7-16-2020

Management of Neonatal Hyperbilirubinemia

David Schutzman

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Hyperbilirubinemia of the Newborn

David Schutzman, MD
7/16/2020
Kernicterus

• Classic Kernicterus
  • Phase 1 – lethargy, hypotonia, poor feeds
  • Phase 2 – hypertonia, high pitched cry
  • Phase 3 – hypotonia
  • Long term – chorioathetoid CP, hearing loss, normal intelligence
  • Histology – neuronal necrosis

• NICU kernicterus
  • No symptomatology
  • “Normal” bilirubin levels
  • Histology – spongy changes and gliosis
How do we get kernicterus?
Fig. 27-9. Neonatal bile pigment metabolism.
How does bilirubin enter the brain?
Blood Brain Barrier

• Keeps things out of the brain
• Endothelial lining of the blood vessels
• Excludes most water soluble substances
  • Proteins
  • Large molecules
    • Albumin
    • Albumin with bilirubin attached
• Allows in lipid soluble substances
  • Free bilirubin
• Large complexes enter if the barrier is opened
Free bilirubin hypothesis

• Bilirubin insoluble at pH 7.4
• Normally bound to albumin in the blood
• Albumin – one high affinity site
  • ≥ one weak affinity sites
• Bilirubin:albumin molar ratio 1:1
  • 1 g albumin binds 8.8 mg bilirubin (if high affinity site completely saturated)
• Term – 3.5 g albumin with 1:1 binding affinity
  • Bili level 31.1 before free bilirubin available
• Preterm – 2 g albumin with only 0.5 binding affinity
  • Bili level 8.9 before free bilirubin available
Displacers of bilirubin

• Free fatty acids – Intralipid
• Drugs
  • Sulfisoxasole
  • Benzyl alcohol
• pH
Factors that open the BBB

• Hypertonic solutions
  • Levine’s rat studies
• Severe asphyxia
• Acidosis
• Meningitis
How does bilirubin cause damage?

• WE DON’T KNOW
• Depress cellular respiration
  • Uncouple oxidative phosphorylation
• Bind specific proteins
• Damage DNA
How do we prevent kernicterus?
Exchange transfusion

• Last resort
• Very invasive

• Double volume exchange
  • Insert central lines
  • Remove and replace aliquots of 1/15 baby’s blood volume with O- PRBC reconstituted with AB FFP
  • Repeat (again and again) until replace what’s calculated to be twice baby’s blood volume
    • $y=1-e^{-x}$
      • $y$-fraction of blood removed  $x$-number of exchanges
  • Single volume exchange replaces 63% of blood volume
  • Double volume exchange replaces 87% of blood volume

• Removes actual circulating bilirubin
• Removes potential bilirubin
Hsia, DY, Allen FH, Gellis SS, et.al. Erythroblastosis fetalis VIII. Studies of serum bilirubin in relation to kernicterus
NEJM 1952;247:668

• Retrospective study
• Bilirubin 16-30  18% kernicterus
• Bilirubin >30    50% kernicterus
• Recommended keeping bilirubin <20
  • No kernicterus in their subsequent 200 consecutive cases of erythroblastosis
  • Accumulated these patients in <1 year!
Phototherapy
How does phototherapy work?
Fig 8. $Z \rightarrow E$ carbon-carbon double bond configurational isomerization of bilirubin in humans.

Fig 7. Intramolecular cyclization of bilirubin in presence of light to form lumirubin.
“What did he know and when did he know it?”
What do we do and when do we do it?
<table>
<thead>
<tr>
<th>Serum Bilirubin mg/100 ml</th>
<th>&lt; 24 hrs</th>
<th>24-48 hrs</th>
<th>49-72 hrs</th>
<th>&lt; 72 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 and +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Use phototherapy after any exchange [ ] Observe [ ] Investigate Jaundice

*Consider immediate phototherapy but exchange if bilirubin continues to rise
†Consider exchange, particularly if previous phototherapy not effective

In presence of:
1. Perinatal asphyxia
2. Respiratory distress
3. Metabolic acidosis (pH 7.25 or below)
4. Hypothermia (temp below 35°C)
5. Low serum protein (5g./100 ml or less)
6. Birth weight 1500 g
7. Signs of clinical or CNS deterioration

Treat as in next higher bilirubin category

Figure 11-2 Guidelines for the management of hyperbilirubinemia taking age, birth weight, and bilirubin into consideration. (Usage of phototherapy lights in clinical icterus as employed at University Hospitals, Cleveland, Ohio. Courtesy of Dr. M. J. Maisels.)
Bhutani Nomogram

- 13,003 healthy term and near term
- Screening TSB at time of newborn screen with age in hours determined
- Racially diverse
- 60% breast fed
- Exclusions
  - Phototherapy before 60 hours of life
  - Hemolysis indicated by DAT+
- 2840 in hospital supervised F/U program
<table>
<thead>
<tr>
<th>Location of Predictive Predischarge TSB Vector</th>
<th>Outcome: Subsequent Significant Hyperbilirubinemia</th>
<th>Predictive Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predischarge Hour-specific TSB Risk Zone</td>
<td>Present (P)*</td>
<td>Absent (A)</td>
</tr>
<tr>
<td>High-risk zone</td>
<td>&gt;95th</td>
<td>172</td>
</tr>
<tr>
<td>Upper-intermediate</td>
<td>76th–95th</td>
<td>356</td>
</tr>
<tr>
<td>Lower-intermediate</td>
<td>40th–75th</td>
<td>556</td>
</tr>
<tr>
<td>Low-risk zone</td>
<td>&lt;40th</td>
<td>1756</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
<td>2840</td>
</tr>
</tbody>
</table>
Results of Bhutani nomogram for daily practice

• Zone 1 – no F/U needed

• Zone 2 – F/U bilirubin in 48 hours

• Zone 3 – F/U bilirubin in 24 hours

• Zone 4 – consider phototherapy
Hour-Specific Bilirubin Nomogram in Infants with ABO Incompatibility and Direct Coombs-Positive Results.

- 700 babies ≥ 35 weeks gestation
  - 460 DAT neg
  - 240 DAT+
- Age specific screening bilirubins plotted on Bhutani nomogram
- Sensitivity and specificity for infants in zone 4 or zone 3 & 4 combined similar to Bhutani
- LR zone 4 twice Bhutani’s
- All infants zone 3 and 4 followed post D/C
  - No XT or bilirubin encephalopathy
- Bhutani nomogram works equally well for F/U of DAT+ infants
Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. AAP Subcommittee on Hyperbilirubinemia. Pediatrics 2004;114:304

- 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.
Guidelines for exchange transfusion in infants 35 or more weeks gestation.
AAP Subcommittee on Hyperbilirubinemia. Pediatrics 2004;114:304
Adjustments to AAP recommendations
Risk factors

• Use total bilirubin – do not subtract direct fraction
• Risk factors
  • Isoimmune hemolytic disease
  • G6PD deficiency
  • Asphyxia
  • Significant lethargy
  • Temperature instability
  • Sepsis
  • Acidosis
  • Albumin <3 g/dL (if measured)
Isoimmune Hemolytic Disease

• Variability in need for phototherapy in DAT+ infants
    • African American cohort
    • 12.9 % DAT+ infants required phototherapy
  • Kaplan, et.al. E-PAS 2008:635841.21
    • Israeli Sephardi cohort
    • 49% DAT+ infants required phototherapy
    • Italian cohort
    • 100% DAT+ infants required phototherapy
### 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)
- Jaundice observed in the first 24 h
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (e.g., G6PD deficiency), elevated ETCO
- Gestational age 35–36 wk
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
- East Asian race

#### Minor risk factors
- Predischarge TSB or TcB level in the high intermediate-risk zone
- Gestational age 37–38 wk
- Jaundice observed before discharge
- Previous sibling with jaundice
- Macrosomic infant of a diabetic mother
- Maternal age _< 25 y
- Male gender
- 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)
- Gestational age _< 41 wk
- Exclusive bottle feeding
- Black race

* Race as defined by mother’s description.
CO - a better measure of hemolysis and hence risk
(Not yet endorsed by the AAP or necessarily agreed to by the Bilirubin club at PAS)
How can we measure CO in the body?

• Schutzman, et. al. J Perinatology 2016:36:386-388

• 180 AA infants
  • All mothers O+
    • 60 O+  60 ABO/DAT neg  60 ABO/DAT+

• Mean COHbc in O+ and ABO/DAT neg  0.77±0.23%

• 2SD > mean 1.22%

• 15/60 DAT+ >1.22%

• 4/120 DAT neg >1.22%
Capnia CoSense Monitor – End Tidal CO (ETCO)
<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Clinical relevance</th>
<th>n</th>
<th>ETCO (p.p.m.)</th>
<th>Device(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vreman et al.</td>
<td>To compare the performance of a point-of-care, non-invasive ETCO analyzer to an established marketed device</td>
<td>87</td>
<td>0.4–29.1</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer, Vitalograph BreathCO Monitor</td>
</tr>
<tr>
<td>Vreman et al.</td>
<td>To show that a portable breath sampler can be used to non-invasively measure ETCO in neonates and adults</td>
<td>34</td>
<td>1.5–35.9</td>
<td>Natus Medical Inc. Baby's Breath Carbon Monoxide Analyzer</td>
</tr>
<tr>
<td>Vreman et al.</td>
<td>To determine if the measurements yielded by the EC-CO instrument are comparable with those obtained by the GC assay</td>
<td>108</td>
<td>0–18.0</td>
<td>Stanford University EC-CO Instrument</td>
</tr>
<tr>
<td>Stevenson et al.</td>
<td>To determine whether measurements of CO in breath can be used as an index of bilirubin production</td>
<td>535</td>
<td>1.0–1.8</td>
<td>Stanford University EC-CO Instrument</td>
</tr>
<tr>
<td>Stevenson et al.</td>
<td>To determine whether ETCOc as a single measurement or in combination with TB levels can predict the development of hyperbilirubinemia in the first 7 days of life</td>
<td>1370</td>
<td>0.1–3.5</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
<tr>
<td>Blok et al.</td>
<td>To study the predictive value of ETCOc and cytokine levels for long-term outcome</td>
<td>105</td>
<td>1.4–3.0</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
<tr>
<td>James et al.</td>
<td>To examine the role of ETCOc as a screening tool for hemoglobinopathies and as an indicator for when transfusions would be required in patients receiving chronic transfusions</td>
<td>101</td>
<td>1.2–13.5</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
<tr>
<td>Sylvester et al.</td>
<td>To assess whether ETCOc levels in children with SCD could be measured reproducibly, reflected hemolysis and whether ETCOc levels were elevated compared to children without SCD</td>
<td>113</td>
<td>1.3–4.9</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
<tr>
<td>Herschel et al.</td>
<td>To determine the sensitivity, specificity and positive predictive value of the DAT or Coombs’ test compared to ETCOc and to evaluate the predictive value of these two methods to detect significant jaundice</td>
<td>614</td>
<td>0.6–11.0</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
<tr>
<td>Barak et al.</td>
<td>To test the hypothesis that in normal neonates, CO production, estimated by ETCOc correlates with estimates of RBC mass such as Hct and Hgb concentration</td>
<td>58</td>
<td>1.3–3.4</td>
<td>Everest COCO2 Puff</td>
</tr>
<tr>
<td>Javier et al.</td>
<td>To evaluate the clinical usefulness of ETCOc in healthy, term, Coombs-positive neonates and correlate these measurements to the corrected RCs</td>
<td>100</td>
<td>0.6–6.1</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
<tr>
<td>Herschel et al.</td>
<td>Case study: to describe the relationship between G6PD deficiency and severe hyperbilirubinemia</td>
<td>1</td>
<td>2.5–3.1</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
<tr>
<td>Kaplan et al.</td>
<td>To compare hemolysis and the risk of hyperbilirubinemia among African-American, G6PD-deficient neonates</td>
<td>500</td>
<td>1.7–2.9</td>
<td>Natus Medical Inc. CO-Stat End Tidal Breath Analyzer</td>
</tr>
</tbody>
</table>

Abbreviations: DAT, direct antiglobulin test; EC-CO, electrochemical carbon monoxide; ETCO, end-tidal carbon monoxide; ETCOc, end-tidal carbon monoxide, corrected for ambient CO; GC, gas chromatography; G6PD, glucose-6-phosphate dehydrogenase; Hct, hematocrit; Hgb, hemoglobin; RBC, red blood cell; RCs, reticulocyte counts; SCD, sickle cell disease; TB, total serum/plasma bilirubin.  
*Range reported for adults (n = 25).  
*Reported range of device.  
*Range of reported means.  
*Interquartile range report.
What is a normal ETCOc?

• Christensen, et. al. Neonatology 2016;109:1-5
  • 100 infants Intermountain Health Group
  • Caucasian 76%  Non-Caucasian 24%
  • ETCO 95% >2.0ppm

  • 247 infants
    • Caucasian 46%  African American 23%  Asian 10%  Hispanic 18%
    • ETCO 90% >2.0ppm
    • ETCO 95% >2.5ppm
Why Use ETCO rather than DAT

- ElSaie, Taleb, Nicosia, Zangaladze, Pease, Newton, Schutzman in submission
- 191 babies with DAT+ or ETCO for HIR or HR zones
- Theoretical decision to use photo or not based on AAP recommendations and using DAT OR ETCO to delineate hemolysis
- 27% of DAT+ actually hemolyzing per ETCO
- 29% of DAT neg actually hemolyzing per ETCO
- Management of 9.4% differed if used ETCO instead of DAT
- 8 fewer babies would have received photo using ETCO
**Table 1. INDICATIONS FOR SERUM BILIRUBIN**

<table>
<thead>
<tr>
<th>Age in Hours</th>
<th>TcBili</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>≥ 5</td>
</tr>
<tr>
<td>21-24</td>
<td>≥ 6</td>
</tr>
<tr>
<td>25-27</td>
<td>≥ 6.5</td>
</tr>
<tr>
<td>28-31</td>
<td>≥ 7</td>
</tr>
<tr>
<td>32-36</td>
<td>≥ 8</td>
</tr>
<tr>
<td>37-40</td>
<td>≥ 9</td>
</tr>
<tr>
<td>41-45</td>
<td>≥ 10</td>
</tr>
<tr>
<td>46-49</td>
<td>≥ 10.5</td>
</tr>
<tr>
<td>50-55</td>
<td>≥ 11</td>
</tr>
<tr>
<td>&gt;55</td>
<td>≥ 12</td>
</tr>
</tbody>
</table>

**Table 2. RISK FACTORS FOR HYPERBILIRUBINEMIA IN NEWBORN NURSERY**

- Jaundice before 24 hours
- Direct Coombs +
- Late preterm
- Previous sibling received phototherapy
- Cephalhematoma or significant bruising
- Excessive weight loss
- East Asian race

**If started on Phototherapy:**
1. Obtain Hgb/Hct, Reticulocyte.
2. If suspect dehydration and/or exclusive breast feeding, obtain BMP.
3. If ABO set-up, may repeat Type and Coombs if initially negative.

---

**TN Bilirubin Guideline**

**Page 1**

All infants  Gestational Age ≥ 35 weeks

Transcutaneous Bilirubin (TcBili) on discharge day (@ midnight to 0400 AM)

Refer to Table 1 to assess need for Total Serum Bili (TSB)

- TSB Not indicated
  - Low Risk zone
  - Follow-up PCP

- TSB indicated
  - TSB Low Risk Zone or Low intermediate zone
    - Follow pathway on the left
  - TSB High intermediate zone
  - TSB High risk zone
    - Follow AAP phototherapy* parameter
      - <1.6 ppm
        - Discharge with TSB in 24 hrs
      - 1.6 - 2.4 ppm
        - Assess Risk Factors (Table 2)
          - No
            - Follow AAP phototherapy* parameter or Hour-specific Bilirubin Normogram
          - Yes
            - Repeat TSB 6-8 hrs
      - ≥ 2.5 ppm (moves infant to next higher risk category in AAP parameter)

*TSB follow-up when phototherapy started

---

Revised 10/17/2019
Infant DAT or Direct Coombs + Gestational Age ≥ 35 weeks

TcBili, Hgb/Hct, Reticulocyte @ 12 hrs

TCBili Low Risk zone or Low Intermediate zone

ETCO@ 12-24 hrs

<1.6 ppm

TcBili on d/c day

1.6-2.4 ppm

TSB Q 24 hrs

≥ 2.5 ppm

TSB Q 8 hrs

Follow AAP phototherapy*

Follow AAP phototherapy* parameter or Hour-specific Bilirubin Normogram

TCBili High Intermediate zone

ETCO@ 12-24 hrs

<1.6 ppm

1.6-2.4 ppm

≥ 2.5 ppm (moves infant to next higher risk category in AAP parameter)

TSB Q 24 hrs

TSB Q 12 hrs

TSB Q 8 hrs

TcBili High Risk Zone

ETCO@ 12-24 hrs

≥ 2.5 ppm (moves infant to next higher risk category in AAP parameter)

*TSB follow-up when phototherapy started

Refer to TN Bili Guideline page 1

Follow AAP phototherapy*

Revised 10/17/2019
Date and time of birth to closest hour:

2020 July 14

Date and time of blood sampling to closest hour:

2020 July 15

Total Bilirubin*: [ ] mg/dl (US) [Submit]

*Note: The default unit of measure for total bilirubin is mg/dl. Please select µmol/L if your bilirubin values are captured in the global standard SI metric units. Bilirubin conversion from US to SI units is 17.1.

Results are based on the Hour-Specific Nomogram for Risk Stratification published in “Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation” (2004) by the AAP journal.
Hour-Specific Nomogram for Risk Stratification

<table>
<thead>
<tr>
<th>Infant age</th>
<th>36 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>10.7 mg/dl</td>
</tr>
<tr>
<td>Risk zone</td>
<td>High Intermediate Risk</td>
</tr>
</tbody>
</table>

Risk zone is one of several risk factors for developing severe hyperbilirubinemia.

Recommended Follow-up

<table>
<thead>
<tr>
<th>Hyperbiliru Risk Level</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Risk (&gt;= 38 weeks and well)</td>
<td>Follow-up within 48 hours and consider TcB/TSB at follow-up</td>
</tr>
<tr>
<td>Medium Risk (&gt;=38 weeks + hyperbiliru risk factors OR 35 to 37 6/7 weeks and well)</td>
<td>Evaluate for phototherapy and check TcB/TSB within 24 hours</td>
</tr>
<tr>
<td>Higher Risk (35 to 37 6/7 weeks and hyperbiliru risk factors)</td>
<td>Evaluate for phototherapy and check TcB/TSB in 4-24 hours</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Neurotoxicity Risk Level</th>
<th>Start phototherapy?</th>
<th>Approximate threshold at 36 hours of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Risk (&gt;= 38 weeks and well)</td>
<td>No</td>
<td>13.6 mg/dl</td>
</tr>
<tr>
<td>Medium Risk (&gt;=38 weeks + neurotoxicity risk factors OR 35 to 37 6/7 weeks and well)</td>
<td>No</td>
<td>11.7 mg/dl</td>
</tr>
<tr>
<td>Higher Risk (35 to 37 6/7 weeks and neurotoxicity risk factors)</td>
<td>Yes</td>
<td>9.6 mg/dl</td>
</tr>
</tbody>
</table>

It is an option to provide conventional phototherapy in the hospital or at home at TSB levels 2-3 mg/dl (35-50 µmol/L) below those shown. Home phototherapy should not be used in infants with risk factors.

If phototherapy threshold is exceeded, please also review AAP Guidelines for Exchange Transfusion.
The Curious Case of the Missing Bilirubin
Inspector: Is there any point to which you wish to draw my attention?

Gregory: To the curious incident of the dog in the night-time.

Holmes: The dog did nothing in the night-time.

Gregory: That was the curious incident.
• Full term female born by SVD
• Mother O+
• Infant O+ DAT+
• Mother anti c +
  • Titer <1:1  2 months PTD
  • Titer 1:32 2 weeks PTD
• Infant labs
  • H/H 11.3/34.1
  • Reticulocytes 17.7%
  • ETCO 6.8 PPM (>>>95%)
  • Tcbili @33 hr 3.9
  • TSB @48 hr 4.1
  • TSB@61 hr 6.0
• HO-1 promoter variant (GT)n repeats
  • 23 and 30 repeats for the two alleles
  • Long repeats (>33) would have decreased function

• SLCO1B1 transporter
  • Heterozygous *5 (c.521C>T)
  • No effect

• UGT1A1
  • Homozygous *60 (c.3275T>G) may be associated with decreased function
  • Heterozygous *89 (c.3436C>A) no effect
  • Heterozygous *66/*88 (c.997-82C>T) possible decreased activity due to compound heterozygote
  • NO TA5 repeat in promoter region which ENHANCES activity