The management of hyperbilirubinemia in preterm infants
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Uniform treatment thresholds for hyperbilirubinemia in preterm infants: Background and synopsis of a national guideline

Deirdre E. van Imhoff, Peter H. Dijk, Christian V. Hulzebos and on behalf of the BAR Trial study group of the Netherlands Neonatal Research network

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Abstract

**Background:** To prevent severe hyperbilirubinemia and bilirubin neurotoxicity, the American Academy of Pediatrics’ management guideline for hyperbilirubinemia in near term infants is used worldwide. A leading guideline for jaundiced preterm infants is lacking whereas the risk on severe hyperbilirubinemia is high in these infants. Our aim was to define uniform treatment thresholds for jaundiced preterm infants. In this article we present the history and a synopsis of this novel national guideline.

**Study design:** A survey on guidelines for hyperbilirubinemia in preterm infants was sent to all Dutch Neonatal Intensive Care Units (NICUs). After comparison with international guidelines, a new consensus-based guideline was developed.

**Results:** Treatment thresholds of all 10 NICUs were based on Total Serum Bilirubin (TSB) and related to birth weight (n=9) and gestational age (n=1). NICUs used age-specific (n=6) or fixed (n=4) TSB-thresholds resulting in a large range of thresholds (maximal 170 µmol/L for phototherapy and 125 µmol/L for exchange transfusion). Acidosis, asphyxia, sepsis, active hemolysis and intraventricular hemorrhage were most frequently used risk factors. Consensus was agreed upon TSB-based treatment thresholds, categorized in 5 birth weight groups and divided in high and low risk infants.

**Conclusion:** There was no standardized care for jaundiced preterm infants in the Netherlands. In addition to the internationally used guideline for (near) term infants, a novel ‘consensus based’ guideline for preterm infants with a gestational age of less than 35 weeks has been developed and implemented in The Netherlands. This guideline is approved and recommended by the Dutch Society of Pediatrics.
Introduction

Neonatal jaundice due to unconjugated hyperbilirubinemia is very common in term and preterm infants. Despite effective treatment strategies for hyperbilirubinemia, i.e. phototherapy and exchange transfusion, bilirubin induced neurotoxicity still occurs.\(^1\)\(^–\)\(^4\)

To reduce the incidence of severe neonatal hyperbilirubinemia and bilirubin-induced neurological damage, the American Academy of Pediatrics’ (AAP) recommended a guideline for the prevention and management of unconjugated hyperbilirubinemia in infants of 35 or more weeks of gestational age (GA). This AAP-hyperbilirubinemia guideline has been adopted by many hospitals world-wide including the Netherlands.\(^\text{3,5,6}\) Uniform guidelines for hyperbilirubinemia in preterm infants (of 35 or less weeks of GA) are lacking. The limited evidence on safe treatment thresholds and risk factors for preterm infants is reflected in the well-known large variation in applied (inter)national guidelines.\(^\text{1,3,7–16}\)

Preterm infants are more at risk for developing bilirubin encephalopathy compared to their term counterparts. Kernicterus, even in the absence of classical neurological signs, has been described in preterm infants at total serum bilirubin (TSB) concentrations which were generally considered safe.\(^\text{1}\) Therefore, lower TSB-based treatment thresholds are usually applied in preterm infants. Yet, legitimate evidence on these TSB-thresholds is lacking and many different guidelines are used.\(^\text{10,17,18}\) Our aim was to define uniform TSB-based treatment thresholds and risk factors for hyperbilirubinemia in preterm infants.

Methods

In 2006, a survey was sent to all 10 Dutch Neonatal Intensive Care Units (NICUs) on their local guidelines for the management of hyperbilirubinemia in preterm infants. Treatment thresholds for phototherapy and exchange transfusion were analyzed as well as criteria determining the height and slope of the TSB-threshold curve i.e. birth weight, postnatal age and applied risk factors. TSB treatment thresholds were categorized in 3 birth weight groups, postnatal age in hours and 2 (high or standard) risk groups for analysis in Microsoft Office Excel (Microsoft corporation, Redmond, Washington) and SPSS for Windows (version 16.0, Chicago, IL).

After comparison with (inter)national guidelines on hyperbilirubinemia, a novel consensus-based guideline was developed.
Results

All NICUs (n=10) responded to our request. Treatment thresholds were based on TSB in all 10 NICUs. One NICU used gestational age and 9 NICUs used birth weight to determine TSB-thresholds. Birth weight was categorized in 2 (n=1), 3 (n=7) or 5 (n=1) groups. Postnatal age in hours determined TSB-thresholds in 6 NICUs. The remaining 4 NICUs used fixed TSB-thresholds. After day 4, fixed TSB-thresholds were used in all NICUs.

Risk factors were incorporated in all NICU guidelines, although large variability in the applied risk factors existed. Table 1 shows the fourteen risk factors used in the NICUs. Sepsis, acidosis (pH < 7.20), asphyxia (Apgar score < 6 at five minutes or umbilical cord pH < 7.10), active hemolysis and intraventricular hemorrhage were most frequently used.

Table 1. Risk factors used in the Netherlands in the management of unconjugated hyperbilirubinemia in preterm infants

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Number of NICUs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidosis (pH &lt; 7.25)</td>
<td>9</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>8</td>
</tr>
<tr>
<td>Active hemolysis</td>
<td>7</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>5</td>
</tr>
<tr>
<td>Cerebral ultrasonography corresponding with asphyxia</td>
<td>3</td>
</tr>
<tr>
<td>Albumin &lt; 20 g/L</td>
<td>3</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>2</td>
</tr>
<tr>
<td>Fluctuating temperature</td>
<td>2</td>
</tr>
<tr>
<td>IRDS</td>
<td>1</td>
</tr>
<tr>
<td>Convulsions</td>
<td>1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1</td>
</tr>
<tr>
<td>Fluid restriction</td>
<td>1</td>
</tr>
<tr>
<td>Rapid rise in TSB (&gt; 17 µmol/L/hour)</td>
<td>1</td>
</tr>
</tbody>
</table>

Asphyxia was defined as Apgar < 6 after 5 minutes or umbilical cord pH < 7.10, hypoxemia was defined as an arterial pO_2 < 5.0 kPa for more than 2 hours. NICU = Neonatal Intensive Care Unit, IRDS = Infant Respiratory Distress Syndrome, TSB = Total Serum Bilirubin in µmol/L (17 J µmol/L = 1 mg/dL).

Table 2 shows the ranges in TSB-thresholds for phototherapy and exchange transfusion used in the 10 Dutch NICUs; TSB-thresholds of the first 4 postnatal days were categorized in the 3 most commonly used birth weight groups, and in standard or high risk infants. Maximum TSB ranges were consequently found on day 4 (T = 96 hours)
Table 2. Ranges in TSB-thresholds in the Netherlands for preterm infants with unconjugated hyperbilirubinemia

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>Risk</th>
<th>T=24h</th>
<th>T=48h</th>
<th>T=72h</th>
<th>T=96h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT</td>
<td>ET</td>
<td>PT</td>
<td>ET</td>
<td>PT</td>
</tr>
</tbody>
</table>

Total serum bilirubin (TSB in µmol/L) ranges for phototherapy (PT) and exchange transfusion (ET) expressed in postnatal age (T) in hours (h) and categorized in standard risk (Standard) and high risk (High). Bold values represent the highest ranges in TSB-thresholds.
for phototherapy thresholds. Ranges of 120, 155 and 150 µmol/L were found for preterm infants with a standard risk and a birth weight of < 1000 grams, 1000 – 1500 grams or 1500 – 2500 grams, respectively. For infants considered to have high risk factors and birth weights of <1000 grams, 1000 – 1500 grams or 1500 – 2000 grams, maximum ranges were 100, 135 and 170 µmol/L, respectively.

Figure 1 shows phototherapy and exchange transfusion thresholds for standard risk infants with a birth weight of 1000 to 1500 grams.

![Figure 1. TSB-thresholds of phototherapy and exchange transfusion in the Netherlands for standard risk preterm infants with a birth weight between 1000 and 1500 grams](image)

Ranges in TSB-thresholds used in the Netherlands for phototherapy and exchange transfusion (17.1 µmol/L = 1 mg/dL) for the postnatal age (hours) of the preterm infant. The median is marked by the horizontal line in the central box. The boxes are limited by the 25th and 75th percentiles. The whiskers (—) represent the lowest and highest TSB-thresholds within 1.5 interquartile distance below or above the box. Outliers (○) represent TSB-thresholds between 1.5 and 3 interquartile distances below or above the box.

Based on these results and on published recommendations for treatment of unconjugated hyperbilirubinemia in preterm infants, consensus between the Dutch
NICUs was reached and uniform guidelines were developed. (10,17) Arbitrarily, 5 birth weight groups were defined (i.e. < 1000 g, 1000 – 1250 g, 1250 – 1500 g, 1500 – 2000 g and > 2000 g) as well as most commonly applied risk factors on either the risk of hyperbilirubinemia or the risk on bilirubin neurotoxicity (i.e. active hemolysis (with positive Coombs), asphyxia, hypoxemia, acidosis, and clinical/neurological deterioration (sepsis/meningitis or intracranial hemorrhage > grade 2 according to Papile). All 5 birth weight nomograms are shown in Figure 2 and on https://www.babyzietgeel.nl/index.php?id=135.

**Figure 2.** Phototherapy and exchange transfusion thresholds for preterm infants of less than 35 weeks of gestation

TSB-thresholds of phototherapy (PT) and exchange transfusion (ET) in preterm infants of 35 or less weeks of gestational age. TSB-thresholds (17.1 μmol/L = 1 mg/dL) versus postnatal age (days). Standard or high risk is based on presence of risk factors. All nomograms can be downloaded from http://www.babyzietgeel.nl/index.php?id=135.
After a gradual increase of the TSB-threshold in the first 24–48 postnatal hours a plateau is reached. Since 2008, this guideline is approved and recommended by the Dutch Society of Pediatrics to use for all preterm infants of less than 35 weeks of gestational age in the Netherlands.

**Discussion**

Large variability existed in TSB treatment thresholds for unconjugated hyperbilirubinemia in preterm infants in the Netherlands. Age-specific TSB-thresholds were not used in 4 NICUs, which partially explains the large range of applied TSB-thresholds.

Our results are in agreement with previous (inter)national data and support the lack of evidence on specific TSB-thresholds and neurological outcome. \(^{1,7–9,14,15,19–23}\) To the best of our knowledge, only 3 prospective studies have analyzed effects of different TSB-thresholds on biochemical, phototherapy, and/or outcome data in preterm infants (Table 3). \(^{24–26}\) In 1985, Curtis-Cohen et al. randomly assigned 22 preterm infants with a birth weight of less than 1250 gram to a prophylactic or a conservative treatment. Phototherapy was initiated immediately postnatal in the prophylactic group \((n = 11)\), whereas in the conservative group phototherapy was started above TSB concentrations of 85 µmol/L. Mean TSB concentrations at onset of phototherapy were significantly different \((102 \mumol/L \text{ versus } 39 \mumol/L, \text{ conservative versus prophylactic phototherapy, respectively; } p < 0.001)\) and total duration of phototherapy was 48 hours longer in the prophylactic group \((p<0.05)\), whereas maximum TSB concentrations, age at maximum TSB concentrations and rate of rise of TSB were similar. \(^{24}\) Long-term neurodevelopmental outcome has been analyzed in two prospective trials on prophylactic versus conservative phototherapy in preterm infants. Jangaard et al. started prophylactic phototherapy \((n = 46)\) 12 hours after birth, and conservative phototherapy \((n = 49)\) at a predefined TSB concentration of 150 µmol/L in newborn infants with a birth weight lower than 1500 gram. Maximum TSB concentrations did not differ significantly except in a subgroup of infants weighing less than 1000 grams: Maximum TSB concentrations were highest in the conservative group \((171 \mumol/L \text{ versus } 139 \mumol/L, \text{ conservative versus prophylactic phototherapy, respectively; } p < 0.02)\). A non-significant tendency towards poor long term neurodevelopmental outcome in conservative-treated extreme low birth weight infants was reported. \(^{25}\) Recently, a randomized controlled trial investigated the effects of prophylactic phototherapy (started immediately postnatal) versus conservative phototherapy (based on predefined TSB concentrations) on outcome in hyperbilirubinemic preterm infants with a birth weight of < 1000 grams. Maximum TSB concentrations were higher in the conservative group \((168 \mumol/L\)
Table 3. Studies on TSB thresholds and outcome

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Population</th>
<th>TSB</th>
<th>Short term outcome</th>
<th>Long-term outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris 2008 (26)</td>
<td>Extreme low birth weight infants (&lt;1000g)</td>
<td>PT start directly postnatal versus 137 µmol/L (BW 501–750 g) or 171 µmol/L (BW 751–1000 g)</td>
<td>Peak TSB higher in conservative versus prophylactic group (168 versus 120 µmol/L, P&lt;0.001) Duration of PT longer in prophylactic versus conservative group (88 versus 35 hrs P&lt;0.001)</td>
<td>No significant difference in combination of death or neurological impairment Lower risk of neurodevelopmental impairment in prophylactic group but in this group also a NS increase in mortality for infants with BW 501–750 g</td>
</tr>
<tr>
<td>Jangaard 2007 (25)</td>
<td>Low birth weight infants (&lt;1500g)</td>
<td>PT start 12 hours postnatal versus 150 µmol/L</td>
<td>No difference in peak TSB No difference in duration of PT Subgroup of infants &lt;1000g: Peak TSB higher in the conservative versus prophylactic group (171 versus 139 µmol/L, P&lt;0.02)</td>
<td>No differences in cerebral palsy and/or death No differences in mental developmental index Subgroup of infants &lt;1000g: NS tendency towards poor long term neurodevelopmental outcome in conservative group</td>
</tr>
<tr>
<td>Curtis-Cohen 1985 (24)</td>
<td>Low birth weight infants (&lt;1250g)</td>
<td>PT start directly postnatal versus 85 µmol/L</td>
<td>No difference in peak TSB Lower age (P&lt;0.001) and lower TSB (P&lt;0.001) in prophylactic group at onset of PT Longer duration of PT for prophylactic group versus conservative group (168 versus 121 hrs, P&lt;0.05)</td>
<td>Not described</td>
</tr>
</tbody>
</table>

PT = Phototherapy, ET = Exchange Transfusion, BW = Birth weight, TSB = Total Serum Bilirubin (171 µmol/L = 1 mg/dL bilirubin), NS = not significant, g = grams, hrs = hours
versus 120 µmol/L, conservative versus prophylactic phototherapy, respectively, \( p < 0.01 \). There was no difference between groups in the composite primary endpoint: a combination of death or neurodevelopmental impairment. The risk of neurodevelopmental impairment was lower in the prophylactic group, but mortality was slightly higher, especially in preterm infants with a birth weight between 501 – 750 grams. (26) Unfortunately, we can not deduce ‘safe’ TSB-thresholds from these studies. Until now, there is no specific TSB concentration known at which phototherapy is more beneficial than harmful. (18)

Next to variation in the TSB-thresholds, the present study showed differences in the criteria used to determine TSB-thresholds (gestational age versus birth weight) and in applied risk factors. Various risk factors for hyperbilirubinemia have been used the last 50 years. Risk factors reflect conditions associated with a high bilirubin production on the one hand, and conditions associated with bilirubin neurotoxicity on the other hand. Some examples of frequently used factors are: low birth weight, hypothermia, asphyxia, acidosis, hypoalbuminemia, sepsis, meningitis, intracranial haemorrhage and medication competing with bilirubin to bind albumin. Clinical evidence of most of these risk factors is limited; most factors are based on anecdotal clinical evidence or theoretical and experimental animal data. (1,3,10,27–34)

Variability in management guidelines will for obvious reasons negatively influence standardizing care for jaundiced newborn infants. Standardizing care based on the best available evidence, has been demonstrated to improve pediatric and adult patient outcomes. (35) Based on the best available evidence, i.e. the analysis of the guidelines used in the Dutch NICUs and on (inter)national guidelines, consensus was reached between the ten Dutch NICUs. (10,17)

The novel, ‘consensus based’ guideline is based on TSB-thresholds and includes five nomograms categorized in birth weight groups; < 1000 grams, 1000 – 1250 grams, 1250 – 1500 grams, 1500 – 2000 grams and > 2000 grams. TSB-thresholds for phototherapy and exchange transfusion are age-specific and depend on risk factors. TSB-thresholds at birth are not zero and rise to a plateau TSB-threshold 24–48 hours postnatal. Several reasons exist for this course of TSB-threshold concentrations. Data of TSB concentrations in umbilical cord blood show mean (±SD) TSB concentrations of 30 ± 9 µmol/L. (36) The slope of the curve which allows for treatment at lower TSB thresholds is chosen because: 1) bilirubin production is cumulative over time, 2) initially high TSB concentrations (exceeding TSB thresholds) inform the attending physician for the possibility of imminent severe hyperbilirubinemia (e.g. due to active hemolysis), and 3) bilirubin binding affinity for albumin is initially low which may be associated with higher free bilirubin concentrations. (37) Differences between standard or high risk infants are based on the commonly applied risk fac-
tors asphyxia (Apgar < 3 after 5 min), hypoxemia (PaO2 < 5.3 kPa > 2 hour), acidosis (pH < 7.15 > 1 hour), active hemolysis (with positive Coombs), and clinical or neurological deterioration (such as sepsis with the need for vasopressants, meningitis or intracranial hemorrhage > grade 2 according to Papile).(38)

Other European guidelines for preterm infants are recently published in the UK and Norway.(15) In contrast to the Norwegian and Dutch guideline, the UK guideline is related to gestational age (and not birth weight) and includes specific nomograms for preterm infants of 23 to 37 weeks of gestational age.(16)

In The Netherlands, all preterm infants of less than 32 weeks of GA are admitted to a NICU. Therefore, this ‘consensus-based’ guideline was primarily developed for infants of 32 or less weeks of GA. Based on data of mean birth weights of newborn infants included in a Dutch national database (the Netherlands Perinatal Registry), 2 TSB-threshold nomograms of infants with a birth weight of 1500–2000 grams and more than 2000 grams seemed applicable for infants with gestational ages between 32 to 35 weeks.

In addition to the adapted American Academy of Pediatrics’ Subcommittee on Hyperbilirubinemia 2004 guideline for infants of 35 or more weeks of GA, a novel, ‘consensus-based’ guideline on unconjugated hyperbilirubinemia in the preterm infant is available. In 2008, the Dutch Society of Pediatrics approved and recommended this guideline for jaundiced infants of 35 or less weeks of GA.

**Conclusion**

Large variation in guidelines on hyperbilirubinemia existed in Dutch NICUs supporting the world wide lack of evidence on treatment thresholds for jaundiced preterm infants. A novel, ‘consensus-based’ guideline for unconjugated hyperbilirubinemia in preterm infants of 35 or less weeks of GA has been developed. This novel guideline consists of TSB-based high and low risk treatment thresholds for five birth weight groups.
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