Consensus Guidelines for Screening & Management of Hyperbilirubinemia in Neonates

UCSF $(NC)^2$ (Northern CA Neonatology Consortium)

Executive summary

Objectives

- Standardize the approach to screening and management of hyperbilirubinemia in neonates ≥ 35 weeks gestational age (GA) across the consortium hospitals using current practice standards and best available evidence
- Improve quality and safety of care for neonates ≥ 35 weeks GA with hyperbilirubinemia; specifically:
    - Improve recognition and efficient management of infants at high risk for complications of hyperbilirubinemia
    - Decrease unnecessary testing
    - Deliver safe, effective, and appropriate phototherapy
    - Decrease unnecessary hospital days

Recommendations

- Promote & support successful breastfeeding
- Perform a systematic assessment before newborn discharge for risk of severe hyperbilirubinemia
- Treat newborns with phototherapy or exchange transfusion when indicated to prevent the development of severe hyperbilirubinemia and kernicterus
    - Revisions to 2004 AAP Guidelines: Provide customized thresholds based on gestational age, neurotoxicity risk factors, and hours of life for each infant
    - Increase the threshold for phototherapy and exchange transfusion for most infants based on recent evidence given the extremely low rates of kernicterus and the possible risk of phototherapy causing adverse outcomes

Methods

This guideline was developed through local consensus based on published evidence and expert opinion as part of the UCSF Northern California Neonatal Consortium.

Metrics Plan

Monitoring of frequency of phototherapy use during the birth admission and readmissions for phototherapy.

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PART I: Introduction

- Jaundice / hyperbilirubinemia is common in newborns
    - Most jaundice is benign, but bilirubin can be toxic at very high levels
    - Severe hyperbilirubinemia can lead to acute bilirubin encephalopathy or kernicterus in rare cases
    - Goal of developing standardized clinical practices is to reduce incidence of severe hyperbilirubinemia and kernicterus while minimizing risks of unintended harm (family anxiety, decreased breastfeeding, unnecessary costs or treatment, potential risk of phototherapy)
- AAP 2004 Clinical Practice Guideline (for newborns ≥35 weeks gestational age)[1]
    - Outline of 2004 recommendations:
        - Promote & support successful breastfeeding
        - Perform a systematic assessment before newborn discharge for risk of severe hyperbilirubinemia
        - Provide early & focused follow-up based on risk assessment
        - Treat newborns with phototherapy or exchange transfusion when indicated to prevent the development of severe hyperbilirubinemia and kernicterus
            - Product = nomogram guidelines for phototherapy & exchange transfusion thresholds
    - Concerns:
        - 2004 guidelines for phototherapy & exchange transfusion are based on limited evidence, insufficient to make specific recommendations
            - No population-based studies of kernicterus incidence
            - No studies to allow estimation of number needed to treat (NNT)
        - 2004 guideline recommends abrupt change in treatment thresholds at 38 weeks gestation
        - Research since 2004 suggests guideline leads to overtreatment with phototherapy and should be changed
            - Rarity of kernicterus[2], especially in term babies without hemolysis[3-7]
            - Lack of subtle adverse effects of bilirubin, even when ≥ 25 mg/dL [7, 8]
            - Internal inconsistency of guideline and high NNT[9]
            - Potential associations between phototherapy and childhood cancer [10-12] and epilepsy [13, 14]

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- UCSF NC^2 Consensus Guidelines goals
    - Update hyperbilirubinemia clinical practice recommendations based on recent research
        - Draw on Kaiser Permanente Northern California (KPNC) experience with updated practice guidelines

[NOTE: Parts II-IV apply to neonates ≥ 35 weeks gestational age (GA)]

PART II: Jaundice & bilirubin screening

- Blood Typing
    - Newborn cord blood should be sent to blood bank on all newborns, with testing in the following circumstances:
        - Rh neg mother → Rh type + direct antiglobulin test (DAT)
        - O pos mother → DAT only
            - *NOTE:* ABO group unnecessary, does not change management (e.g. neonate is low risk if DAT negative, regardless of ABO group)
            - *OPTION:* send cord blood to blood bank to hold on infants born to O pos mothers; order DAT (and other studies) only *IF* clinical jaundice is noted
        - Maternal antibody screen positive → DAT
            - *Consider:* cord blood bilirubin level
        - Maternal blood type and antibody screen unknown → DAT
        - *NOTE:* Blood bank can hold cord blood / peripheral blood specimen for further testing if requested
        - If cord blood was not sent to the blood bank initially, OK to wait for jaundice or other clinical indication for blood type/group/DAT except in Rh-negative mothers
- Transcutaneous Bilirubin (TcB) Screening
    - 24-48hrs of life in all neonates and/or prior to discharge
    - Anytime jaundice is detected
    - Earlier + more frequent screening if DAT positive
    - Frequent re-assessment if TcB close to phototherapy threshold or rapidly rising
- Total Serum Bilirubin (TsB) Testing
    - TcB within 3 mg/dL of phototherapy threshold
    - Consider if TcB >12-13 (TcB less accurate above this range)
    - Follow TsB if TcB >13 or if TsB has been >15 until declining

PART III: Treatment

- Medical Management
    - General recommendations
        - Lactation support; oral hydration if dehydrated

- AGGRESSIVE MEDICAL THERAPY: for babies within two mg/dL of NCNC **exchange transfusion** threshold, or rapidly rising (>7 mg/dL in 24hrs or > 0.3mg/dL per hour)
  - Aggressive IV + PO hydration
  - Intensive phototherapy
  - Monitor TsB every 2-4 hours depending on previous rate of rise
  - Consult with neonatologist re: additional therapies (e.g. IVIG)

- Phototherapy Thresholds[1]
  - Basic recommendations:
    - Identify **neurotoxicity risk factors**:
      - Isoimmune hemolytic disease, G6PD deficiency, or other hemolytic disease
      - Sepsis or suspected sepsis (sufficient to be currently on antibiotics)
      - Acidosis (BE ≤ −8 meq/L or pCO2 >50 mmHg within the last 24 hr)
      - Albumin <3.0 mg/dL
      - Any clinical instability

    - TsB within 1-2 mg/dL below NCNC **phototherapy** threshold = CONSIDER PHOTOTHERAPY
      - Optimize feeding (breastfeeding support, supplement, formula, etc)
      - Repeat TsB @ 4-24hrs (prior to discharge if during birth admission)
      - Consider phototherapy (including home phototherapy if available)
      - *NOTE: NCNC* threshold to initiate phototherapy is lower for younger gestational ages, rapid rate of rise, or neurotoxicity risk factors (i.e. "medium risk" or "higher risk" infants)
    - TsB ≥ NCNC threshold = PERFORM PHOTOTHERAPY
      - Start phototherapy
      - Optimize feeding (as above)
    - If there is suspicion for hemolysis or other underlying causes of hyperbilirubinemia (G6PD, sepsis, etc), it is appropriate to start phototherapy at the threshold for newborns with neurotoxicity risk factors and proceed with an appropriate work up for those causes.

For example, for a 38 0/7-week formula-fed African American male at 96 hours of age, if the TSB were 19.0 mg/dL, it would be appropriate to start phototherapy (and check the G6PD activity) even though the threshold used if neurotoxicity risk factors are absent would be 20.4. This is because the threshold would be 18.2 if neurotoxicity risk factor were present and the clinical picture suggests G6PD deficiency, a neurotoxicity risk factor for which confirmation is often not immediately available.

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    -
        - *CONSIDER:* Higher threshold for readmission for phototherapy if infant at home (≥ 2-3 days of life) versus the threshold for phototherapy during the birth admission

- "Customized thresholds": Individualized thresholds based on exact gestational age, neurotoxicity risk factors, and hours of life:

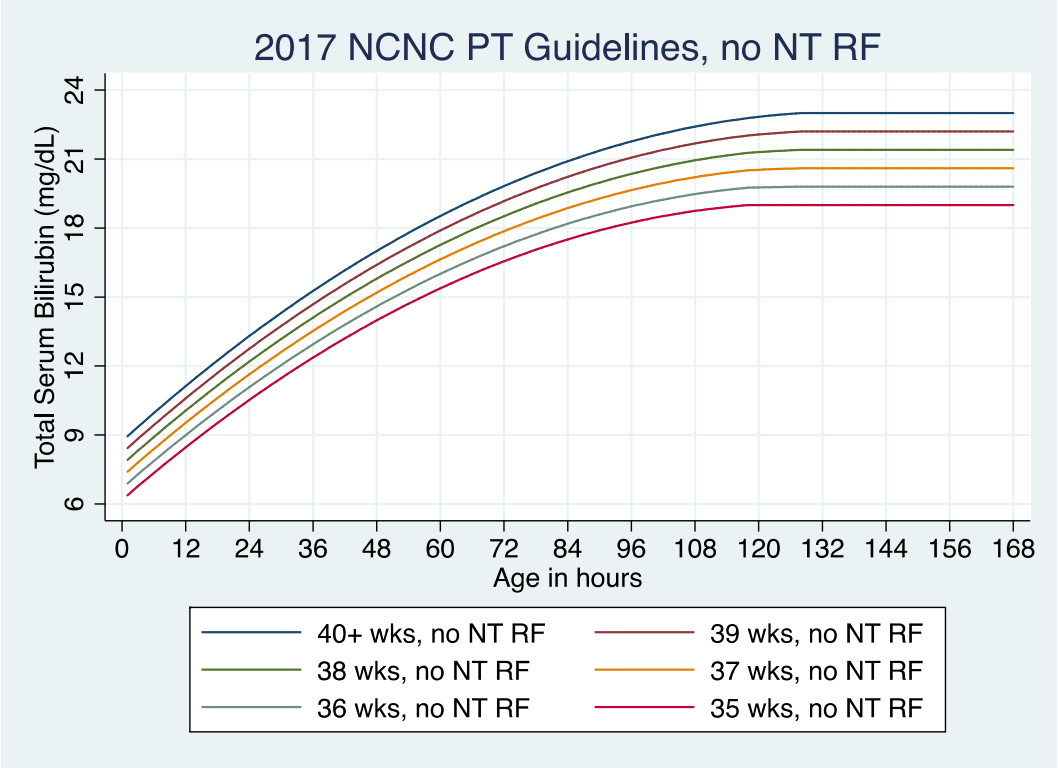

Figure 1: New Phototherapy Thresholds for babies with no neurotoxicity risk factors (NT RF)

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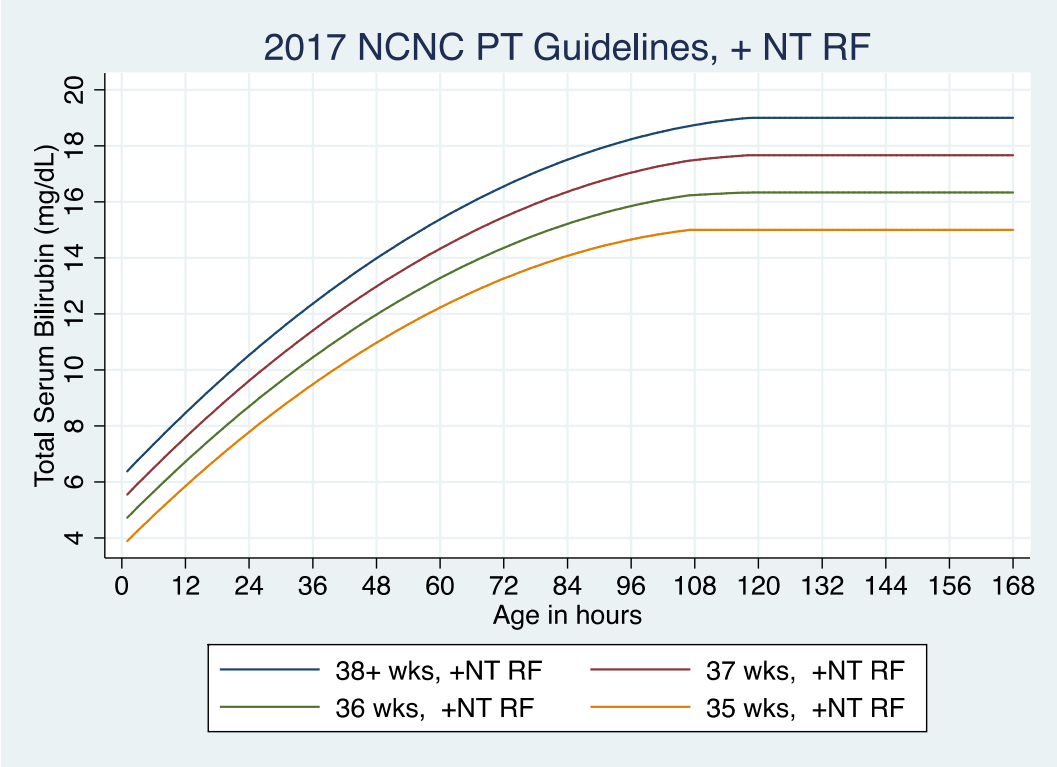

Figure 2: New Phototherapy Thresholds for babies with neurotoxicity risk factors (NT RF)

- See website for calculator: www.phototherapyguidelines.com

  Guideline soon to be housed at:
  https://www.ucsfbenioffchildrens.org/neonatal_consortium/

- Exchange Transfusion Thresholds[2]
  - Basic Recommendations:
    - Consultation with neonatologist when infants have bilirubin within 2 mg/dL of NCNC exchange transfusion threshold or rapidly rising (>7 mg/dL in 24 hours or >0.3mg/dL/hr), particularly in first 48 hours of life
    - INITIAL bilirubin (e.g. no prior bilirubin measurement or intervention)
      - > 2 mg/dL above NCNC Exchange Transfusion threshold = PREPARE FOR IMMEDIATE EXCHANGE TRANSFUSION≤
        - Perform aggressive medical therapy as above while preparing for exchange transfusion OR initiating transfer to institution capable of performing exchange transfusion
      - 0-2 mg/dL above NCNC threshold = CONSIDER EXCHANGE TRANSFUSION
        - Aggressive medical therapy as above

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        - Strongly consider transfer to institution capable of performing exchange transfusion
    - 0-2 mg/dL below NCNC Threshold
        - Aggressive medical therapy as above
- See flow chart for full recommendations

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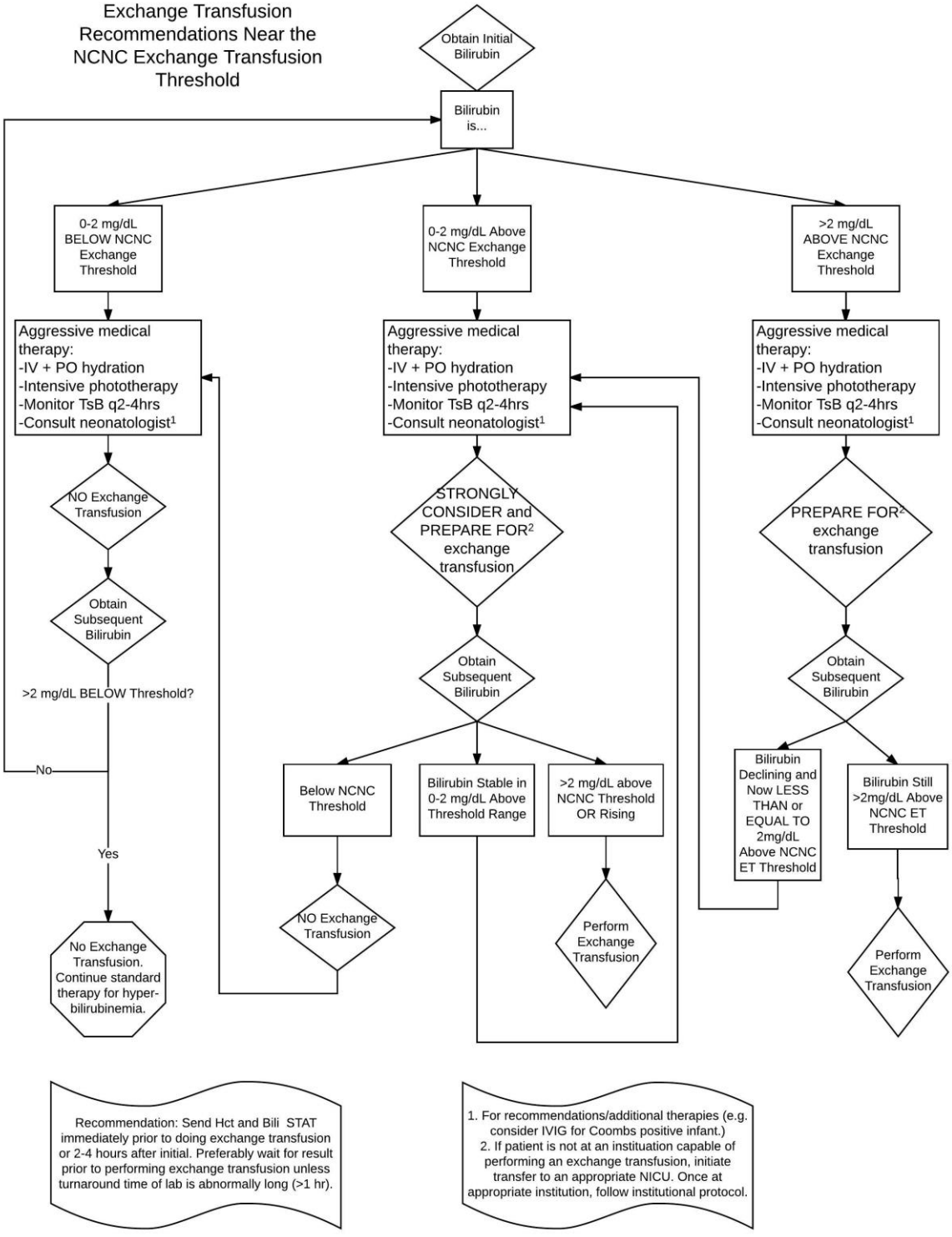

Figure 3: Exchange Transfusion Recommendations Near NCNC Exchange Transfusion Threshold

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- "Customized thresholds": Individualized thresholds based on exact gestational age, neurotoxicity risk factors, and hours of life:

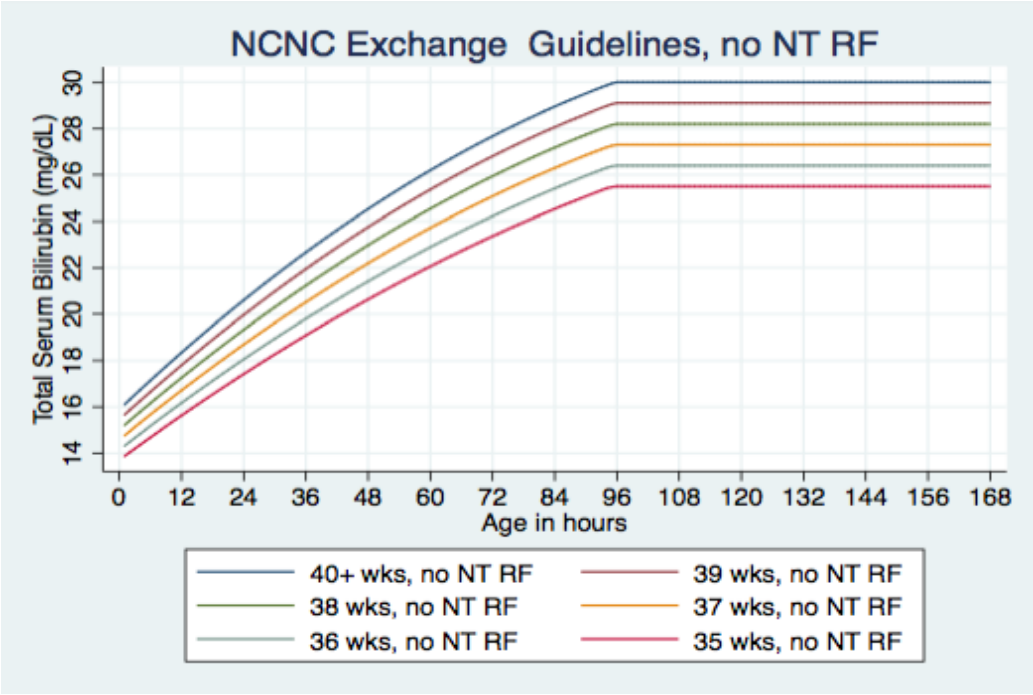

Figure 4: New Exchange Transfusion Thresholds for Babies WITHOUT Neurotoxicity Risk Factors

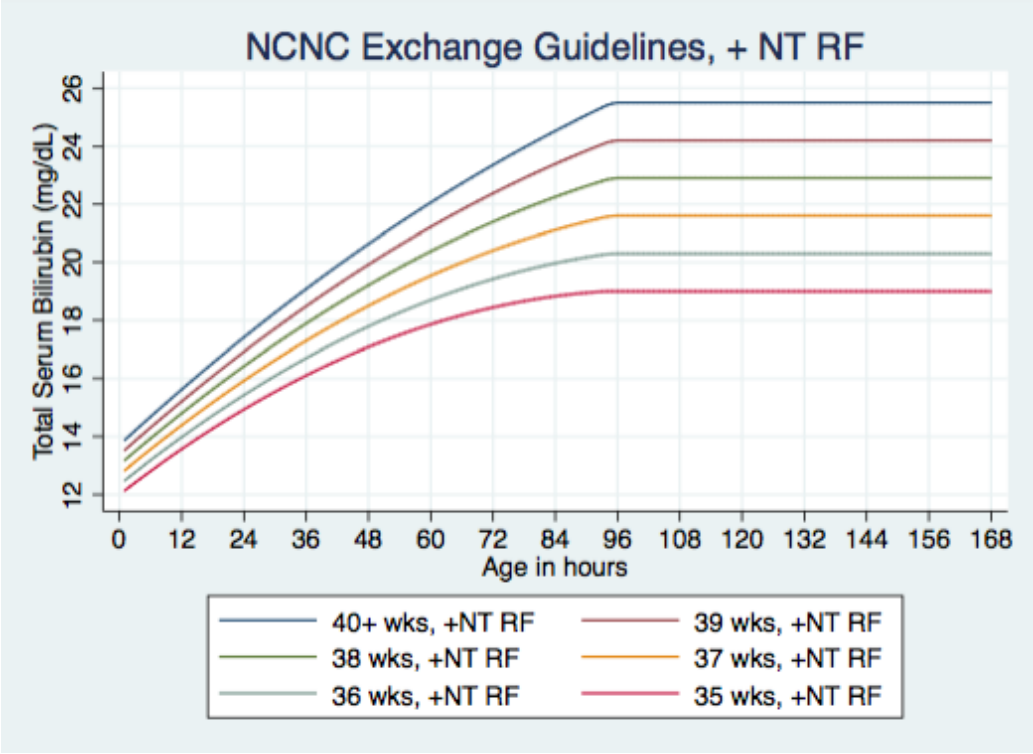

Figure 5: New Exchange Transfusion Thresholds for Babies WITH Neurotoxicity Risk Factors (NT RF)

- IVIG: for isoimmune hemolytic anemia ONLY
    - IVIG 1g/kg IV over 2 hours if the Total Serum Bilirubin is rising despite intensive phototherapy. May repeat x1 after 12 hours of first dose. (With an acceptable range of 0.5g/kg to 1g/kg – round to vial size)
    - For hemolytic jaundice that is NOT isoimmune, consult Neonatologist or Hematologist

- Bilirubin monitoring
    - Prior to initiation of phototherapy:
        - *NOTE:* For infants readmitted for phototherapy, if last TsB was >4-6 hours prior, repeat TsB
    - During phototherapy:
        - For all infants, check TsB within 12 hours of initiation of phototherapy
            - TsB ~ q12 hours:
                - No hemolytic disease or rapid rate of rise
            - TsB within 6-8 hours:
                - Evidence or suspicion of hemolytic disease
                - Rapid rate of rise (>7 mg/dL/24 hours or >0.3mg/dL/hr)
                - Other neurotoxicity risk factors (i.e. sepis or acidosis)
            - TsB q2-4 hours:
                - Bilirubin within 1-2 mg/dL of NCNC threshold for exchange transfusion
    - *NOTE*: all bilirubin monitoring during phototherapy should be done via serum bilirubin levels; transcutaneous bilirubin is not accurate

- Discontinuation of Phototherapy
    - Discontinue phototherapy when TsB is at least 2-3 mg/dL below the phototherapy initiation threshold
    - Indications for longer course of phototherapy:
        - Ongoing feeding difficulty
        - Prematurity (< 37 weeks GA)
        - Slow rate of decrease while on phototherapy
        - Hemolytic jaundice

- Hydration and nutrition considerations:
    - Support breastfeeding
    - Consider enteral supplementation with expressed breast milk, formula, etc
    - Consider IV fluids only if close to exchange transfusion or if other indications for IV fluids

- Rebound bilirubin measurement:
    - Indications for ordering rebound TsB:

        - Hemolytic jaundice
        - Prematurity (<37 weeks GA)
        - If phototherapy is discontinued sooner than 2-3 mg/dL below the phototherapy initiation threshold
        - If phototherapy was started prior to 48 hours
    - Timing: 6-24 hours
    - TcB may be inaccurate following phototherapy. Use TsB in this setting.

PART IV: Discharge & Follow-up

- Discharge Criteria
    - Off phototherapy and otherwise well
    - Feeding adequately
    - Follow-up arranged for 24-48hrs
    - Expectation that additional phototherapy will not be necessary

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Footnotes

1. **Methodology for determining new phototherapy thresholds/calculator:**

The starting point for the new thresholds were the 2004 AAP guidelines. On examination of new data, the evidence since 2004 suggested raising thresholds, given the extremely low rates of kernicterus and the possible risk of phototherapy causing adverse outcomes. Therefore, for babies with no NT risk factors we added 2 mg/dL to the 2004 AAP low risk threshold for 40-week babies and 1 mg/dL to the AAP MRT for 35-week babies, then adjusted for individualized gestational age. For babies with NT risk factors we added 1 mg/dL for infants ≥ 38 weeks and nothing for 35 week infants, then adjusted for individualized gestational age.

2. **Methodology for determining new exchange transfusion thresholds/calculator:**

The starting point for the new thresholds were the 2004 AAP guidelines. On examination of new data, the evidence since 2004 suggested raising thresholds, given the extremely low rates of kernicterus. Therefore, for babies with no NT risk factors we added 0 to the AAP low-risk threshold at birth and 5 mg/dL to the 2004 AAP low risk threshold at 96 hours for 40 week babies and 0 at birth and 3 mg/dL at 96 hours to the threshold for 35-week then adjusted for individualized age (if < 96 hours) and gestational age.

For babies with NT risk factors we added 0 to the AAP medium risk threshold for 40 week babies at birth and 3 mg/dL to the AAP medium risk threshold for 40-week babies at 96 hours; the changes from the AAP guidelines increase from 0 at birth to 3 mg/dL at 96 hours. We added nothing to the AAP high-risk threshold for 35-week babies. We then adjusted for individualized age (if < 96 hours) and gestational age.

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