Updates to management of neonatal hyperbilirubinemia: implementing a new clinical practice guideline

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Children's HOSPITAL & MEDICAL CENTER OMAHA

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Objectives

1. Briefly review the underlying physiologic processes that place newborn infants at risk for hyperbilirubinemia
2. Be able to recognize hyperbilirubinemia neurotoxicity risk factors
3. Known when to initiate phototherapy and exchange transfusion based on the recent AAP clinical practice guideline
4. Understand when and how to escalate care in the event of severe neonatal hyperbilirubinemia

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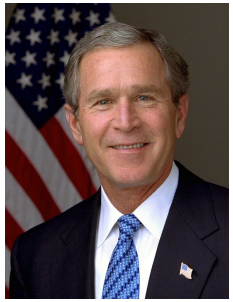
Back to 2004

ATHENS 2004



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Also in 2004…

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation
Pediatrics 2004;114;297
DOI: 10.1542/peds.114.1.297

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…and 18 years later

CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation

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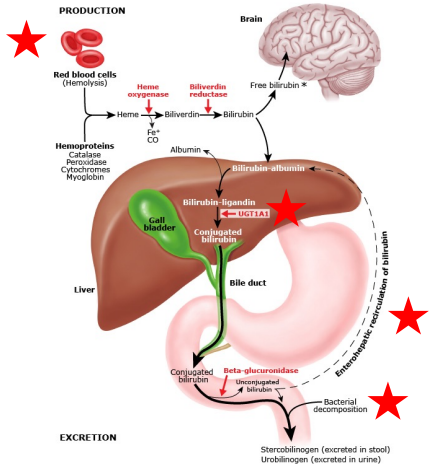
Bilirubin production, metabolism, and transport



UpToDate, 2022

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Benign neonatal hyperbilirubinemia

- "Physiologic jaundice"
- Immaturity of hepatic conjugation system
- RBC (HbF) turnover after birth
- Median peak TSB of 8-9 mg/dL on DOL 3-5
- ALL infants should be screened for hyperbilirubinemia (with TcB or TSB) while in the nursery!

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Benign neonatal hyperbilirubinemia

- Breast **FEEDING** jaundice
  - First week of life
  - Inadequate oral intake → dehydration → increased enterohepatic circulation
  - Optimize feeding
- Breast **MILK** jaundice
  - After first week of life
  - Component(s) of breast milk that de-conjugate bilirubin and increase enterohepatic circulation
  - Continue feeding, consider trial of formula

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Pathologic hyperbilirubinemia

Increased production	Decreased conjugation / clearance

• **Hemolytic disease**
  • **Immune medicated**
  • RBC enzyme deficiencies
  • RBC structural membrane defects
  • Hemoglobinopathies
• Extravascular blood (i.e. birth injury)
• Polycythemia
• Enhanced enterohepatic circulation
  • Delayed passage of meconium
  • Poor intake
  • Exclusive breast milk feeding
	• Prematurity
	• Hypothyroidism
	• Hypopituitarism
	• Disorders of conjugation
	  • Crigler-Najjar syndrome
	  • Gilbert syndrome
	• Enhanced enterohepatic circulation

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Pathologic hyperbilirubinemia – hemolysis

Increased production

- Etiologies of hemolysis
  - **Isoimmune mediated** – Rh incompatibility, ABO incompatibility, minor blood group incompatibilities
  - Enzymatic deficiencies – G6PD deficiency, pyruvate kinase deficiency
  - Structural defects of RBCs – hereditary spherocytosis / elliptocytosis
  - Hemoglobinopathies – α-thalassemia
- Results in increased production of bilirubin that needs to be conjugated by an immature / non-existent hepatic system
- Considered to be a **neurotoxicity risk factor** and thus presence lowers PT/ET thresholds

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Screening for isoimmune hemolysis

2004

SECONDARY PREVENTION

RECOMMENDATION 2.0: Clinicians should perform ongoing systematic assessments during the neonatal period for the risk of an infant developing severe hyperbilirubinemia.

Blood Typing

RECOMMENDATION 2.1: All pregnant women should be tested for ABO and Rh (D) blood types and have a serum screen for unusual isoimmune antibodies (evidence quality B: benefits exceed harms).
RECOMMENDATION 2.1.1: If a mother has not had prenatal blood grouping or is Rh-negative, a direct antibody test (or Coombs' test), blood type, and an Rh (D) type on the infant's (cord) blood are strongly recommended (evidence quality B: benefits exceed harms).
RECOMMENDATION 2.1.2: If the maternal blood is group O, Rh-positive, it is an option to test the cord blood for the infant's blood type and direct antibody test, but it is not required provided that there is appropriate surveillance, risk assessment before discharge, and follow-up[20] (evidence quality C: benefits exceed harms).

2022

KAS 1: If the maternal antibody screen is positive or unknown because the mother did not have prenatal antibody screening, the infant should have a direct antiglobulin test (DAT) and the infant's blood type should be determined as soon as possible using either cord or peripheral blood. (Aggregate Evidence Quality Grade B, Recommendation)

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Screening for isoimmune hemolysis

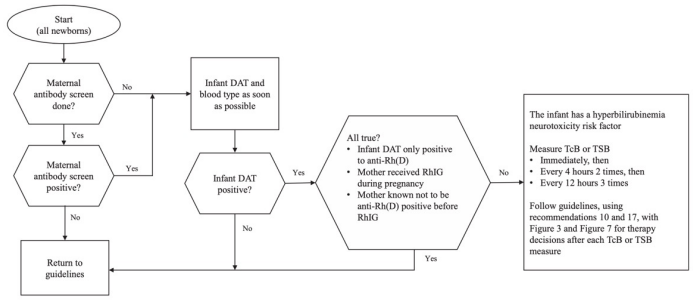

FIGURE 1
Approach to identify newborns with maternal anti-erythrocyte antibodies and to guide early management.[15]

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Bilirubin-induced neurologic dysfunction (BIND)

- Acute bilirubin encephalopathy (ABE)
  - Clinical signs develop after several hours of "high" bilirubin levels
  - Initial phase – Lethargy, hypotonia, poor suck
  - Advanced stages – Hypertonia (retrocollis, opisthotonos), fever, high-pitched cry, inability to feed, apnea
  - Warrants immediate escalation of care and exchange transfusion – even if TSB is below ET threshold

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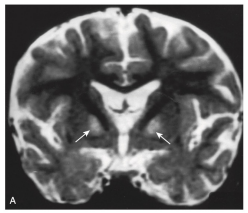
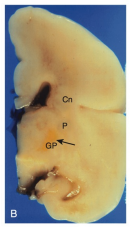
Bilirubin-induced neurologic dysfunction (BIND)

- Chronic bilirubin encephalopathy (CBE, "kernicterus")
  - Permanent neurologic sequelae of bilirubin neurotoxicity
  - Extrapyramidal movement disorder (dystonia / choreoathetosis)
  - Hearing loss
  - Upward gaze paresis
  - Highly specific deposition into globus pallidus and subthalamic nuclei





Avery's Diseases of the Newborn, 10th Ed, 2018

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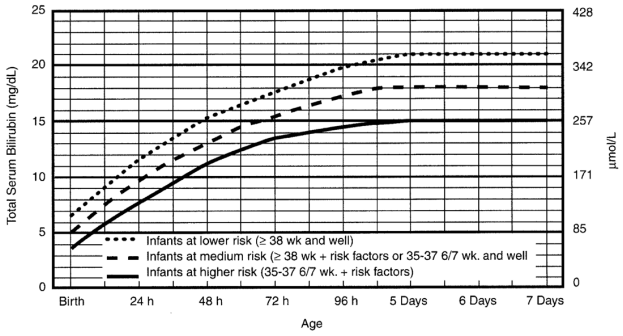
Risk factors – 2004 CPG



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

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Also listed as risk factors

- Risk factors for the development of **severe hyperbilirubinemia** but not necessarily neurotoxicity
- Some overlap
  - Hemolytic disease
  - Prematurity

TABLE 2. Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance)

Major risk factors
Predischarge TSB or TcB level in the high-risk zone (Fig 2)[25,31]
Jaundice observed in the first 24 h[30]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk[39,40]
Previous sibling received phototherapy[40,41]
Cephalohematoma or significant bruising[39]
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive[39,40]
East Asian race[39*]
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone[25,31]
Gestational age 37–38 wk[39,40]
Jaundice observed before discharge[40]
Previous sibling with jaundice[40,41]
Macrosomic infant of a diabetic mother[42,43]
Maternal age ≥25 y[39]
Male gender[39,40]
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone (Fig 2)[25,31]
Gestational age ≥41 wk[39]
Exclusive bottle feeding[39,40]
Black race[38*]
Discharge from hospital after 72 h[40,44]

* Race as defined by mother's description.

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Neurotoxicity risk factors – 2022 CPG revision

TABLE 2 Hyperbilirubinemia Neurotoxicity Risk Factors

Risk Factors
• Gestational age <38 wk and this risk increases with the degree of prematurity[a]
• Albumin <3.0 g/dL
• Isoimmune hemolytic disease (ie, positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
• Sepsis
• Significant clinical instability in the previous 24 h

[a]Gestational age is required to identify the phototherapy thresholds (Figs 2 and 3; Supplemental Tables 1 and 2, and Supplemental Figs 1 and 2) and the exchange transfusion thresholds (Figs 5 and 6; Supplemental Tables 3 and 4, and Supplemental Figs 3 and 4).

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Key changes

2004 AAP

- Hemolysis
- Asphyxia
- Significant lethargy
- Temperature instability
- Acidosis
- Sepsis
- Hypoalbuminemia (< 3.0 mg/dL)

2022 AAP CPG

- Hemolysis
- Significant clinical instability in the previous 24 hours
- Sepsis
- Hypoalbuminemia (< 3.0 mg/dL)

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A word about hypoalbuminemia

- Unconjugated bilirubin
  - Lipophilic in plasma
  - Can cross blood brain barrier to cause bilirubin encephalopathy
  - Binds to albumin to increase solubility
- Hypoalbuminemia (< 3.0 g/dL)
  - Greater proportion of serum unconjugated bilirubin is unbound
  - Increases risk for neurotoxicity
  - Not necessary to measure in all jaundiced infants
  - Should check as part of escalation of care

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Bilirubin to albumin (B:A) ratio

- Milligrams bilirubin per gram albumin
- Can be used in conjunction with TSB to determine need for ET
- Consider ET if B:A ratio is:
  - ≥8.0 if GA ≥38 weeks and no NT risk factors
  - ≥7.2 if GA ≥38 weeks and at least one NT risk factor
  - ≥7.2 if GA 35-37 weeks and no NT risk factors
  - ≥6.8 if GA 35-37 weeks and at least one NT risk factor

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Why is this changing?

- Ebbsen et al, 2012; Denmark, 2000-2007 (**N=502,766** infants ≥35 weeks)
  - 224 infants with TSB ≥26.3 mg/dL
  - 3 cases of kernicterus – peak TSBs 38.1, 42.9, 57.1 due to ABO incompatibility (2) and G6PD deficiency
- Kaiser Permanente Northern CA, 1995-2011 (**N=525,409** infants ≥35 weeks)
  - 47 infants with TSB ≥30 mg/dL
  - 3 cases of kernicterus – peak TSBs 48.5, 49.1, 28.4 due to G6PD deficiency (2) and in utero volvulus with DIC (1)
- Incidence of kernicterus: 6 / 1,028,175 = 0.0006%

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Why is this changing?

- Possible association between phototherapy and later development of seizures
  - Maimburg et al, 2006 →aHR 1.98, 95% CI 1.40-2.78 for MALES, no association for females
  - Newman et al, 2018 → aHR 1.22, 95% CI 1.05-1.42, higher for MALES

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Why is this changing?

- Conclusions
  - Interim evidence suggests that bilirubin neurotoxicity does not occur until TSB levels well above 2004 ET threshold
  - Evidence for possible harm
  - Concern for overtreatment
  - Justified raising the PT thresholds by a narrow range

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Methodology – phototherapy curves

- No neurotoxicity risk factors
  - 40 weeks → 2022 PT threshold increased by 2 mg/dL above 2004 "low risk" threshold
  - 35 weeks → 2022 PT threshold increased by 1 mg/dL above 2004 "medium risk" threshold
  - 36-39 weeks → 2022 PT thresholds spaced evenly between thresholds for 35 and 40 weeks

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Methodology – phototherapy curves

- At least 1 neurotoxicity risk factor
  - ≥38 weeks → 2022 PT threshold increased by 1 mg/dL above 2004 "medium risk" threshold
  - 35 weeks → 2022 PT threshold increased by 1 mg/dL above 2004 "high risk" threshold
  - 36-37 weeks → 2022 PT thresholds spaced evenly between thresholds for 35 and ≥38 weeks

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Methodology – exchange transfusion curves

- Difference calculated between ET and PT thresholds based on 2004 guidelines for each group
- Difference added to new PT threshold in the current guideline

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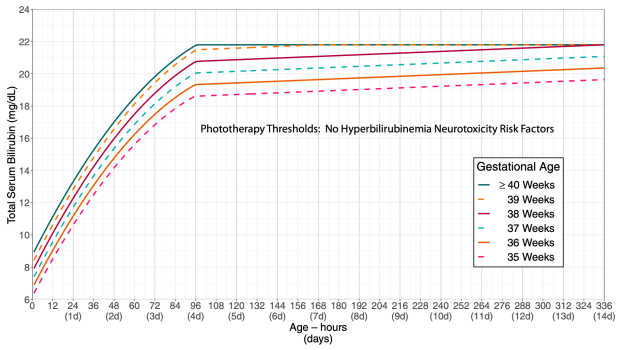
What's new – phototherapy

Criteria for phototherapy for infants with **NO** neurotoxicity risk factors other than gestational age



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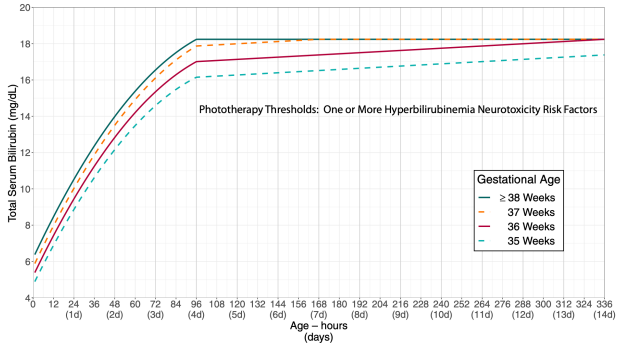
What's new – phototherapy

Criteria for phototherapy for infants **WITH** neurotoxicity risk factors other than gestational age



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What's new – exchange transfusion

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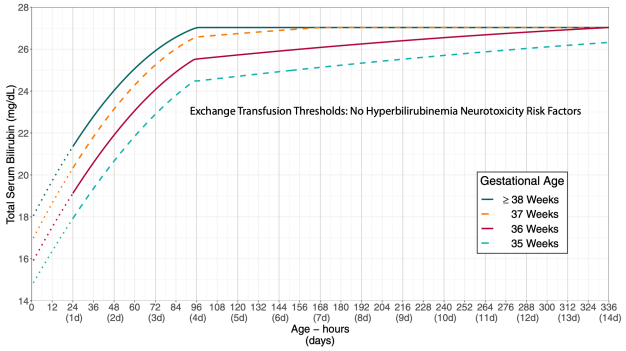

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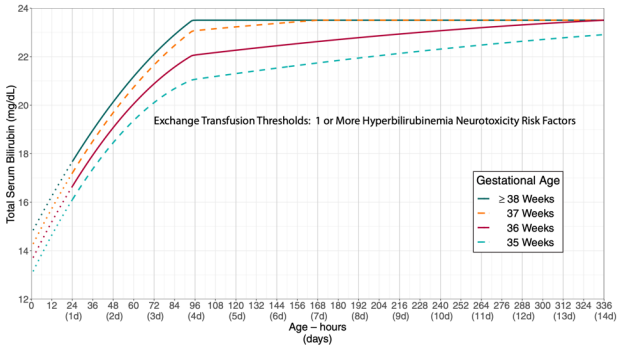

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Escalation of care

- Intensive care needed with elevated or rapidly increasing TSB
- Goal is to avoid exchange transfusion and prevent CBE

- Threshold is TSB within **2 mg/dL** of the exchange transfusion threshold
- As always – **include any direct-reacting bilirubin** and use TSB as the definitive test to guide management

- Optimal location for management – **NICU** capable of performing ET if necessary

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Escalation of care

- If infant is not at a location appropriate for ET, arrange transfer
  - Continue intensive PT
  - Continue PO and IV hydration

- Labs
  - Complete blood count
  - Serum electrolytes
  - Serum albumin
  - Coombs test (DAT)
  - Frequent reassessment of TSB

- Consider IVIG (0.5-1 g/kg) over 2 hours **IF** isoimmune hemolytic disease present
  - Unclear effectiveness

- Frequent neurologic assessments

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Escalation of care

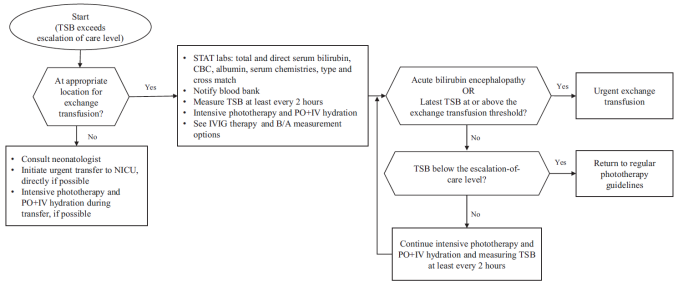

FIGURE 4
Approach to escalation of care. The escalation-of-care threshold is 2 mg/dL below the exchange transfusion threshold. IVIG, intravenous immune globulin; B/A, bilirubin to albumin ratio.

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Timing of follow up after discharge

- Previous guidelines for follow up (2004 CPG, 2009 revision) – did not take into account GA, NT risk factors, excluded DAT+ infants
- Use difference between TSB and PT threshold to determine timing of follow up
- New process incorporates GA, NT risk factors into follow up decision making process

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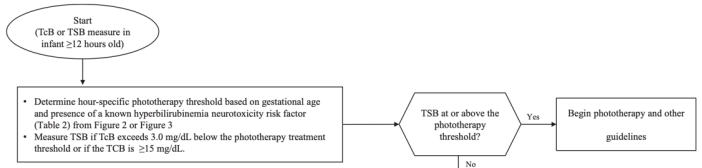
Timing of follow up after discharge



Phototherapy threshold minus TcB or TSB measure		Discharge Recommendations
0.1–1.9 mg/dL	Age <24 hours	Delay discharge, consider phototherapy, measure TSB in 4 to 8 hours
	Age≥24 hours	Measure TSB in 4 to 24 hours[a] Options: • Delay discharge and consider phototherapy • Discharge with home phototherapy if all considerations in the guideline are met • Discharge without phototherapy but with close follow-up
2.0–3.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 4 to 24 hours[a]
3.5–5.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 1– 2 days
5.5–6.9 mg/dL	Discharging <72 hours	Follow-up within 2 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]
≥7.0 mg/dL	Discharging <72 hours	Follow-up within 3 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]

FIGURE 7
Flow diagram for infants during the birth hospitalization to determine postdischarge follow-up for infants who have not received phototherapy.
[a]Use clinical judgment and shared decision making to determine when to repeat the bilirubin measure within this 4 to 24 hour time window.
[b]Clinical judgment decisions should include physical examination, the presence of risk factors for the development of hyperbilirubinemia (Table 1) or hyperbilirubinemia neurotoxicity risk factors (Table 2), feeding adequacy, weight trajectory, and family support.

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Clinical case reviews

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Case 1

You are rounding in the newborn nursery at your hospital and are examining a 6 hour old male infant born overnight at 37 weeks born by SVD. He is not jaundiced. Reviewing his mother's chart, you note that his mother was late to prenatal care and does not have a blood type or antibody screen done. What is the most appropriate course of action?

A. No interventions are needed since the infant is not jaundiced
B. Check a CBC and TSB and repeat exam in the morning
C. Check blood type and DAT on the infant as soon as possible to determine risk for isoimmune hemolysis

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Case 1

The infant's DAT is positive and his blood type is B positive. You discuss the mother's history with her obstetrician and confirm that the mother did not receive Rhogam during the pregnancy and that labs drawn during labor confirmed that the mother's blood type is O negative. Which of the following options are true?

A. The infant is at risk for significant hyperbilirubinemia
B. The infant has a neurotoxicity risk factor
C. The infant should have TSB's trended in the newborn nursery
D. Screening for jaundice with a TcB daily is sufficient
E. A and D only
F. A, B, and C

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Screening for isoimmune hemolysis

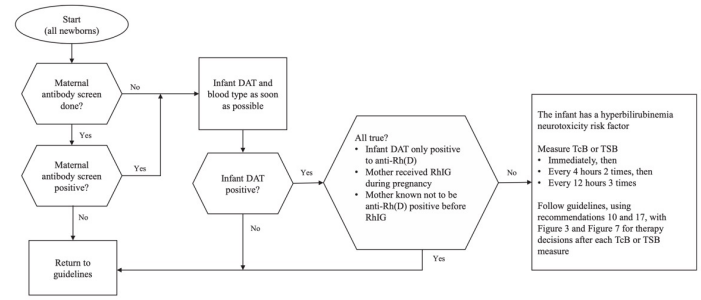

FIGURE 1
Approach to identify newborns with maternal anti-erythrocyte antibodies and to guide early management.[15]

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Case 1

You trend TSB's in the newborn nursery and at 60 hours of life, the infant's TSB is 12 mg/dL with a rate of rise of 0.18 mg/dL/hour. Mother is being discharged from the postpartum unit. What is the most appropriate course of action?

A. Delay discharge and consider PT in the nursery
B. Discharge infant with follow up and TSB check the next day
C. Discharge infant and schedule follow up with TSB check in 2-3 days
D. Discharge infant with scheduled follow up, but no need to recheck TSB since TSB at time of discharge is <PT threshold

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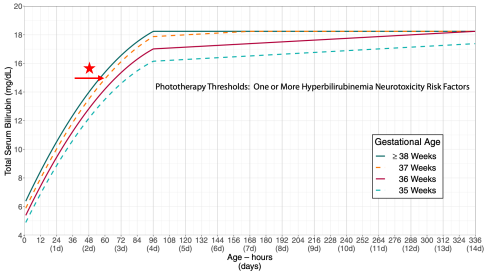
Timing of discharge for jaundiced infant

- Step 1: Determine if there are neurotoxicity risk factors (in this case, YES)
- Step 2: Determine PT threshold based TSB and age in hours (in this case, threshold is 15 mg/dL)



- Step 3: Calculate difference between PT threshold and TSB (in this case, 3 mg/dL)

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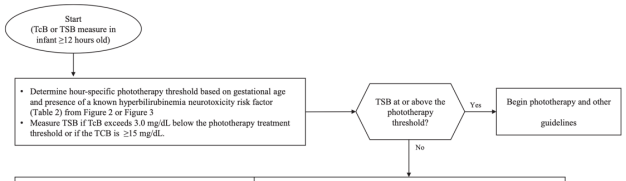
Timing of discharge for jaundiced infant

- Step 4: Consult AAP clinical practice guideline



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2.0–3.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 4 to 24 hours[a]
3.5–5.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 1– 2 days
5.5–6.9 mg/dL	Discharging <72 hours	Follow-up within 2 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]
≥7.0 mg/dL	Discharging <72 hours	Follow-up within 3 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]

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Case 2

You are seeing a 4 day (96 hour) old female infant who was born at 36 weeks due to maternal pre-eclampsia and gestational diabetes. Vacuum extraction was required with a resulting cephalohematoma. The infant was discharged from the nursery at 2 days (48 hours) of life, with a screening TcB of 14 mg/dL at the time of discharge. Maternal serologies were negative and mom is AB positive blood type, with a negative antibody screen. There are two other older siblings who required inpatient hospitalization for phototherapy. On exam, the infant is quite jaundiced but otherwise clinically well. She is exclusively breast feeding, and mom is worried her milk supply has not come in yet. Yesterday the baby only made 2 wet diapers. Which of the following are risk factors for significant hyperbilirubinemia?

A. Gestational age of 36 weeks
B. Infant of a diabetic mother
C. History of siblings requiring phototherapy
D. Maternal AB positive blood type
E. Female sex
F. Vacuum extraction with cephalohematoma
G. Exclusive breast feeding with suboptimal intake
H. Screening TcB at 48 hours of life

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Risk factors for significant hyperbilirubinemia

TABLE 1 Risk Factors for Developing Significant Hyperbilirubinemia

Risk Factors
★ • Lower gestational age (ie, risk increases with each additional week less than 40 wk)
• 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

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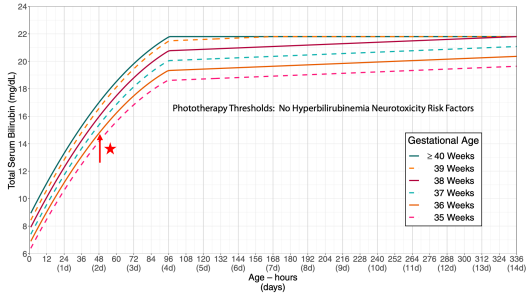
What about her discharge TcB?

- First step is to determine if there are neurotoxicity risk factors (in this case, NO)
- Determine PT threshold based on TcB and age in hours (in this case, threshold at time of discharge was approx. 15)



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Case 2

You appropriately check a TSB on the female infant and it is 21 mg/dL. What is the most appropriate course of action?

A. Recommend formula supplementation while maternal milk supply is low and recheck TSB in 24 hours
B. Prescribe home phototherapy
C. Admit the patient to the hospital for intensive phototherapy
D. Admit the patient, start phototherapy, administer IVIG and IV fluids
E. Request transport to Children's for exchange transfusion

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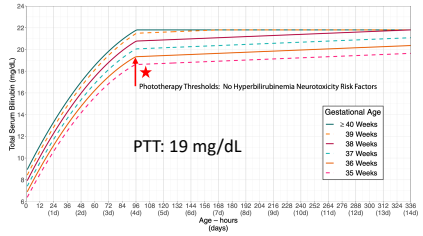
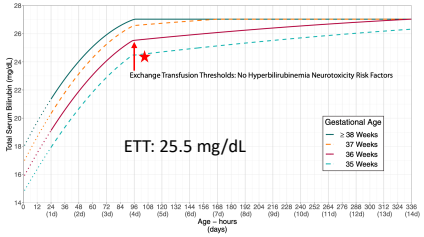
Case 2

- Use PT/ET thresholds for NO neurotoxicity risk factors





- Infant DOES qualify for PT so choice A is incorrect
- TSB is NOT within 2 mg/dL of ET threshold (25.5 mg/dL) so escalation of care (choice D) is not correct
- TSB is NOT at/above ET threshold so choice E is not correct

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A brief word about home phototherapy

- Infant must meet ALL criteria
  - Gestational age 38 weeks or greater
  - >48 hours old
  - Clinically well with adequate feeding
  - No known neurotoxicity risk factors
  - No previous phototherapy
  - TSB no more than 1 mg/dL above PT threshold
  - LED-based home PT device available without delay
  - TSB can be measured daily

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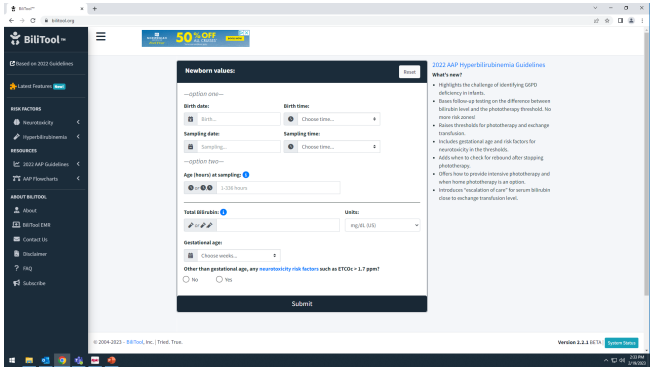
BiliTool 2.0 (http://www.bilitool.org)



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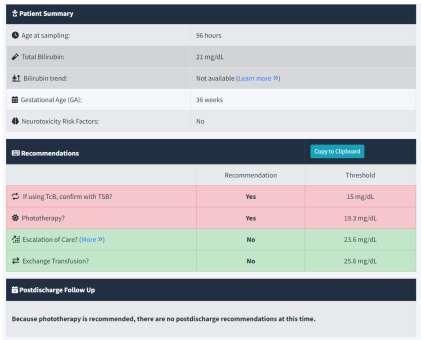
BiliTool 2.0 (http://www.bilitool.org)

- From Case 2:



Patient Summary

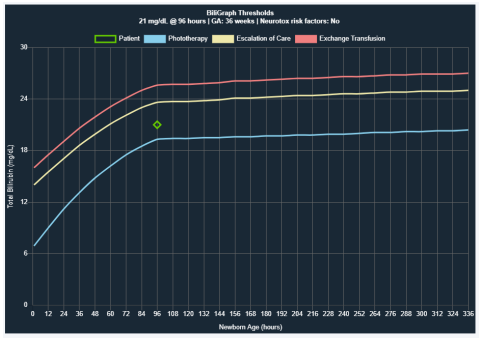
Age at sampling:	96 hours
Total Bilirubin:	21 mg/dL
Bilirubin trend:	Not available (Learn more »)
Gestational Age (GA):	36 weeks
Neurotoxicity Risk Factors:	No

Recommendations — Copy to Clipboard

	Recommendation	Threshold
If using TcB, confirm with TSB?	Yes	15 mg/dL
Phototherapy?	Yes	19.3 mg/dL
Escalation of Care? (More »)	No	23.6 mg/dL
Exchange Transfusion?	No	25.6 mg/dL

Postdischarge Follow Up

Because phototherapy is recommended, there are no postdischarge recommendations at this time.



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BiliTool 2.0 (http://www.bilitool.org)

- From Case 1 – post-discharge follow-up

Recommendations — Copy to Clipboard

	Recommendation	Threshold
If using TcB, confirm with TSB?	Yes	12 mg/dL
Phototherapy?	No	14.9 mg/dL
Escalation of Care? (More »)	No	18.8 mg/dL
Exchange Transfusion?	No	20.8 mg/dL

Postdischarge Follow Up

For the baby **2.9 mg/dL** below the phototherapy threshold (**Δ-TSB**) at 60 hours of age (during birth hospitalization with no prior phototherapy):

Check TSB or TcB in 4 to 24 hours. Use clinical judgment and shared decision making to determine when to repeat the bilirubin measure within this 4 to 24 hour period.

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Take home points

- First and foremost – please start to use the 2022 guidelines if you are not yet doing so!
- Information needed to determine PT and ET thresholds – GA, age in hours, and +/- neurotoxicity risk factors
- Recognition of neurotoxicity risk factors is extremely important as this guides which graph to use to determine PT and ET threshold
- Avoid sub-threshold phototherapy as it is not a completely benign therapy
- Avoid IV fluid use unless escalation of care is needed or infant is obviously dehydrated – focus on optimizing enteral intake
- If infant meets escalation of care threshold (TSB within 2 mg/dL of ET threshold) and you are not located in a place capable of ET, call Children's neonatologist to discuss transfer

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