Neonatal Jaundice & Bilirubin Measurement: Are we doing it right?

Martha E Lyon, PhD, DABCC, FACB
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Disclosures

• Speaking Honoraria
  – Radiometer (Canada)
  – Nova Biomedical,
  – Draeger

• Research Support (Reagents, Instrumentation, Travel)
  – Nova Biomedical
  – Abbott Laboratories (Canada)
  – Roche Diagnostics (Canada)
  – Radiometer (Canada)
  – Instrumentation Laboratories (Canada)

• ALOL Biomedical Inc
  – Clinical Laboratory Consulting Business
Case Report:

Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

(Med Malpract Verdict Settlements 2003:19(12):30)
Case Report:
Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

Friday (Birth)
20d premature
TBIL 239 umol/L;
14 mg/dL
(10.4-180 umol/L)

(Med Malpract Verdict Settlements 2003:19(12):30)

Case Report:
Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

Saturday
Discharged home
Bring baby to hospital (Sunday)
Blood test (TSB)
Case Report: Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

Sunday
Back to hospital
Blood collected for TSB
Left without knowing results

Case Report: Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

Sunday
TSB = 318 umol/L (18.6 mg/dL)
Call pediatrician
No answer
Did not call another healthcare provider
Case Report:
Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

Monday
Mom called pediatrician
Told the office would call her if problem present

Wednesday
Pediatrician called to inform elevated TSB
Infant back to hospital
Repeat TSB = 465 umol/L (27.2 mg/dL)
Case Report: Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

Thursday
Infant transferred for phototherapy

Case Report: Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

Diagnosis Months Later
Bilateral hearing loss
Case Report:
Delayed Diagnosis & Treatment of Infant Hyperbilirubinemia

- Massachusetts case settled for $600,000

(Med Malpract Verdict Settlements 2003:19(12):30)

What went wrong?
Review of Bilirubin Metabolism
Neonatal Jaundice & Bilirubin Measurement:
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Monday, October 5, 2015
13:15 – 14:15

Nothing is ever simple!
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Nothing is ever simple!

4Z,15Z UCB IXα
- Occurs normally
- Intramolecular hydrogen bonds
- Lipophilic
- Not water soluble
- NEUROTOXIC

Accessed Nov 1, 2014
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Neonatal Jaundice

May result from a combination of the following:

- **Production**

- **Removal**

Bilirubin

Neonatal Jaundice

May be due to:

- Larger hemoglobin mass in the neonate relative to an adult
- Enhanced hemolysis can lead to increased bilirubin production
Neonatal Jaundice

May be due to:

- Larger hemoglobin mass in the neonate relative to an adult
  - Enhanced hemolysis can lead to increased bilirubin production

MCH (neonate): 31-37 pg/cell
MCH (adult): 25-33 pg/cell

Neonatal Jaundice

May result from:

- Lower plasma albumin levels in the neonate relative to an adult
  - May reduce bilirubin transport to the liver
Neonatal Jaundice

May result from:

• Lower plasma albumin levels in the neonate relative to an adult
  • May reduce bilirubin transport to the liver

<table>
<thead>
<tr>
<th>Albumin (neonate):</th>
<th>20-36 g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (adult):</td>
<td>37-56 g/L</td>
</tr>
</tbody>
</table>

Neonatal Jaundice

May be due to:

• Decreased rate of conjugation with glucuronic acid
  • Due to immaturity of UDP- GT
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There are numerous forms of bilirubin
There are numerous forms of bilirubin

- Albumin bound unconjugated bilirubin
- Conjugated bilirubin (mono or di glucuronic acid)
There are numerous forms of bilirubin

- Albumin bound unconjugated bilirubin
- Conjugated bilirubin (mono or di glucuronic acid)
- Delta Bilirubin (conjugated bilirubin covalently bound to albumin)

There are numerous forms of bilirubin

- Albumin bound unconjugated bilirubin
- Conjugated bilirubin (mono or di glucuronic acid)
- Delta Bilirubin (conjugated bilirubin covalently bound to albumin)
- .....
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How does phototherapy work?

Spectrum of light
Blue most effective (especially around 460-480 nm)

Increasing skin transmittance


http://emedicine.medscape.com/article/1894477-overview


http://galleryhip.com/bili-blanket.html

Accessed Nov 1, 2014

Accessed Nov 2, 2014
How do we measure bilirubin?

Bilirubin Measurement Timeline

1826 1883 1913 1916 1920 1937 1938 1950s 1960s 2000s

L. Gmelin
Paul Ehrlich
Van de Bergh & Snapper
Mallory & Evelyn
Meulengracht
Van de Bergh & Muller
Delta-bilirubin
Direct & indirect bilirubin
Jendrassik and Grof
Transcutaneous bilirubin
Paul Ehrlich (1854-1915)

- German bacteriologist
- In 1883, described the “diazo reaction” for bilirubin measurement
- In 1908, he received the Nobel prize for medicine
  - Discovered “arsphenamine” which was used to treat syphilis
  - Used until 1945 when penicillin superseded it

What is the Diazo Reaction?

![Diazo Reaction Diagram]
What is the Diazo Reaction?

- Diazo reagent does not react well with unconjugated bilirubin
- Need to use a substance (urea, ethanol, DMSO) to break up the internal H bonds of free bilirubin

Difficult for the Diazo Reagent to Interact with 4Z,15Z Free Bilirubin
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Bilirubin Standards...A Dilemma

- 1971
  - Certified high purity of bilirubin became available
  - Standard reference material (SRM 916) from NIST

National Institute of Standards & Technology
Certificate of Analysis

Standard Reference Material® 916a

Bilirubin

This Standard Reference Material (SRM) consists of a sample of unconjugated bilirubin that is certified as a chemical of known purity. It is intended primarily for use in the development and evaluation of procedures used for the determination of bilirubin in clinical samples and for routine evaluation of daily working standards used in these procedures. This material can also be used for quality assurance when assigning values to in-house control materials. A unit of SRM 916a consists of one bottle containing 100 mg of crystalline bilirubin.

Due to concerns that the molar absorptivities for bilirubin and its isomers in the original June 1989 Interlaboratory exercise to measure the molar absorptivity assignments are reported in Table 2 of this certificate, for further Supplemental Information.

Uncertainty in the accuracy is that all known or suspected NIST. The certified molar absorptivity and estimated applied to this SRM in the certification process. The uncertainty is meant to approximate two standard deviation limits for the certified value.

Reference Values and Uncertainties: Reference concentration values for the molar absorptivity in caffeine reagent [2] and the blue and red assayment products, obtained by the Reference Method for Total Bilirubin (developed by the Committee on Standards of the American Association for Clinical Chemistry [AACC]) [2] will be derived from results reported by six collaborating laboratories in 1988 and are listed in Appendix A. The reference values for molar absorptivity are presented in Table 2. The molar absorptivity value of the red assayment at 530 nm was obtained by omitting the addition of alkaline tetrathionate in the Reference Method. Reference values are not certified values that are the best estimate of the true value, however, the values do not meet the NIST criteria.
UNCONJUGATED BILIRUBIN

"CALIBRATION AND STANDARDIZATION OF PROCEDURES FOR THE DETERMINATION OF BILIRUBIN IN CLINICAL SAMPLES..."

98.3%
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98.3%
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Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
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<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albunin (g/L)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>0</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
<td>0</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

17.1 μmol/L = 1 mg/dL bilirubin

Table 2

<table>
<thead>
<tr>
<th>Devices used for bilirubin measurement</th>
<th>Method</th>
<th>Number of NICUs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche Modular</td>
<td>DPD</td>
<td>6</td>
</tr>
<tr>
<td>Resilient Unistat bilirubinometers</td>
<td>Spectrophotometric</td>
<td>1</td>
</tr>
<tr>
<td>Bilimeters</td>
<td>Spectrophotometric</td>
<td>1</td>
</tr>
<tr>
<td>Beckman Coulter</td>
<td>Jendraski Cerf</td>
<td>1</td>
</tr>
<tr>
<td>Abbott Arieset</td>
<td>Jendraski Cerf</td>
<td>1</td>
</tr>
</tbody>
</table>

Devices used for albumin measurement

<table>
<thead>
<tr>
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<th>Method</th>
<th>Number of NICUs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche Modular</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>P810 module</td>
<td>Brown-red green</td>
<td>6</td>
</tr>
<tr>
<td>Automatic</td>
<td>Brown-red purple</td>
<td>1</td>
</tr>
<tr>
<td>Beckman Coulter</td>
<td>Brown-red purple</td>
<td>2</td>
</tr>
<tr>
<td>Synchrolab Lx20</td>
<td>Brown-red green</td>
<td>1</td>
</tr>
<tr>
<td>Dec 800</td>
<td>Brown-red purple</td>
<td>1</td>
</tr>
<tr>
<td>Abbott Arieset</td>
<td>Brown-red purple</td>
<td>1</td>
</tr>
</tbody>
</table>

DPD: 2,5-Dichlorophenyl-diazonium
Study Conclusions

- Bilirubin concentrations were underestimated in the absence of albumin
- With albumin concentrations of 10 or 20g/L, the bilirubin concentrations were overestimated
- Larger variability was observed with higher bilirubin concentrations
Study Conclusions

- Bilirubin concentrations were underestimated in the absence of albumin.
- With albumin concentrations of 10 or 20g/L, the bilirubin concentrations were overestimated.
- Larger variability was observed with higher bilirubin concentrations.

What extent of variability can been seen between clinical laboratory methods?

External Proficiency Testing Results
College of American Pathology:
Accuracy expectations
+/- 0.4 mg/dL or 20%
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Once we have TSB results
plot them on the Bhutani Phototherapy nomogram
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Bhutani Nomogram

- 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, retraccolis, opisthotonos, 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

Serum based
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Bhutani Nomogram

Serum based

"Note: These guidelines are based on limited evidence and the levels shown are approximations."

We know the TSB method used but how was it calibrated?

and the levels shown are approximations.
1) How applicable are percentile curves generated retrospectively with a small sample of infants from a hospital in Philadelphia to the overall US or international population?
1) How applicable are percentile curves generated retrospectively with a small sample of infants from a hospital in Philadelphia to the overall US or international population?

2) To accurately estimate test sensitivity, specificity, PPV, NPV, all samples need to be confirmed with a gold standard confirmatory test.

More Problems with Total Serum Bilirubin

• Hemolysis
How did we detect hemolysis?

- Visual inspection of plasma

- Problems:
  - time consuming (requires centrifugation)
  - manual qualitative assessment
  - between observer variability

How do we currently detect hemolysis?

- Hemolysis Index (Automated Clinical Chemistry Systems)

- Spectrophotometric assessment
  - Blanked bichromatic measurements
    - 405 nm and 700 nm

- Problems:
  - Some time consumed
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75-80% of all specimens are visually hemolyzed

Potential Problems with using Total Serum Bilirubin (TSB) in Neonatal Jaundice Cases
Potential Problems with using Total Serum Bilirubin (TSB) in Neonatal Jaundice Cases

• Method and Calibration dependent changes
Potential Problems with using Total Serum Bilirubin (TSB) in Neonatal Jaundice Cases

- Method and Calibration dependent changes
- Blood Collection
  - Heel Poke

- Hemolysis
  - 80-90% of specimens are hemolysed
Potential Problems with using Total Serum Bilirubin (TSB) in Neonatal Jaundice Cases

- Method and Calibration dependent changes
- Blood Collection
  - Heel Poke
- Hemolysis
  - 80-90% of specimens are hemolysed
- Inaccurate TSB because of hemolysis

Length of Time it takes to get a TSB result
Any other possible methods to measure bilirubin?

Calgary started a Newborn Screening Program for Hyperbilirubinemia using TcB Meters in June 2007.
What is Transcutaneous Bilirubinometry?

- measures the difference in the optical densities for light in the blue and green wavelength regions to determine the “yellowness” of the infant’s subcutaneous tissue.

How do TcB results compare with TsB results?
How do TcB results compare with TsB results?

TcB results = TsB results

Bhutani Nomogram

Serum based

- 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, retrolental, opisthotonos, 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.
Study Group

- Prospectively enrolled 938 healthy infants born to 932 mothers
  - Infant > 36 weeks gestation
  - Born between 1 Dec 2004 and 31 Dec 2005 with two month hiatus during July and August

- Study group represented approximately 22% of the entire birth cohort of 4297 infants born in CHR during the study period

- TcB measurements were scheduled for approximately 24 hours, 48-72 hrs and 7 days; TsB measurement was conducted along with routine metabolic studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=938</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>Mean: 3334 g SD: 461g Range: 2250-5145g</td>
</tr>
<tr>
<td>Male:Female</td>
<td>455(48.5):483(51.5)</td>
</tr>
<tr>
<td>Gestational Age (wk)</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>97(10.4)</td>
</tr>
<tr>
<td>38</td>
<td>189(20.3)</td>
</tr>
<tr>
<td>39</td>
<td>278(29.8)</td>
</tr>
<tr>
<td>40</td>
<td>239(25.7)</td>
</tr>
<tr>
<td>41</td>
<td>127(13.6)</td>
</tr>
<tr>
<td>42</td>
<td>2(0.2)</td>
</tr>
<tr>
<td>Caesarean Section (%)</td>
<td>23.8</td>
</tr>
<tr>
<td>Direct Coombs Positive (%)</td>
<td>6.9</td>
</tr>
<tr>
<td>Skin Tone</td>
<td></td>
</tr>
<tr>
<td>Light (&lt;= light ref. colour)</td>
<td>421(44.9)</td>
</tr>
<tr>
<td>Medium (between ref. colours)</td>
<td>484(51.6)</td>
</tr>
<tr>
<td>Dark (&gt; dark ref. colour)</td>
<td>16(1.7)</td>
</tr>
<tr>
<td>Not available</td>
<td>17(1.8)</td>
</tr>
</tbody>
</table>
Skin tone reference colors

Beige 304

Bronze 708

Calgary Community TcB program nomogram
Infants ≥37 wks

Use dashed action line if following risk factors present:
- Poor feeding
- Lethargy
- Weight loss >10%

Repeat TcB in 24 hrs

Routine care

Date Time TcB Device #
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TcB Meter

• How do we know the instruments are working properly?
• Can we be confident the brand new instrument just out of the box will perform adequately?

Quality Control: An Essential Step!
Quality Control: An Essential Step!

- Need to do this daily to confirm that the instrument is working properly
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Quality Control: An Essential Step!

- Need to do this daily to confirm that the instrument is working properly

PROBLEM:
No Quality Control Material Existed for TcB Meters

Calgary Neonatal Hyperbilirubinemia Screening Team
Calgary Neonatal Hyperbilirubinemia Screening Team

Kudos

Calgary Neonatal Hyperbilirubinemia Screening Team

Kudos

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Kudos

Calgary Neonatal Hyperbilirubinemia Screening Team

How do we know if the TcB Meters are working properly?
Neonatal hyperbilirubinemia Screening Program (Urban Calgary)

- Implemented a regional TcB screening program using Konica Minolta JM-103 jaundice meters at normal nurseries and postpartum community clinics in Calgary in Jun 2007 for all healthy infants ≥35 weeks gestation using a locally developed and validated nomogram.

- The program was integrated into an existing post-partum home and clinic-based service for all mothers and infants in the Calgary Health Region.

Incidence of severe, extreme and hazardous initial TSB levels for 8 month pre-and post-program implementation periods

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>Severe ≥ 342 µmol/L</th>
<th>Extreme ≥ 427 µmol/L</th>
<th>Hazardous ≥ 513 µmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-TcB</td>
<td>91 (850.9)</td>
<td>6 (56.1)</td>
<td>3 (28.1)</td>
</tr>
<tr>
<td>(N=10694)</td>
<td>1:118</td>
<td>1:1782</td>
<td>1:3565</td>
</tr>
<tr>
<td>Post-TcB</td>
<td>43 (385.2)</td>
<td>3 (26.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>(N=11162)</td>
<td>1:260</td>
<td>1:3721</td>
<td></td>
</tr>
</tbody>
</table>
Calgary TcB Neonatal Screening Program

- Population screening with a TcB meter can be effective
- TcB results will not equal TsB results (but how good is the TsB result?)
- TcB meter is unaffected by hemolysis but it is affected by skin tone

Any other possible methods to measure bilirubin?
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Blood Gas Analyzers

Construction

The optical system is based on a 138-nm spectrophotometer with a measuring range of 467-672 nm. The spectrophotometer is connected via an optical fiber to a combined hemolysis meter and measuring chamber.
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Example of the spectrum obtained from unconjugated bilirubin at a concentration of 200 µmol/L.

The spectrum of conjugated bilirubin is slightly different.

Determination of total bilirubin in whole blood from neonates: results from a French multicenter study

Jean-Pierre Bergard1,a, Anton Szymanowicz2,a, Isabelle Pellae3, Valérie Szmidt-Adjidi3 and Michele Rota4

1 Biochemistry Laboratory, Centre Hospitalier Intercommunal de Créteil, Créteil, France
2 Biochemistry Laboratory, Centre Hospitalier de Roanne, Roanne, France
3 Biochemistry-Hematology Laboratory, Centre Hospitalier d’Alençon, Alençon, France
4 Biochemistry Laboratory, Centre Hospitalier de Valenciennes, Valenciennes, France

TBIL ranged from 0.969 to 0.994. Polynomial equations were \( y = 1.17x + 9.7 \) (site 1 (IPB)), \( y = 1.17x + 12 \) (site 2 (UPB, MRJ)), and \( y = 1.00x - 20 \).

Only 10% of the results fell outside the bias-corrected Bland-Altman difference from the reference method.

Conclusions: The ABL 735 instrument is useful for measuring TBIL in 70-µL whole blood samples from neonates. This method might allow for good follow-up of patients.
Study Conclusions

- Co-oximetry method (blood gas analyzers) can be used to measure bilirubin in babies
- Advantage of co-oximetry is that it requires very little blood volume (65-70 ul whole blood)
- (Unaffected by hemolysis)
Conclusions

• Free unconjugated bilirubin (4Z,15Z) is the neurotoxic form of bilirubin and currently it cannot be easily measured
• TsB analytical methodology is NOT mature enough to be incorporated into a clinical nomogram
• TcB meters can be effectively deployed in a population screening program to detect neonatal hyperbilirubinemia
• Co-oximetry methodology using in blood gas analyzers can be used to measure neonatal bilirubin
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Canadian Association of Neonatal Nurses – ONE Day of Education
Monday, October 5, 2015
13:15 – 14:15

Accessed Nov 2, 2014

Alternative Title
Neonatal Jaundice & Bilirubin Measurement: Are we doing it right?

Alternative Title

Yellow Icterus
A New Greek Tragedy

Acknowledgement

• Dr. Andrew W Lyon
• Mr. Geoff Miller
Thank you for your time

Questions?