TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Hyperbilirubinemia in the > 24 Hour < 10 Day Old Late Preterm/Term Neonate
Evidence-Based Guideline

Definition: Hyperbilirubinemia is the elevation of bilirubin in the blood of a newborn above the expected normal range. [1-3] Clinical jaundice describes the yellowish staining of the sclera, skin, and subcutaneous tissue as a result of the deposition of bilirubin in the tissue. Clinical jaundice is recognized in > 60% of newborns within the first week. [4-5] Most neonatal jaundice is benign but must be monitored due to the rare yet extremely harmful occurrence of acute bilirubin encephalopathy (ABE). ABE may be reversible if treated aggressively or may evolve into a non-reversible neurotoxic state with long term sequelae known as kernicterus. [3,6-12]

Etiology: Bilirubin is derived from the breakdown of heme-containing proteins in the reticuloendothelial system. The major heme-containing protein in blood cells is hemoglobin. [1-4,6-12] Bilirubin is normally cleared from the body after hepatic conjugation into a water soluble form by the liver enzyme glucuronyl transferase. Conjugated forms of bilirubin (bilirubin glucuronides) are eliminated in bile and urine. [1-4,10-13] A transient liver enzyme insufficiency in the newborn (exaggerated in preterm infants) contributes to the development of physiologic hyperbilirubinemia.[12,14] Other factors that contribute to neonatal hyperbilirubinemia are: increased production, decreased removal/excretion, and increased re-absorption of bilirubin. Certain genetic disorders are also contributory. [1-2,9-12]

Unconjugated bilirubin is bilirubin that is NOT metabolized. This unconjugated form of bilirubin is suspected to be the causal agent in ABE and/or kernicterus. [1-4,8-13,15] The fat soluble unconjugated bilirubin crosses cell membranes and is potentially neurotoxic. [14]

Guideline Eligibility Criteria:
Clinically jaundiced infants > 24 hours and < 10 days of age born at ≥ 35 weeks gestation.

Guideline Exclusion Criteria:
Acutely septic or severely ill infants.

Differential Diagnosis between physiologic and nonphysiologic jaundice may be difficult.

Physiologic jaundice occurs within the first week of life. The unconjugated bilirubin level usually peaks in term infants around the 3rd to 5th day of life and in late preterm infants around the 5th-7th day of life. [1-2,16-18]

Etiology of physiologic jaundice: [1-2,8-9]
- increased bilirubin production
- increased enterohepatic circulation of bilirubin
- defective bilirubin uptake
- defective bilirubin conjugation
- decreased hepatic excretion of bilirubin

Table1: Risk Factors for Developing Significant Hyperbilirubinemia[19]

Lower gestational age (i.e. risk increases with each additional week less than 40 weeks)
Predischarge 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 of >0.3 mg/dL per hour in the first 24 hour 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

Breastfeeding Jaundice versus Breast Milk Jaundice
Breastfeeding jaundice is a misnomer that describes "suboptimal intake" hyperbilirubinemia. It appears to be the result of an inadequate ingestion of milk related to poor feeding technique or a deficient milk supply, and is often associated with significant weight loss. [20]

Breast Milk Jaundice or Breast Milk Jaundice Syndrome is a distinct process that affects 2-4% of breastfed infants. Unlike physiologic jaundice, breast milk jaundice generally develops after 7-14 days and lasts much longer. The etiology is unknown; however, there is some support for hormonal factors acting on the infant's hepatic metabolism. High levels of β-glucuronidase activity in breast milk have also been implicated. [21]

Nonphysiologic jaundice is unrelated to inadequate intake of breast milk or the transitional physiology of the neonate.
Situations suggestive of nonphysiologic jaundice include:
- Onset of jaundice < 24 h of birth
- Rise of serum bilirubin of >0.3 mg/dL/h in the first 24 hours or ≥0.2 mg/dL/h thereafter
- Signs of illness (e.g., lethargy, poor feeding, vomiting, apnea, tachypnea, temperature instability, excess weight loss)

Etiologies of nonphysiologic jaundice: [9]
- Isoimmune hemolytic disease [1,22,23] or RBC membrane or enzymatic defects
- Inherited biochemical abnormalities [2,24-27]
- Viral or bacterial infections (sepsis) [15,28]
- GI/Liver diseases (including metabolic liver disease) [1,24]
- Polycythemia (Infants of diabetic mothers) or sequestration (bruising, cephalohematoma)

Diagnostic Evaluation:
History, assess for:
- risk factors (Table 1) [20]
- sibling/family history of jaundice, anemia, splenectomy, or early gallbladder disease suggestive of hereditary diseases [3]
- exclusive inadequate/ineffective breastfeeding [29]

Physical Examination:
Clinical observation for jaundice can be performed by blanching the skin with finger pressure and assessing the dermis and underlying subcutaneous tissue for the presence of a yellow color. This visual assessment does not correlate well with total serum bilirubin levels. [5,16,17] The absence of jaundice, however, has close to 100% negative predictive value for a TSB ≥ 12 mg/dL.[16,30-32] Assessment of a jaundiced infant should include a thorough neurological and abdominal assessment for signs suggestive of ABE and/or kernicterus.

Signs of ABE are often subtle and non-specific. [14] A directed history from a caregiver along with close observation may elucidate one or more of the following signs.
***Early Signs*:**
- Feeding difficulty
- Lethargy with altered wake-sleep cycles
- Irritability, fussiness, difficult to console
- Intermittent arching

Late signs:[19]
- Increasing hypertonia especially of extensor muscles with retrocollis and opisthotonus, and
- Varying degrees of drowsiness, poor feeding, and hypotonia.
- High pitched cry
- Arching
- Recurrent apnea

Risk for Kernicterus cannot be defined based on total serum bilirubin (TSB) levels alone. [33] Other factors to consider include:[19]
- Gestational age <38 wk and this risk increases with the degree of prematurity
- Albumin <3.0 g/dL
- Isoimmune hemolytic disease (i.e. positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
- Sepsis
- Significant clinical instability in the previous 24 hours

Laboratory Testing:
- Total serum bilirubin (TSB)
- Complete Blood Count (CBC) with differential and reticulocyte
- Direct Antigen Test (DAT), if mother had a positive antibody screening, blood group O regardless of Rh(D) status, or Rh(D)-.
- Albumin

Other labs may be considered:
- Conjugated bilirubin* if not previously documented.
- G6PD, if infant has jaundice of unknown cause AND TSB increases despite phototherapy.

*If conjugated bilirubin is elevated, contact Gastroenterology to determine if a consult is needed.

For infants requiring escalation of care, obtain the following labs STAT if not already done:
- Total and conjugated bilirubin
- Complete Blood Count (CBC)
- Albumin
- Serum chemistries
- Type and screen

Critical Points of Evidence

Recommendations Adopted/Adapted from National Guidelines [19]

- Patients at high risk for developing significant hyperbilirubinemia have the risk factors below. Infants with risk factors for hyperbilirubinemia require closer monitoring than infants without risk factors.
  - Lower gestational age
  - 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
- Patients at high risk for developing hyperbilirubinemia neurotoxicity have the risk factors below. The presence of these risk factors lower the threshold for treatment with phototherapy and the level at which care should be escalated.
  - Gestational age <38 wk and this risk increases with the degree of prematurity
  - Albumin <3.0 g/dL
  - Isoimmune hemolytic disease (i.e., positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
  - Sepsis
  - Significant clinical instability in the previous 24 h

- Intensive phototherapy is recommended at the total serum bilirubin phototherapy threshold on the basis of gestational age, hyperbilirubinemia neurotoxicity risk factors, and age of the infant in hours.
- For hospitalized infants, TSB should be measured within 12 hours after starting phototherapy. The timing of the initial TSB measurement after starting phototherapy and the frequency of TSB monitoring during phototherapy should be guided by the age of the child, the presence of hyperbilirubinemia neurotoxicity risk factors, the TSB concentration, and the TSB trajectory.
- Care should be escalated when an infant's TSB reaches or exceeds the escalation-of-care threshold, defined as 2 mg/dL below the exchange transfusion threshold.
- Infants requiring escalation of care should receive intravenous hydration and emergent intensive phototherapy. A neonatologist should be consulted about urgent transfer to a NICU that can perform an exchange transfusion.
- TSB should be measured at least every 2 hours from the start of the escalation-of-care period until the escalation-of-care period ends.
- Intravenous immune globulin (IVIG; 500 to 1000 mg/kg) over 2 hours may be provided to infants with isoimmune hemolytic disease (i.e., positive DAT) whose TSB reaches or exceeds escalation of care threshold. The dose can be repeated in 12 hours.
- An urgent exchange transfusion should be performed for infants with signs of intermediate or advanced stages of acute bilirubin encephalopathy (e.g. hypertonia, arching, retrocollis, opisthotonos, high pitched cry, or recurrent apnea).
- 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.
- Discontinuing phototherapy is an option 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 (e.g., gestational age <38 weeks, age <48 hours at the start of phototherapy, hemolytic disease).
- Repeat bilirubin measurement after phototherapy is based on the risk of rebound hyperbilirubinemia.

Principles of Clinical Management

The need for phototherapy and/or exchange transfusion is based upon presence of neurotoxicity risk factors, gestational age, and hour-specific TSB. [34] The need for these therapies will affect decisions to admit/hospitalize.

TCH Admission Criteria:

Signs of ABE or Kernicterus are a medical emergency and require immediate admission to the NICU 3 or 4 with full monitoring and exchange transfusion capabilities.

Acute Care Units:

- Well appearing neonate ≥ 35 weeks gestation at birth
- TSB level at or above phototherapy threshold on the hour-specific nomogram but below the escalation of care threshold[19]

NICU 3 or 4:

- Ill-appearing, jaundiced neonate
- Neonate meeting the escalation of care threshold, which is TSB level 2 mg/dL below the exchange transfusion threshold on the hour specific nomogram
- TSB increase of >0.25-0.5 mg/dL/h or ≥ 5mg/dL/DAY

Treatment Recommendations:

Phototherapy Threshold (See Figures on p. 5)

Phototherapy recommendations are determined by plotting the TSB level on the phototherapy hour-specific nomogram with special consideration of gestational age, neurotoxicity risk factors and age of the infant in hours.[19] Patients should be treated with intensive phototherapy when the TSB is at the phototherapy threshold. Phototherapy should not be delayed if patient meets criteria for phototherapy. Phototherapy preferably should be started within 1 hour after the decision to admit. Clinicians may choose to treat at lower levels, based on individual circumstances.

Phototherapy causes photoisomerization of bilirubin into water-soluble stereoisomer forms that can be excreted in bile or urine.[10] Phototherapy effectively decreases the TSB in jaundiced newborn infants and decreases the need for exchange transfusion.[35-38] The effectiveness of phototherapy is determined by the spectrum or wavelength of light, the surface area of the skin exposed, and the distance of the light source to the skin surface.[10]

Intensive phototherapy is achieved when the narrow spectrum LED blue light has an irradiance ≥30 μw/cm^2/nm and emits wavelengths of 460-490 nm.[19]

- **All** currently available appropriately used phototherapy lights at TCH qualify as *intensive phototherapy.*
- It is safe to provide a fiberoptic Biliblanket in conjunction with intensive phototherapy.

Please review the TCH Phototherapy in Infants Policy and Procedure for more details on providing phototherapy.

Supportive Care:

- Support and encouragement of breastfeeding during phototherapy is recommended.
- Promote frequent and unrestricted breastfeeding with evaluation of feeding technique and adequacy. Promote breast pumping if needed to enhance milk supply. Offer lactation support.
- Offer formula feedings with adequate frequency and volume to maintain hydration in non-breastfed infants.
- Provide uninterrupted rest periods in a neutral thermal environment to preserve energy expenditures for feeding.
- Assess intake and output.

Discontinuing Phototherapy[19]

- Phototherapy may be discontinued when the TSB is at least 2 mg/dL below the threshold at **initiation** of phototherapy
- Phototherapy may be extended longer if there are risk factors for rebound.
    - Gestational age <38 weeks
    - Age <48 hours at the start of phototherapy
    - Hemolytic disease

Rebound Hyperbilirubinemia[19]

Repeat bilirubin measurement after phototherapy should be obtained based upon patient risk for rebound hyperbilirubinemia. Risk factors for rebound hyperbilirubinemia include:

- TSB at the time of discontinuation in relationship to phototherapy threshold
- Gestational age <38 weeks
- Adequacy of feeding and weight gain
- Phototherapy during birth hospitalization

- Hemolytic disease
- Postnatal age <48 hours at the start of phototherapy
- Hyperbilirubinemia neurotoxicity risk factors

Patient Criteria	Repeat Total Serum Bilirubin
Infants who exceeded the phototherapy threshold during birth hospitalization AND • (1) received phototherapy before 48 hours of age; • (2) had a positive DAT; or • (3) had known or suspected hemolytic disease	6 to 12 hours after phototherapy AND repeat measurement on the day after phototherapy discontinuation
Infants who received phototherapy during birth hospitalization and who were later readmitted for exceeding the phototherapy threshold	Day after phototherapy discontinuation
• Infants readmitted for exceeding phototherapy threshold but who did not receive phototherapy during birth hospitalization • Infants treated with home phototherapy who exceeded the phototherapy threshold	1 to 2 days after phototherapy discontinuation

Escalation of Care Threshold[19] (See Figures on p. 6)
Patients should be transferred to the NICU 3 or 4 when their TSB reaches the escalation of care threshold which is 2 mg/dL below the exchange transfusion threshold. Initiating escalation of care is a medical emergency. The escalation of care period starts from the time the TSB level rises above threshold until the TSB levels return to below the escalation of care threshold. Infants requiring escalation of care should receive IV hydration, intensive phototherapy and have TSB measured at least every 2 hours. Escalation of care labs should be obtained STAT.

Exchange Transfusion Threshold[19] (See Figures on p. 6)
Exchange transfusion (ET) will remove products of hemolysis (bilirubin) and antibody-coated red blood cells and replace them with donor red blood cells that lack the sensitizing antigen. [25] This reduction of sensitized cells results in a reduction in RBC hemolysis.

Exchange transfusion recommendations are determined by signs of bilirubin encephalopathy OR by plotting the TSB level on the exchange transfusion hour-specific nomogram with special consideration of gestational age, neurotoxicity risk factors and age of the infant in hours. [19]

- An urgent exchange transfusion should be performed for infants with signs of intermediate or advanced stages of acute bilirubinemia encephalopathy (e.g. hypertonia, arching, retrocollis, opisthotonos, high-pitched cry, or recurrent apnea).
- An urgent exchange transfusion should be performed when the TSB is at or above the exchange transfusion threshold. If the TSB decreases below the exchange transfusion threshold prior to starting the exchange transfusion AND there are no signs of intermediate or advanced stages of acute bilirubin encephalopathy, the exchange transfusion may be held while continuing intensive phototherapy.
- A double volume exchange (DVE) is recommended and involves replacing 160-180 mL/kg of neonatal blood with CMV safe, irradiated donor blood.
- Cross-matched washed packed red blood cells (PRBCs) mixed with thawed adult fresh-frozen plasma to a hematocrit approximating 40% is preferred for exchange transfusions. The plasma provides additional albumin that aides in bilirubin removal.
- The bilirubin (TSB mg/dL) to albumin (g/dL) ratio can be used with TSB levels to determine the need for exchange transfusion. Exchange transfusion may also be considered if the bilirubin to albumin ratio is:
  - ≥8 if the gestational age is ≥38 weeks' gestation and there are no hyperbilirubinemia neurotoxicity risk factors, or
  - ≥7.2 if the gestational age is ≥38 weeks' gestation and there is at least 1 hyperbilirubinemia neurotoxicity risk factor, or
  - ≥7.2 if the gestational age is 35 through 37 weeks' gestation with no neurotoxicity risk factors, or
  - ≥6.8 if the gestational age is 35 through 37 weeks' gestation and at least 1 hyperbilirubinemia neurotoxicity risk factor.

Pharmacologic Therapy:
Intravenous hydration is recommended during the escalation of care period.[19]

Intravenous immunoglobulin (IVIG) has an unclear effectiveness in the prevention of exchange transfusion. A 500 to 1000 mg/kg dose of IVIG over 2 hours may be administered if hydration and phototherapy are not effective in stabilizing or reducing the TSB when a diagnosis of isoimmune hemolytic disease (i.e. positive DAT) is made. A second 500 mg/kg dose may be given 12 hours later. When deciding whether to treat with IVIG, consider the response to phototherapy, TSB rate of rise and the ability to provide a timely exchange transfusion.[19] Escalation of care guidelines should continue to be followed.

Medication Effects on Bilirubin Levels
Several medications may displace bilirubin from albumin binding sites and are classified by this ability.[39] Consider alternative medications that have minimal or no displacing effects if available and discuss with pharmacy as needed.

- ***Moderate to strong displacing effect* (Use alternative medication when available):** sulfiSOXAZOLE, sulfamethoxazole, dicloxacillin, ceftriaxone, cefotetan, ceFAZolin, ibuprofen lysine, and diatrizoate (contrast). Note: Medications with moderate to strong displacing effects should be avoided in infants with hyperbilirubinemia.
- ***Minimal displacing effect*:** nafcillin, ampicillin, furosemide, phenobarbital
- ***No displacing effect*:** cefUROxime, gentamicin, amikacin, rifampin, indomethacin, cefTAZidime, and clindamycin

Parent/Caregiver Education:[19]
- Basic understanding of jaundice
- Adequacy of infant feeding and elimination
- Recognition of clinical changes, including skin color, urinary output as a reflection of hydration, infant behavior, and illness
- When and how to seek medical assistance
- Importance of follow-up

Outcome Measures (will apply to all gestational ages):
- Repeat EC visit for hyperbilirubinemia within 48 h after Observation Unit management
- Readmission for hyperbilirubinemia
- Use of hour-specific nomogram TSB phototherapy treatment level as the level at which phototherapy is discontinued
- Time interval to treat in infants with a TSB level above the exchange transfusion treatment line
- Use of medications that are HIGH bilirubin displacers
- Percent of infants for whom breastfeeding was discontinued during phototherapy
- Complications related to exchange transfusion

Guidelines for Phototherapy in Hospitalized Infants ≥ 35 Weeks Gestation[19]

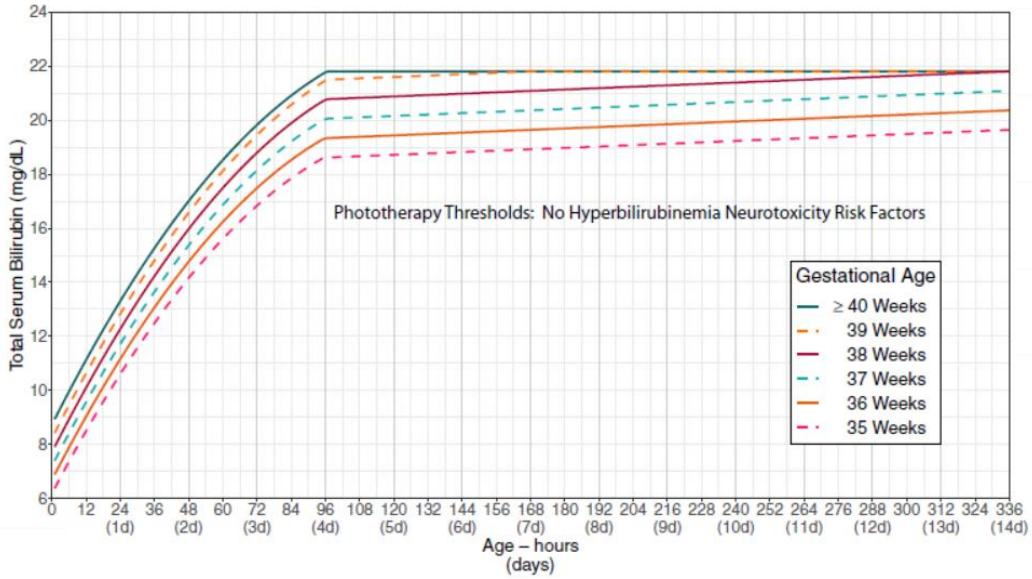


FIGURE 2

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.

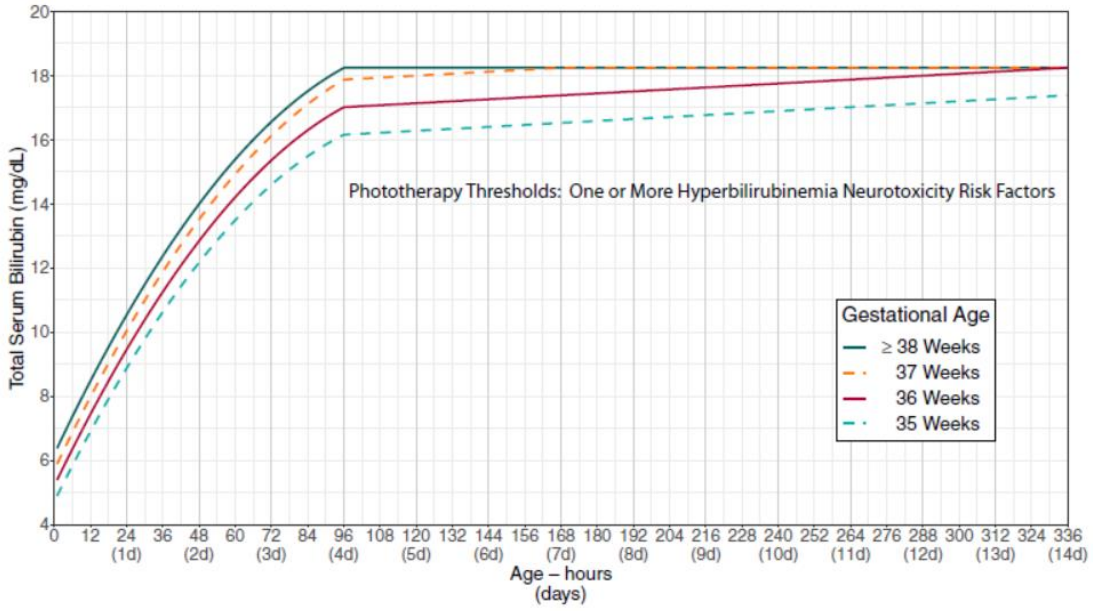


FIGURE 3

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.

Guidelines for Exchange Transfusion in Infants 35 or more Weeks Gestation[19]

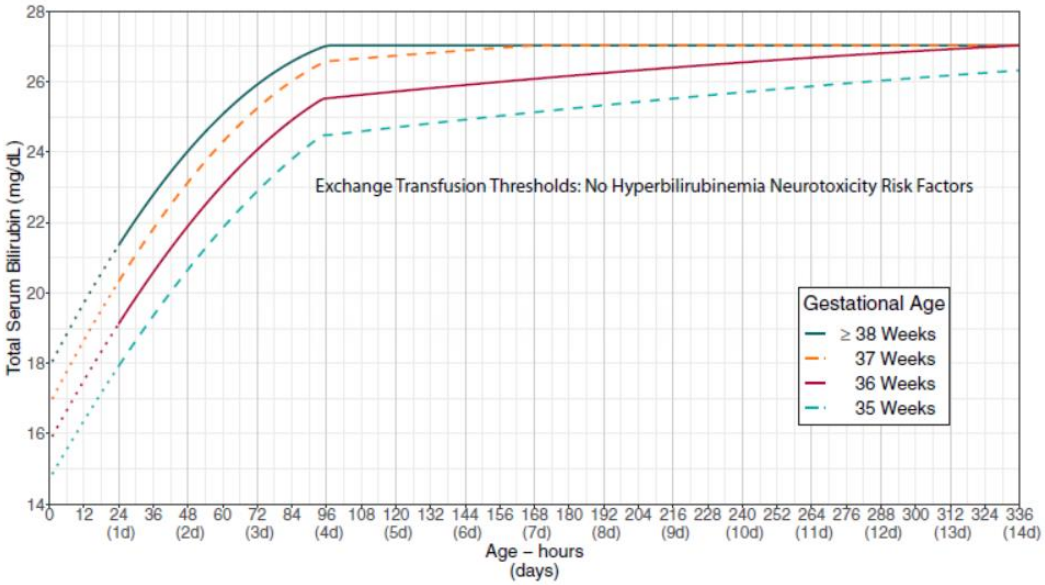


FIGURE 5

Exchange transfusion thresholds by gestational age for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. See Fig 4, which describes escalation of care. 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. See Supplemental Fig 4.

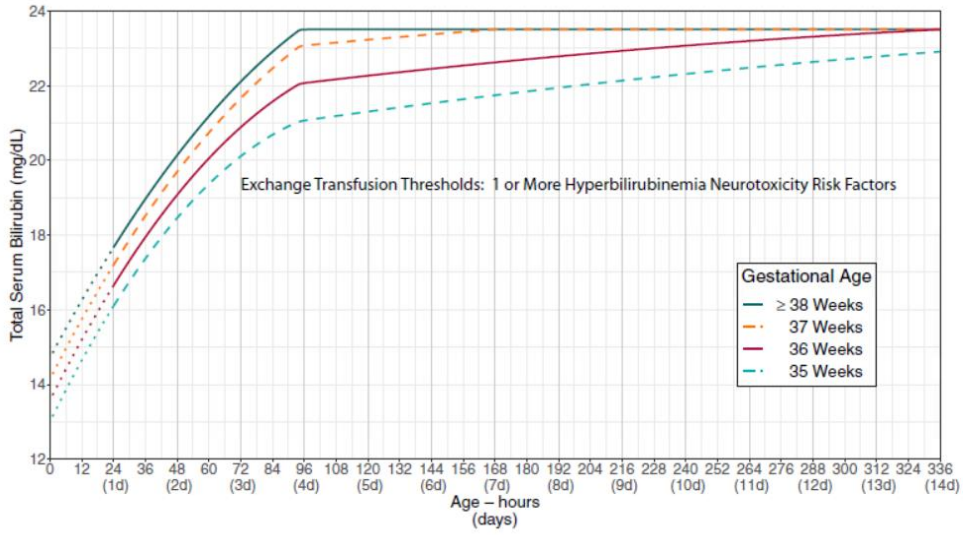
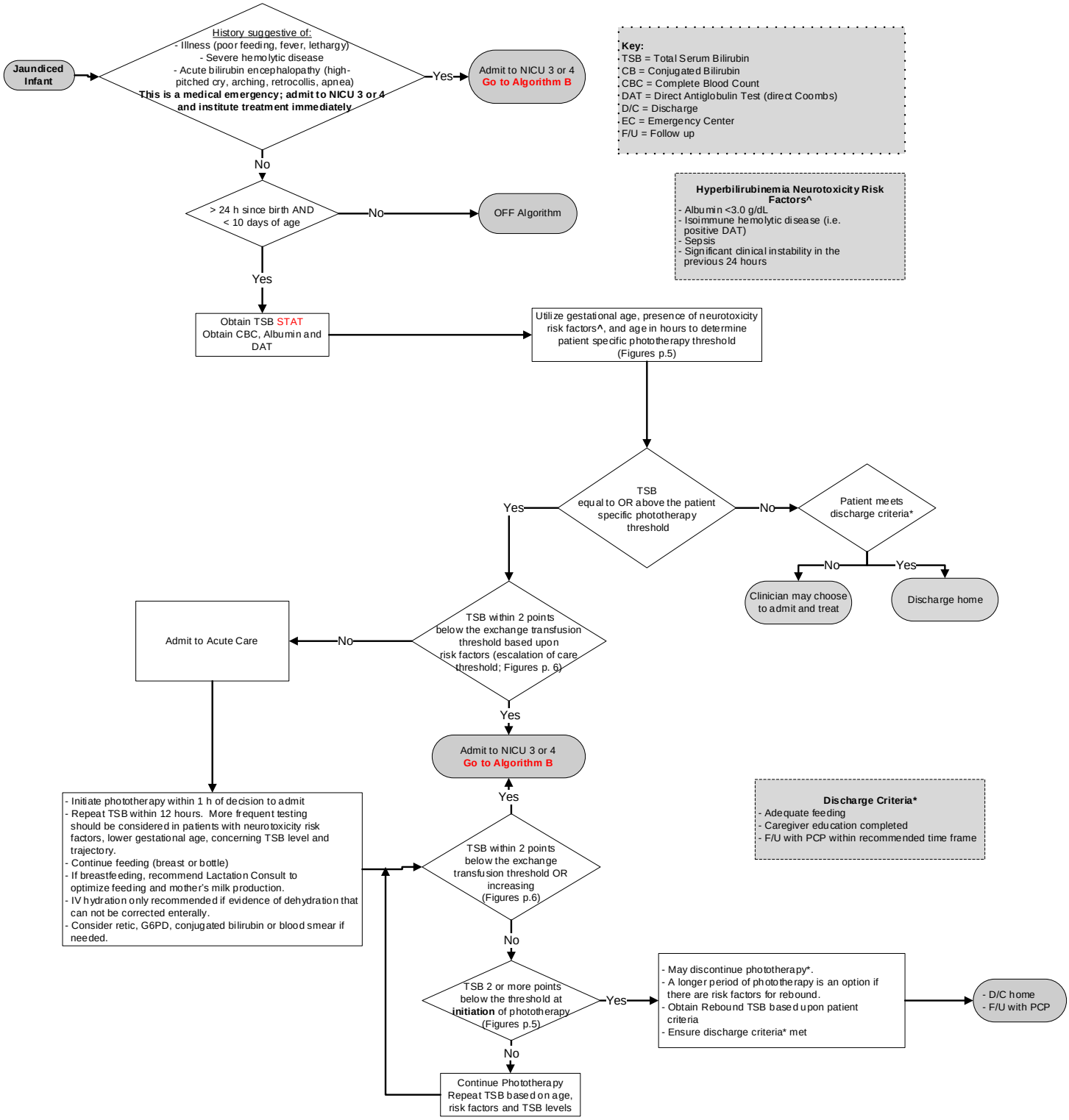


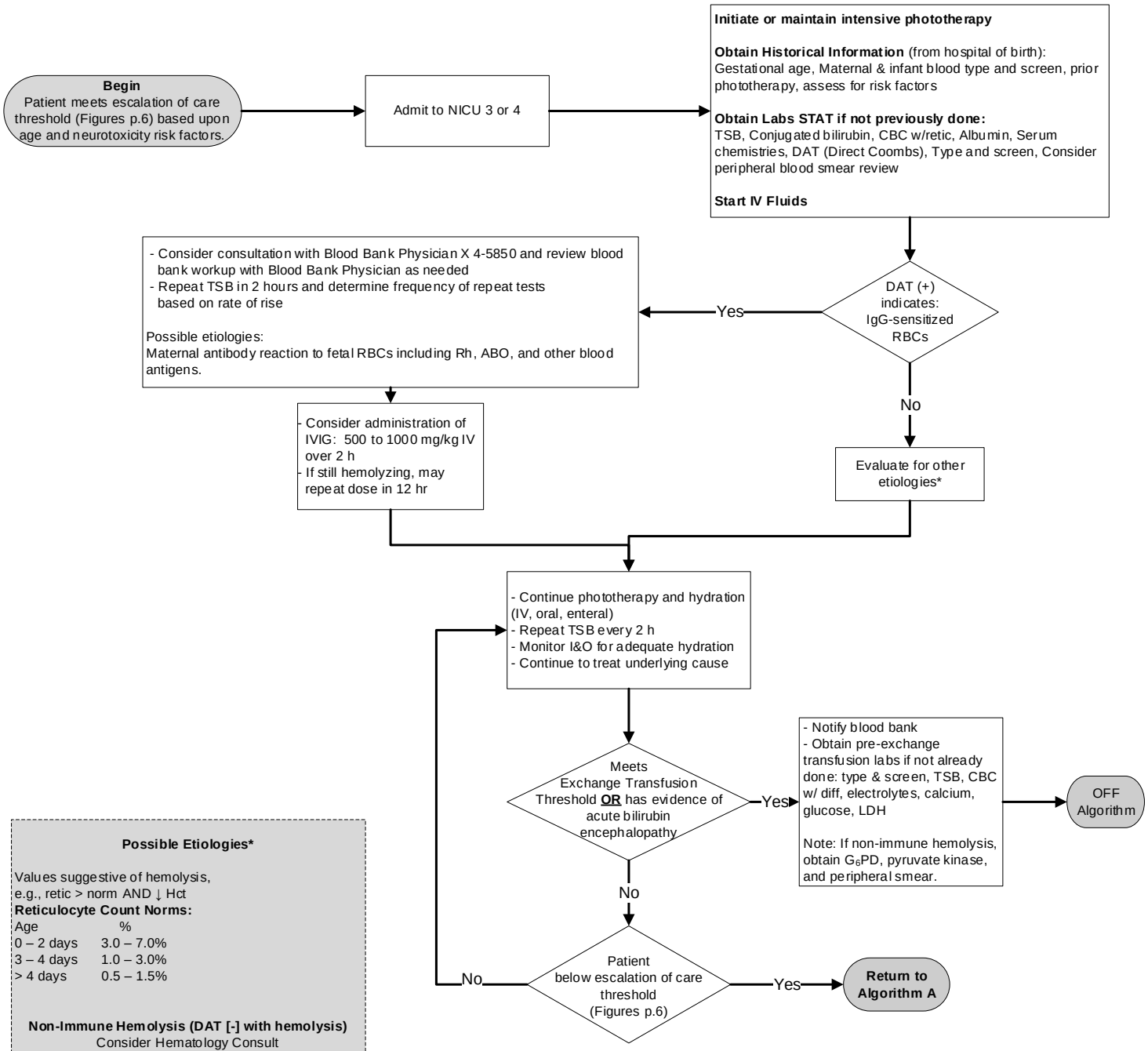
FIGURE 6

Exchange transfusion thresholds by gestational age for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. See Fig 4, which describes escalation of care. 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. See Supplemental Fig 5.

TCH Evidence-Based Outcomes Center
Management of Hyperbilirubinemia in the Late Preterm/Term Newborn (Algorithm A)



TCH Evidence-Based Outcomes Center
Escalation of Care Management of Hyperbilirubinemia (Algorithm B)



Possible Etiologies*

Values suggestive of hemolysis,
e.g., retic > norm AND ↓ Hct
Reticulocyte Count Norms:

Age	%
0 – 2 days	3.0 – 7.0%
3 – 4 days	1.0 – 3.0%
> 4 days	0.5 – 1.5%

Non-Immune Hemolysis (DAT [-] with hemolysis)
Consider Hematology Consult
Possible etiologies include but not limited to:
- RBC abnormalities
- Polycythemia –Hyperviscosity
- G6PD deficiency
- Extravascular source (e.g., bruising, cephalohematoma, IVH)

DAT (-) without hemolysis
Possible etiologies include but not limited to:
- Infection: sepsis, TORCH, UTI
- Hyperviscosity/Polycythemia
- GI abnormalities. If conjugated bilirubin elevated, contact GI/Liver to determine if a consult needed

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Guideline Preparation

This guideline was prepared by the Evidence-Based Outcomes Center (EBOC) Team in collaboration with content experts at Texas Children's Hospital. Development of this guideline supports the TCH Quality and Patient Safety Program initiative to promote clinical guidelines and outcomes.

Hyperbilirubinemia in the Late Preterm/Term Neonate Content Expert Team

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Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - American Academy of Pediatrics, Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, 2022
   - American Academy of Pediatrics, Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation, 2004
3. Literature Review of Relevant Evidence
4. Critically Analyze the Evidence
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Hyperbilirubinemia in the Greater Than 24 Hour, Less Than 10 Day Old Late Preterm/Term Neonate evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence.*
The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**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, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of hyperbilirubinemia in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

Version History

Date	Comments
May 2010	First Iteration
Jan 2017	Revision; Hospital unit titles updated to reflect new NICU 4 designation and patient placement in the Abercrombie Units. References to the transcutaneous bilirubin measurement removed.
August 2018	Guideline reaffirmed. PICO Questions 1, 4 and 9 archived. Remainder of PICO questions reaffirmed.
Feb 2023	Guideline Update