MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA

A REVIEW OF THE 2022 AAP GUIDELINES

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DISCLOSURES: NONE

NO DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

NO REFERENCES TO OFF-LABEL OR INVESTIGATIONAL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS
LEARNING OBJECTIVES

1. Recall rationale for treating hyperbilirubinemia in newborns
2. Summarize risk factors for the development of significant hyperbilirubinemia in newborns
3. Practice screening and follow up as recommended in the updated 2022 American Academy of Pediatrics Clinical Practice Guideline for Management of Hyperbilirubinemia in the Newborn Infant
4. Develop plans of care for infants with clinically significant hyperbilirubinemia
5. List “not to miss” differential diagnoses for hyperbilirubinemia
CASE
3-DAY-OLD TERM INFANT PRESENTING FOR HOSPITAL FOLLOW UP

- Breastfeeding
- Down 8% from birthweight
- Increasing jaundice
2004 – AAP hyperbilirubinemia management guidelines

2009 Update – Recommendation for universal predischarge TcB/TSB screening

2022 – Revised risk assessment approach, narrow increase in phototherapy thresholds
Clinical Practice Guideline Revision:
Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation

Caveats for use:
Late preterm and term infants

High-resource countries – management and risk of kernicterus may differ significantly in areas of limited resources
GUIDELINE UPDATES

Organized into Key Action Statements

KAS 25!
BACKGROUND
BACKGROUND

JAUNDICE IS COMMON IN NEWBORN INFANTS

80%
BACKGROUND
Hyperbilirubinemia

- Bilirubin penetration of the blood-brain barrier
  - Acute bilirubin encephalopathy
    - Hypertonia
    - Arching
    - Retrocollis
    - High pitched cry
    - Recurrent apnea

- Kernicterus
  - Choreoathetoid cerebral palsy
  - Upward gaze paresis
  - Enamel dysplasia of deciduous teeth
  - Sensorineural hearing loss
  - Characteristic brain MRI findings

It can lead to badness.

Like acute bilirubin encephalopathy

And kernicterus.
PATHOGENESIS OF NEONATAL HYPERBILIRUBINEMIA

• Increased production
  • Isoimmune-mediated hemolysis (e.g. ABO incompatibility)
  • Inherited RBC membrane defects
  • Erythrocyte enzymatic defects (e.g. G6PD deficiency)
  • Sepsis
  • RBC breakdown (e.g. polycythemia, cephalohematoma)

Heme → Hemolysis → Heme oxygenase → Biliverdin reductase → Biliverdin → Bilirubin
PATHOGENESIS OF NEONATAL HYPERBILIRUBINEMIA

- Increased production
- Decreased clearance
  - Deficiency in hepatic enzyme UGT1A1

Activity in term infants at 7 days of age 1% level of adult liver → adult levels at 14 weeks of age
PATHOGENESIS OF NEONATAL HYPERBILIRUBINEMIA

- Increased production
- Decreased clearance
  - Mutations in the UGT1A1 gene
    - Crigler-Najjar syndrome
    - Gilbert syndrome
  - Other causes
    - Maternal diabetes
    - Congenital hypothyroidism
PATHOGENESIS OF NEONATAL HYPERBILIRUBINEMIA

• Increased production
• Decreased clearance
• Increased enterohepatic circulation
  • Limited bacterial conversion of conjugated bilirubin to urobilin
  • Ileus or anatomic causes of intestinal obstruction
PREVENTION
BEGINS DURING PREGNANCY

- ACOG recommends testing to assess risk for isoimmune hemolytic disease of the fetus or newborn
  - ABO blood group and Rh(D) type
  - Antibody screen
IDENTIFICATION OF NEWBORNS WITH MATERNAL ANTI-ERYTHROCYTE ANTIBIOTICS AND GUIDANCE FOR EARLY MANAGEMENT

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

Start (all newborns)

- Maternal antibody screen done?
  - Yes
    - Infant DAT and blood type as soon as possible
  - No
    - Maternal antibody screen positive?
      - Yes
      - Infant DAT positive?
        - Yes
          - All true?
            - Infant DAT only positive to anti-Rh(D)
            - Mother received RhIG during pregnancy
            - Mother known not to be anti-Rh(D) positive before RhIG
              - No
                - The infant has a hyperbilirubinemia neurotoxicity risk factor
                  - Measure TcB or TSB
                    - Immediately, then
                    - Every 4 hours 2 times, then
                    - Every 12 hours 3 times
                  - Follow guidelines, using recommendations 10 and 17, with Figure 3 and Figure 7 for therapy decisions after each TcB or TSB measure
              - Yes
                - Return to guidelines
        - No
          - Infant DAT positive?
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                  - Yes
                    - Return to guidelines
    - No
      - Return to guidelines
ADDITIONAL TESTING

- Determining infant’s blood type and/or DAT
  - Necessary
    - When unable to follow the clinical practice guideline and arrange appropriate post-discharge follow up
  - Optional
    - If following bilirubin surveillance and risk assessment as outlined

Maternal blood O+ with negative antibody screen
FEEDING SUPPORT

**Suboptimal intake hyperbilirubinemia**

- “Breastfeeding jaundice”
- Peaks on days 3-5 after birth
- Associated with excess weight loss

**Breast milk jaundice syndrome**

- Prolonged unconjugated hyperbilirubinemia
- Lasting up to 3 months

**KAS 2:**

- Oral supplementation with water or dextrose water

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RISK ASSESSMENT
<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Lower gestational age (ie, risk increases with each additional week less than 40 wk)</td>
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<tr>
<td>Jaundice in the first 24 h after birth</td>
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<tr>
<td>Predischarge transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) concentration close to the phototherapy threshold</td>
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<tr>
<td>Hemolysis from any cause, if known or suspected based on a rapid rate of increase in the TSB or TcB of &gt;0.3 mg/dL per hour in the first 24 h or &gt;0.2 mg/dL per hour thereafter.</td>
</tr>
<tr>
<td>Phototherapy before discharge</td>
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<tr>
<td>Parent or sibling requiring phototherapy or exchange transfusion</td>
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<tr>
<td>Family history or genetic ancestry suggestive of inherited red blood cell disorders, including glucose-6-phosphate dehydrogenase (G6PD) deficiency</td>
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<tr>
<td>Exclusive breastfeeding with suboptimal intake</td>
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<tr>
<td>Scalp hematoma or significant bruising</td>
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<tr>
<td>Down syndrome</td>
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<tr>
<td>Macrosomic infant of a diabetic mother</td>
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</tbody>
</table>
IDENTIFYING NEED FOR TREATMENT

- Gestational age
- Hour-specific TSB
  - TSB = definitive test  **KAS 3**
- Hyperbilirubinemia neurotoxicity risk factors

Gestational age <38 wks (and ↑ risk with greater prematurity)
Albumin <3.0 g/dL (measure with escalation of care)
Isoimmune hemolytic disease (i.e. +DAT, G6PD deficiency, other hemolytic conditions)
Sepsis
Significant clinical instability in the previous 24 h
VISUAL ESTIMATE OF TSB

• Statistically significant correlation, but clinically uncertain
  • Differences of 13-15 mg/dL between actual TSB/TcB and bilirubin values estimated by jaundice level

• Consistent finding
  • If infant is not jaundiced at all, or visual bilirubin estimate is <4 mg/dL, then TSB ≥12 mg/dL highly unlikely

• Visually assess for jaundice at least every 12 hours after delivery until discharge.
• Measure TSB/TcB ASAP for infants jaundiced <24 hours after birth
BILIRUBIN MONITORING

- TSB/TcB 24-48 hours after birth
  - KAS 5

- TSB if TcB ≤3 mg/dL from phototherapy threshold (or if TcB ≥15)
  - KAS 6

- Think hemolysis and check DAT
  - ≥0.3 mg/dL per hour increase in 1st 24 hrs, or ≥0.2 thereafter
  - KAS 7
Delay discharge if unable to arrange appropriate outpatient follow-up bilirubin measure
After TSB/TcB declines spontaneously over at least 6 hours, risk of subsequent hyperbilirubinemia is low.

Recheck only with clinical status change.
DIRECT (CONJUGATED) HYPERBILIRUBINEMIA CONSIDERATIONS

**Conjugated bilirubin**
- Conjugation with glucuronic acid in the liver makes bilirubin water-soluble, facilitating excretion
- ≥0.3 mg/dL is abnormal

**Direct bilirubin**
- Consists of conjugated bilirubin and small amount of unconjugated bilirubin that reacts without the addition of an accelerating agent ("reacts directly") in the chemical reaction to measure bilirubin concentration
- Higher and more variable that conjugated bilirubin
- Tends to increase with TSB
- ≥1.0 mg/dL is abnormal
DIRECT (CONJUGATED) HYPERBILIRUBINEMIA CONSIDERATIONS

All elevated direct (conjugated) bilirubin = biliary atresia

- On the differential, but consider:
  - Urinary tract infection
  - Isoimmune hemolytic disease
  - Sepsis
  - Inborn errors of metabolism
TREATMENT
PHOTOTHERAPY

KAS 10

Gestational age

Hyperbilirubinemia risk factors

Age in hours

Crosses recommended TSB threshold
PHOTOTHERAPY
HOME PHOTOTHERAPY
KAS 11

- ≥38 weeks gestation & ≥48 hours old
- TSB ≤1 mg/dL above phototherapy treatment threshold
- Remeasure TSB daily
- No prior phototherapy
- Available in the home without delay
- No hyperbilirubinemia neurotoxicity risk factors
MONITORING
LABS AFTER STARTING PHOTOTHERAPY

- CBC/DAT upon initiation
- TSB within 12 hours
- TSB daily
PHOTOTHERAPY DISCONTINUATION
FOLLOW UP BILIRUBIN TESTING

- TSB at 6-12 hours AND repeat the next day
  - + DAT
    - Known/suspected hemolytic disease
    - Phototherapy before 48 hours of age
  - Otherwise, at 12-24 hours
ESCALATION OF CARE THRESHOLD

2 mg/dL below exchange transfusion threshold

- **MEDICAL EMERGENCY**
  - Optimally managed in a NICU  **KAS 19**

**KAS 17**

- Start (TSB exceeds escalation of care level)
  - At appropriate location for exchange transfusion? (Yes/No)
    - Yes: STAT labs: total and direct serum bilirubin, CBC, albumin, serum chemistries, type and cross match
    - Notify blood bank
    - Measure TSB at least every 2 hours
    - Intensive phototherapy and PO+IV hydration
    - See IVIG therapy and B/A measurement options

- No: Consult neonatologist for urgent transfer to NICU, directly if possible
  - Intensive phototherapy and PO+IV hydration during transfer, if possible

**KAS 18, 20, 21**

- Acute bilirubin encephalopathy
  - OR
  - Latest TSB at or above the exchange transfusion threshold?
    - Yes: Urgent exchange transfusion
    - No: TSB below the escalation-of-care level? (Yes/No)
      - Yes: Return to regular phototherapy guidelines
      - No: Continue intensive phototherapy and PO+IV hydration and measuring TSB at least every 2 hours
POST DISCHARGE FOLLOW UP
POSTDISCHARGE FOLLOW-UP

KAS 24

Phototherapy threshold

Difference informs timing of follow up and TSB/TcB remeasurement

TSB
# Postdischarge Follow Up

<table>
<thead>
<tr>
<th>Phototherapy threshold minus TcB or TSB</th>
<th>Discharge Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1-1.9 mg/dL</td>
<td>Delay discharge, consider phototherapy, measure TSB in 4 to 8 hours</td>
</tr>
<tr>
<td>Age &lt; 24 hours</td>
<td></td>
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<tr>
<td>Age ≥ 24 hours</td>
<td>Measure TSB in 4 to 24 hours&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Options:</td>
</tr>
<tr>
<td></td>
<td>• Delay discharge and consider phototherapy</td>
</tr>
<tr>
<td></td>
<td>• Discharge with home phototherapy if all considerations in the guideline are met</td>
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<tr>
<td></td>
<td>• Discharge without phototherapy but with close follow-up</td>
</tr>
<tr>
<td>2.0-3.4 mg/dL</td>
<td>TSB or TcB in 4 to 24 hours&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Regardless of age or discharge time</td>
<td></td>
</tr>
<tr>
<td>3.5-5.4 mg/dL</td>
<td>TSB or TcB in 1-2 days</td>
</tr>
<tr>
<td>Regardless of age or discharge time</td>
<td></td>
</tr>
<tr>
<td>5.5-6.9 mg/dL</td>
<td>Follow-up within 2 days; TcB or TSB according to clinical judgment&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Discharging &lt; 72 hours</td>
<td></td>
</tr>
<tr>
<td>Discharging ≥ 72 hours</td>
<td>Clinical judgment&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥ 7.0 mg/dL</td>
<td>Follow-up within 3 days; TcB or TSB according to clinical judgment&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Discharging &lt; 72 hours</td>
<td></td>
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EDUCATION
KAS 25

Pediatric Patient Education™
Expert advice from the American Academy of Pediatrics

Jaundice and Your Newborn
“CLINICIANS SHOULD UNDERSTAND THE RATIONALE FOR WHAT IS RECOMMENDED, USE THEIR CLINICAL JUDGMENT, AND, WHEN APPROPRIATE, ENGAGE IN SHARED DECISION MAKING
QUESTIONS & ANSWERS