identify preterm (i.e., less than 37 weeks), breastfed infants and provide close monitoring
- Perform a thorough risk assessment for all infants
- Provide parents with written and verbal information about newborn jaundice
- Provide appropriate follow-up
- Treat newborns, when indicated, with phototherapy or exchange transfusion

Outcome Measures:

- Length of Stay - Time from admission orders to time of discharge order is entered
- Readmission rate - Number of infants readmitted for phototherapy or complications related to hospitalization. (Will not include babies readmitted for RSV bronchiolitis for example.)
- Cost of stay
- IV fluid usage - Percentage of infants with inappropriate IV fluid usage (inappropriate defined as giving IVF to infants who are not dehydrated or who are dehydrated and can drink)
- Time to initiate PTX - Time from admission on inpatient unit to initiation of phototherapy
- Usage of powerplan - Percentage of infants with initiation and compliance of powerplan orders.
- DBili collection - Percentage of infants with Dbili collection on admission.
- Appropriate PTX ordered - Percentage of infants with Irradiance measurement documented on admission and per shift.
- ICU admission rate - Percentage of infants with ICU admission orders.
- Lactation Consultations - Percentage of admitted infants who receive a lactation consult
- Duration of PTX - Time from initiation of phototherapy to discontinuation of phototherapy.
- Breastfeeding infants - Percentage of breastfeeding infants who continued to breast feed upon discharge.

Methods

Existing External Guidelines/Clinical Pathways

Existing External Guideline/Clinical Pathway	Organization and Author	Last Update
Algorithm for the management of jaundice in the newborn nursery	American Academy of Pediatrics	2004

Any published clinical guidelines have been evaluated for this review using the **AGREE II criteria**. The comparisons of these guidelines are found at the end of this document. **AGREE II criteria** include evaluation of: Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence.

Review of Relevant Evidence: Search Strategies and Databases Reviewed

Search Strategies	Document Strategies Used
Search Terms Used:	Inclusion: neonatal, neonate, newborn, physiologic Jaundice: hyperbilirubinemia, jaundice, unconjugated, conjugated Nutrition: breastfeeding, IV fluids, intravenous fluids, formula feeding, donor milk Phototherapy: irradiance, warmer, isolette, overhead lights, biliblanket, phototherapy, Labs: direct bilirubinemia
Years Searched - All Questions	1980-2020
Language	English
Age of Subjects	< 14 days infants, > 35 weeks GA, inpatient admissions
Search Engines	PubMed, Cochrane, Google Scholar
EBP Web Sites	UpToDate
Professional Organizations	American Academy of Pediatrics
Joint Commission	
Government/State Agencies	None
Other	

Evidence Found with Searches

Check Type of Evidence Found	Summary of Evidence – All Questions
x	Systematic Reviews
☐	Meta-analysis articles
x	Randomized Controlled Trials
x	Non-randomized studies
x	Review articles
☐	Government/State agency regulations
x	Professional organization guidelines, white papers, ect.

Evaluating the Quality of the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation	
Strong	Desirable effects clearly outweigh undesirable effects or vice versa
Weak	Desirable effects closely balanced with undesirable effects
Type of Evidence	
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

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6. Cunningham, M., Cox, E. O., Medicine, C. on P. and A., & Bronchoesophagology, S. on O. and. (2003). Hearing Assessment in Infants and Children: Recommendations Beyond Neonatal Screening. Pediatrics, 111(2), 436–440.

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