Neonatal Hyperbilirubinemia Updates

E. Hayes Bakken, MD, IBCLC
Ilse Larson, MD, IBCLC

With gratitude to:
- Ellen Laves, MD, Carrie Phillipi, MD, PhD, and Mina Tahai, MD (for many of the slides)
- Tom Newman, MD, MPH (for all the learnings)
Learning Objectives

1. Review the basic pathophysiology of neonatal hyperbilirubinemia
2. Understand the AAP’s clinical practice guidelines for hyperbilirubinemia in newborns ≥35 weeks
3. Review outcomes of guidelines implementation and emerging data about the possible risks associated with phototherapy
4. Discuss Northern California Neonatal Consortium Consensus Guidelines for Screening & Management
Neonatal Jaundice

60% of healthy newborns will have clinical jaundice
Why Newborns?

- **Increased bilirubin production** (↑Hgb & short RBC lifespan)
- **Limited bilirubin-binding capacity** (low serum albumin)
- **Decreased conjugation** (↓glucoronysyl-transferase activity)
- **Decreased excretion** leading to reabsorption in the bowel (bowel flora, intestinal motility, stool frequency, caloric intake, and feeding frequency)
What’s the significance?

**Acute bilirubin encephalopathy:**
- Lethargy ➔ stupor
- Hypotonia ➔ hypertonia ➔ retrocolis-opisthotonis
- Poor feeding, shrill cry

**Kernicterus (chronic bilirubin encephalopathy):**
- Extrapyramidal signs (athetosis), severe delays/MR
- Sensorineural hearing loss
- Gaze palsies
- Dental dysplasia
AAP Policy Shift
Universal Screening

The Kinder, Gentler Era

→ BF rates

BF rates

Vigintiphobia

Reduced <30
More phototherapy
Reduced kernicterus???

Exchange Transfusions

Rhogam

Phototherapy

20!


AAP Policy Shift
Universal Screening

USPSTF Statement
2004 AAP Guidelines

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to the infant’s age in hours.
6. Recognize that infants at less than 38 weeks’ gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.
**AAP Guideline Graphs**

- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonus, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 μmol/L) above these lines.
- Risk factors: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.
Effect of Universal Screening

Kuzniewicz et al. 2009_38,182 infants. 10.6% were born at facilities with universal bilirubin screening. Compared with infants born at facilities that were NOT screening:

• 62% lower incidence of TSB levels over the AAP threshold (0.17% vs 0.45%; P < .001),

• Had twice the rate of inpatient phototherapy (9.1% vs 4.2%; P < .001), and

• Had slightly longer birth hospitalization lengths of stay (50.9 vs 48.7 hours; P < .001).
Effect of Universal Screening

- Only 56% of those who received phototherapy had TsB above threshold, compared with 70% in facilities without universal screening.
Is this the right approach?
Phototherapy NNT


• 22,547 with a TsB within 3 mg/dL of the AAP phototherapy threshold

• Used multiple logistic regression to estimate the efficacy of hospital phototherapy in preventing the bilirubin level from exceeding the 2004 guideline’s exchange transfusion threshold within 48 hours.
<table>
<thead>
<tr>
<th>Gestational Age, wk</th>
<th>Age at Qualifying TSB: &lt;24 h</th>
<th>Age at Qualifying TSB: 24 to &lt;48 h</th>
<th>Age at Qualifying TSB: 48 to &lt;72 h</th>
<th>Age at Qualifying TSB:≥72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>14 (7–40)</td>
<td>26 (14–57)</td>
<td>83 (36–190)</td>
<td>171 (70–426)</td>
</tr>
<tr>
<td>36</td>
<td>10 (6–19)</td>
<td>19 (12–39)</td>
<td>59 (31–101)</td>
<td>122 (68–236)</td>
</tr>
<tr>
<td>37</td>
<td>16 (10–28)</td>
<td>29 (20–58)</td>
<td>95 (52–168)</td>
<td>196 (100–407)</td>
</tr>
<tr>
<td>39</td>
<td>74 (31–244)</td>
<td>142 (62–554)</td>
<td>476 (197–1385)</td>
<td>989 (373–3607)</td>
</tr>
<tr>
<td>40</td>
<td>106 (44–256)</td>
<td>204 (98–487)</td>
<td>682 (367–1294)</td>
<td>1419 (634–3755)</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>21 (12–49)</td>
<td>40 (21–86)</td>
<td>126 (50–267)</td>
<td>261 (105–585)</td>
</tr>
<tr>
<td>36</td>
<td>15 (11–26)</td>
<td>28 (20–51)</td>
<td>90 (43–146)</td>
<td>186 (102–347)</td>
</tr>
<tr>
<td>37</td>
<td>23 (16–39)</td>
<td>44 (31–75)</td>
<td>145 (73–243)</td>
<td>300 (146–671)</td>
</tr>
<tr>
<td>38</td>
<td>53 (23–134)</td>
<td>102 (43–236)</td>
<td>339 (154–730)</td>
<td>705 (314–2016)</td>
</tr>
<tr>
<td>39</td>
<td>113 (58–342)</td>
<td>217 (103–713)</td>
<td>729 (272–1730)</td>
<td>1516 (614–4520)</td>
</tr>
<tr>
<td>40</td>
<td>162 (75–400)</td>
<td>312 (164–704)</td>
<td>1046 (491–2136)</td>
<td>2176 (922–6107)</td>
</tr>
<tr>
<td>≥41</td>
<td>226 (92–702)</td>
<td>435 (183–1140)</td>
<td>1461 (510–4842)</td>
<td>3041 (888–11096)</td>
</tr>
</tbody>
</table>

In the Setting of Universal Screening, do Infants Exceed Exchange Transfusion Levels?

Flaherman et al., 2012 ~ 18,000 newborns (2005-2007) in the KP Northern California Hospitals after the implementation of universal screening

- 22 infants (14 infants <38 weeks) exceeded exchange transfusion threshold
- Only 1 received an ET
- No documented sequelae
In the Setting of Universal Screening, do Infants Exceed Exchange Transfusion Levels?

• Screening TsB was at least “high-intermediate risk” for all 22 infants and “high-risk” for all ≥38 weeks.

• 4 outcomes may be attributable to incomplete adherence to AAP guideline

• 13 might have been prevented by better adherence to AAP follow-up guideline

BUT...

• Re-testing would have required **2166** additional bilirubin tests to prevent (at most) 13 outcomes
Jaundice Outcomes

Wickremasinghe, et al 2015

- **SNHL**: Only bilirubin levels ≥10mg/dl above exchange transfusion thresholds (or ≥ 35 mg/dl) were associated with a significantly increased risk

Wu, et al 2015

- **Cerebral Palsy** consistent with kernicterus occurred only in infants with 2+ risk factors for NT and TsB >5mg/dl above exchange transfusion threshold

Vandborg, et al 2012

- No significant difference in development at age 1-5 years (ASQ) in infants with a peak serum bilirubin over 25mg/dl
Who Gets Kernicterus?

Kuzniewicz et al 2014: Kaiser Northern California.
525,409 infants ≥35 weeks gestation between 1995-2011
• 47 infants identified with TsB ≥30 (8.6 per 100,000 births)
• Median follow up 7.9 years

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Characteristics of Infants With CBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case no.</td>
<td>Gestational Age, wk</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
</tr>
</tbody>
</table>
Are there risks of phototherapy?
Does Phototherapy affect Breastfeeding?

Waite, et al 2016: small reduction in breastfeeding rates at 12 months and in exclusivity at 1, 2, and 4 months

<table>
<thead>
<tr>
<th>Table 2. Rates of Any Breastfeeding and Exclusive Breastfeeding by Month for Phototherapy Exposed and Phototherapy Unexposed Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breastfeeding rate in</strong></td>
</tr>
<tr>
<td><strong>phototherapy exposed, N=220</strong></td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td>Any breastfeeding</td>
</tr>
<tr>
<td>Month 1</td>
</tr>
<tr>
<td>Month 2</td>
</tr>
<tr>
<td>Month 4</td>
</tr>
<tr>
<td>Month 6</td>
</tr>
<tr>
<td>Month 9</td>
</tr>
<tr>
<td>Month 12</td>
</tr>
<tr>
<td>Exclusive Breastfeeding</td>
</tr>
<tr>
<td>Month 1</td>
</tr>
<tr>
<td>Month 2</td>
</tr>
<tr>
<td>Month 4</td>
</tr>
</tbody>
</table>

ORs based on logistic regression adjusting for maternal age, race, maternal education, household income, gestational age, prenatal intention to breastfeed, supplemental formula use on day of life 1, and breastfeeding problems in the first 2 weeks of life.

OR, odds ratio.
Does Phototherapy lead to increased Seizure Risk?

Maimburg et al 2016

• Increased risk of epilepsy among children treated with phototherapy, the association was seen only in boys (adjusted HR 1.98, 95% CI: 1.40–2.78)

Newman, et al 2018

• Increased risk of epilepsy, adjusted hazard ratio (aHR) of 1.22 (95% CI: 1.05 to 1.42; P = 0.009)

• Boys were at higher risk of seizures overall (aHR = 1.18; 95% CI: 1.10 to 1.27) and had a higher aHR for phototherapy (1.33; 95% CI: 1.10 to 1.61)
Is Phototherapy linked to Childhood Cancer?


Retrospective cohort study of 525,409 children born at ≥35 weeks’ gestation between 1995-2011 at 15 KPNC hospitals

Exclusions: death, transfer, lost to follow-up at <60 days, cancer dx before 60 days

• Initial crude IRRs were uniformly positive with low p-values.
• After adjusting for confounding were no longer significant.

Upper limit of the hazard ratios is most concerning for infant’s with Down syndrome with the NNH being 23 at the upper limit.
Is phototherapy worth even a small risk?
Development of the NCNC Guidelines

Based on concerns that the 2004 AAP Guideline was based on limited evidence, internally inconsistent and recommend a significant practice shift at 38 weeks gestation, the UCSF Northern California Neonatal Consortium members came together to:

• Update hyperbilirubinemia clinical practice based on recent research

• Draw on the KP Northern California experience with updated clinical practice guidelines

Full executive summary and recommendations:
NCNC Graphs
NCNC Hyperbilirubinemia Treatment Guideline

This tool is designed to help guide phototherapy and other treatment decisions in newborns of at least 35 weeks gestational age. The treatment thresholds are based upon expert opinion of members of the Northern CA Neonatal Consortium (NCNC) and do not determine standard of care. The current (2004) treatment thresholds of the American Academy of Pediatrics (AAP) are provided as a comparison. (See the complete NCNC Neonatal Hyperbilirubinemia Guideline or treatment guideline graphs.)

This calculator is intended to provide a user-friendly interface to the NCNC guidelines. Professional judgment should be used in applying the results in clinical settings.

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Total Serum Bilirubin Level</th>
<th>Age at Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks (35-42)</td>
<td>Days (0-6)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>21 mg/dL (0-50)</td>
<td>168 Hours (0-168)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>Get age from dates</td>
</tr>
</tbody>
</table>

Calculate | Clear

Calculated results for the data you entered:

<table>
<thead>
<tr>
<th>Neurotoxicity risk factors*</th>
<th>Start phototherapy?</th>
<th>NCNC Phototherapy Threshold</th>
<th>NCNC Exchange Transfusion Threshold</th>
<th>Within 2 mg/dL of Exchange Transfusion Threshold?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT</td>
<td>No</td>
<td>23.0</td>
<td>30.0</td>
<td>No</td>
</tr>
<tr>
<td>PRESENT</td>
<td>Yes</td>
<td>19.0</td>
<td>25.5</td>
<td>No</td>
</tr>
</tbody>
</table>
NCNC Definition of Neurotoxicity Risk Factors

Neurotoxicity risk factors include:

• 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
AAP vs. NCNC (with risk factors)

Examples for with neurotoxicity risks, 168 HOL infant
40 1/7 NCNC threshold = 19 (vs. 18) Exchange = 25.5 (vs. 22.5)
38 1/7 NCNC threshold = 19 (vs. 18) Exchange = 23.1 (vs. 22.5)
35 1/7 NCNC threshold = 15.2 (vs. 15) Exchange = 19.2 (vs. 19)
AAP vs. NCNC (no risk factors)

Examples for no neurotoxicity risks, 168 HOL infant

40 1/7 NCNC threshold = 23 (vs. 21) Exchange= 30.0 (vs. 25)
38 1/7 NCNC threshold = 21.5 (vs. 21) Exchange 28.3 (vs. 25)
35 1/7 NCNC threshold = 19.1 (vs. 18) Exchange 25.6 (vs. 22.5)
Case Comparisons

A baby boy in clinic is noted to have jaundice at 48 hours of life. Mother is AB+/Ab-, she is expressing colostrum and exclusively breastfeeding. The baby is feeding well with appropriate output. This is mom’s third baby. Infant’s weight is down 7% from birth weight. There is slight facial bruising, but no cephalohematoma. TSB is obtained and is 15.5 mcg/dL.

- Let’s look at AAP vs. NCNC recommendations for a 41w1d, 37w 6d and 36w2d week gestational age infant
### Calculated results for the data you entered:

<table>
<thead>
<tr>
<th>Neurotoxicity risk factors</th>
<th>Start phototherapy?</th>
<th>NCNC Phototherapy Threshold</th>
<th>NCNC Exchange Transfusion Threshold</th>
<th>Within 2 mg/dL of Exchange Transfusion Threshold?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT</td>
<td>No</td>
<td>17.0</td>
<td>24.5</td>
<td>No</td>
</tr>
<tr>
<td>PRESENT</td>
<td>Yes</td>
<td>14.0</td>
<td>20.6</td>
<td>No</td>
</tr>
</tbody>
</table>

### For comparison purposes, here are approximate American Academy of Pediatrics' 2004 guideline phototherapy thresholds:

<table>
<thead>
<tr>
<th>Neurotoxicity risk factors</th>
<th>Start phototherapy?</th>
<th>AAP Phototherapy Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT</td>
<td>Yes</td>
<td>15.0</td>
</tr>
<tr>
<td>PRESENT</td>
<td>Yes</td>
<td>13.0</td>
</tr>
</tbody>
</table>
37w6d:
AAP vs. NCNC Recommendations

Calculated results for the data you entered:

<table>
<thead>
<tr>
<th>Neurotoxicity risk factors*</th>
<th>Start phototherapy?</th>
<th>NCNC Phototherapy Threshold</th>
<th>NCNC Exchange Transfusion Threshold</th>
<th>Within 2 mg/dL of Exchange Transfusion Threshold?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT</td>
<td>No</td>
<td>15.7</td>
<td>22.9</td>
<td>No</td>
</tr>
<tr>
<td>PRESENT</td>
<td>Yes</td>
<td>13.8</td>
<td>19.1</td>
<td>No</td>
</tr>
</tbody>
</table>

For comparison purposes, here are approximate American Academy of Pediatrics' 2004 guideline phototherapy thresholds:

<table>
<thead>
<tr>
<th>Neurotoxicity risk factors*</th>
<th>Start phototherapy?</th>
<th>AAP Phototherapy Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT</td>
<td>Yes</td>
<td>13.0</td>
</tr>
<tr>
<td>PRESENT</td>
<td>Yes</td>
<td>11.0</td>
</tr>
</tbody>
</table>
### Calculated results for the data you entered:

<table>
<thead>
<tr>
<th>Neurotoxicity risk factors*</th>
<th>Start phototherapy?</th>
<th>NCNC Phototherapy Threshold</th>
<th>NCNC Exchange Transfusion Threshold</th>
<th>Within 2 mg/dL of Exchange Transfusion Threshold?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT</td>
<td>Yes</td>
<td>14.8</td>
<td>21.6</td>
<td>No</td>
</tr>
<tr>
<td>PRESENT</td>
<td>Yes</td>
<td>12.3</td>
<td>18.0</td>
<td>Yes - see flow sheet</td>
</tr>
</tbody>
</table>

For comparison purposes, here are approximate American Academy of Pediatrics' 2004 guideline phototherapy thresholds:

<table>
<thead>
<tr>
<th>Neurotoxicity risk factors*</th>
<th>Start phototherapy?</th>
<th>AAP Phototherapy Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT</td>
<td>Yes</td>
<td>13.0</td>
</tr>
<tr>
<td>PRESENT</td>
<td>Yes</td>
<td>11.0</td>
</tr>
</tbody>
</table>
Next Steps??

Steps that reduce phototherapy, but are still in line with the AAP Guidelines:

→ No phototherapy under the AAP thresholds
→ Adjust around the medium risk threshold by gestational age

From the 2004 Nomograms Text:

- 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.
Adopt the NCNC Guidelines

- Evidence base is strong
- Insider intelligence is that forthcoming AAP guidelines will not be lower than the NCNC guidelines (2020? 2021?)
- OHSU’s ED, Ward, MBU, and clinics adopted the NCNC guidelines September 9, 2019
References


