Transcutaneous Bilirubin Measurements in Newborns: Clinical and Cost-Effectiveness, and Guidelines

Acknowledgments:

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.
Research Questions

1. What is the clinical effectiveness and diagnostic accuracy of transcutaneous bilirubin measurements in newborns?
2. What is the cost-effectiveness of transcutaneous bilirubin measurements in newborns compared with serum bilirubin measurements?
3. What are the evidence-based guidelines regarding transcutaneous bilirubin measurements in newborns?

Key Findings

One health technology assessment report, one systematic review with meta-analysis, one randomized controlled trial, 21 non-randomized studies, and one economic evaluation were identified regarding the clinical effectiveness, diagnostic accuracy, or cost-effectiveness of transcutaneous bilirubin measurements in well newborns. Additionally, three evidence-based guidelines were identified.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between November 1, 2013 and November 7, 2017.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Well newborns (under 10 days of age), in hospital</th>
</tr>
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<tbody>
<tr>
<td>Intervention</td>
<td>Transcutaneous devices for measuring bilirubin (e.g., Philips BiliChek, Minolta Jaundice Meter, Drager JM-03)</td>
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<tr>
<td>Comparator</td>
<td>Q1-Q2: Serum bilirubin measurements</td>
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<td></td>
<td>Q3: No comparator required</td>
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<tr>
<td>Outcomes</td>
<td>Q1: Clinical effectiveness; Diagnostic accuracy (i.e., sensitivity and specificity)</td>
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<tr>
<td></td>
<td>Q2: Cost-effectiveness</td>
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<td></td>
<td>Q3: Evidence-based guidelines</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines</td>
</tr>
</tbody>
</table>
Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

One health technology assessment report, one systematic review with meta-analysis, one randomized controlled trial, 21 non-randomized studies, and one economic evaluation were identified regarding the clinical effectiveness, diagnostic accuracy, or cost-effectiveness of transcutaneous bilirubin measurements in well newborns. Additionally, three evidence-based guidelines were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

One health technology assessment (HTA) report, one systematic review (SR) with meta-analysis, one randomized controlled trial (RCT), 21 non-randomized studies (NRS), and one economic evaluation were identified regarding the clinical effectiveness, diagnostic accuracy, or cost-effectiveness of transcutaneous bilirubin (TcB) measurements in well newborns. Detailed study characteristics are provided in Table 2.

The identified HTA concluded that although TcB devices can safely predict neonatal hyperbilirubinemia they cannot be used as a replacement for total serum bilirubin measurements (TSB). The SR with meta-analysis revealed no significant differences between TcB and TSB nomograms, suggesting either can be used to identify subsequent significant hyperbilirubinemia. The conclusions made by the authors of the 23 individual studies varied greatly. Fifteen of these studies suggested TcB measurements were well correlated to serum bilirubin measurements or provided clinical benefit, while seven studies concluded TcB tended to overestimate or underestimate serum bilirubin, resulting in low levels of correlation.

Three evidence-based guidelines were identified regarding transcutaneous bilirubin measurements in well newborns. One guideline, published by the National Institute for Health and Care Excellence, recommends measuring transcutaneous bilirubin in babies (gestational age ≥ 35 weeks) who are over 24 hours old. If the transcutaneous bilirubinometer measurement indicates a bilirubin level greater than 250 micromol/litre, the guideline recommends measuring the serum bilirubin to check the result and to guide treatment decisions. The second guideline was an update by Wan et al., approved by the Ministry of Health Malaysia in 2014, to a previous publication. This guideline states that transcutaneous bilirubinometers may be used in the assessment of neonatal jaundice. This guideline also contained information on the treatment and prevention of neonatal jaundice. Finally, the third guideline by Wilkinson et al. made a “weak recommendation” to support screening for hyperbilirubinemia in newborn infants using transcutaneous bilirubin measurement, early serum bilirubin measurement, or a combination of these methods to prevent severe complications.
Table 2: Summary of Included Studies on the Clinical Effectiveness, Diagnostic Accuracy, or Cost-effectiveness of Transcutaneous Bilirubin Measurements in Well Newborns

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Conclusions</th>
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<tr>
<td><strong>Health Technology Assessments</strong></td>
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<tr>
<td>Institute of Health Economics, 2013</td>
<td></td>
<td>39 primary studies included</td>
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<td>TcB screening</td>
<td>TSB</td>
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<tr>
<td></td>
<td></td>
<td>SR and critical appraisal conducted</td>
<td>Visual assessment</td>
<td>Comparison between TcB devices</td>
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<td>Economic analysis performed</td>
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<td><strong>Systematic Reviews and Meta-Analyses</strong></td>
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<tr>
<td>Yu, 2014</td>
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<td>MA performed</td>
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<td>TcB nomograms</td>
<td>TSB nomograms</td>
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<td></td>
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<td>14 studies included</td>
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<td>N=NR</td>
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<td><strong>Randomized Controlled Trials</strong></td>
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<tr>
<td>van den Esker-Jonker, 2016</td>
<td></td>
<td>Hospitalized jaundiced neonates (gestational age ≥ 32 weeks)</td>
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<td>TcB to determine need for TSB</td>
<td>Visual and clinical assessment to determine need for TSB</td>
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<td>N=430</td>
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<td><strong>Non-Randomized Studies</strong></td>
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**Fine, 2017**
- Preterm and term infants
- N=NR
- TcB measurement
- TSB measurement
- Sensitivity and specificity of TcB

"Median TcB bias was 2.6 and 2.5 mg dl⁻¹ for term and preterm infants in the first 3 days of life, respectively. However, median bias was 2.2 mg dl⁻¹ for preterm infants at 4 to 7 days of life. TcB in preterm infants predicted high-intermediate or high-risk TSB with 94% sensitivity and 56% specificity. TcB screening protocols developed for term infants can be used for late preterm infants in the first 3 days of life."²

**Jain, 2017**
- Healthy, term, appropriate for gestational age neonates
- N=500
- TcB at 24 and 48 hours of age
- TSB at 72 hours of age
- Sensitivity
- Specificity
- Predictive values

TcB cut-off values of 7 mg/dL at 24 hours and 10 mg/dL at 48 hours were identified as the most effective in predicting subsequent hyperbilirubinemia.

The authors concluded 24 hour and 48 hour TcB values were good predictors of subsequent hyperbilirubinemia (24 hour value had stronger predictive ability).

**Jones, 2017**
- Newborns
- N=178
- TcB measurement (with JM-105 and BiliChek devices)
- TSB measurement
- TcB/TSB correlation

The highest TcB/TSB correlation with the JM-105 device was achieved on the sternum, with an overall correlation value of 0.93.

TcB accuracy varied among races.

In 5% of measurements, TcB with JM-105 on the sternum underestimated TSB by ≥2 mg/dL.

**Nahar, 2017**
- Late preterm and term newborns (gestational age ≥ 35 weeks)
- N=160
- TcB measurement
- TSB measurement
- Mean difference of TcB and TSB
- Sensitivity
- Specificity
- Accuracy

A sensitivity of 77%, specificity of 88%, and accuracy of 82% were obtained using a TcB cut off value of 15 mg/dL.

The authors concluded TcB can reduce the...
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</table>
| Olusanya, 2017⁷  | • Infants with paired TcB and TSB measurements  
• N=1,011 | • TcB measurement  
• TSB measurement | • Predictive performance of TcB | • TcB demonstrated NPVs of 99.0-99.9% and PPVs of 7.7-15.5% across all criteria  
• TcB was effective in identifying infants that do not require phototherapy. However, it may identify a high proportion of false positives |
| Yamana, 2017⁷    | • Japanese newborns (gestational age ≥ 35 weeks)  
• N=82 | • TcB measurement (with BiliCare system)  
• TcB measurement (with JM-105) | • TcB/TSB correlation  
• Mean difference of TcB and TSB | • TcB significantly correlated with TSB  
• TcB measured at the scaphoid fossa or conchal cavity were more reliable than those at the earlobe |
| Alsaedi, 2016⁸   | • Healthy, jaundiced Saudi term newborns  
• N=665 | • TcB measurement | • TcB/TSB correlation  
• Sensitivity  
• Specificity  
• PPV  
• NPV | • TcB sensitivity and specificity to predict TSB during the first 72 hours of life were estimated at 83% and 71%, respectively  
• A PPV of 63% and a NPV of 87% were reported  
• The authors concluded TcB measurement provided accurate estimates of TSB values |
| Kitsommart, 2016¹¹| • Healthy late preterm and term infants  
• N=114 paired samples (from 93 infants) | • TcB measurement (with BiliCare system) | • Mean difference of TcB and TSB  
• Sensitivity  
• NPV | "The BiliCare(TM) demonstrated good performance with positive bias for the screening of jaundice in healthy late preterm or term infants. However, if adopted, proper cut-off levels should be chosen because of sub-optimal device precision."¹² |
| Olusanya, 2016¹² | • Black African neonates  
• N=2,107 paired samples (from 1,553 infants) | • TcB measurement (with JM-105 and BiliChek devices) | • Divergence between TcB and TSB values | Both the BiliChek and the JM-103 devices overestimate TSB in black African neonates, which may result in unnecessary treatments  
• JM-103 device was associated with higher |
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| Pratesi, 2016<sup>16</sup> | • Late preterm Caucasian infants with non-hemolytic jaundice (gestational age ≥ 35 weeks)  
• N=458 | • TcB measurement (with BiliCare)  
• TcB measurement (with JM-105)  
• TSB measurement | • Mean difference of TcB between devices | • TcB measurements with both devices were well correlated  
• BiliCare tended to over-estimate TSB for mild and moderate values and under-estimate it for high values compared to JM-103  
• Comparison between TcB and TSB were not made in the abstract |
| Afjeh, 2015<sup>14</sup> | • Neonates weighing ≥ 1,800 g (gestational age ≥ 35 weeks)  
• N=613 | • TcB measurement  
• TSB measurement | • TcB/TSB correlation  
• PPV | • TcB demonstrated a PPV of 81% for the diagnosis of hyperbilirubinemia  
• A correlation coefficient of 72% was observed between TcB and TSB  
• Authors highly recommended TcB to be performed routinely due to high incidence of hyperbilirubinemia in neonates |
| Mahram, 2015<sup>15</sup> | • Neonates admitted to hospital because of neonatal indirect jaundice  
• N=256 | • TcB measurement (with KJ-8000 device)  
• TSB measurement | • TcB/TSB correlation  
• Sensitivity  
• Specificity | • TcB/TSB correlation was observed to be 0.82  
• Sensitivity and specificity were found to be 0.844 and 0.842, respectively  
• The authors concluded that TcB can be used as a reliable tool to bilirubin in neonates |
| Taylor, 2015<sup>10</sup> | • Neonates admitted to participating newborn nurseries  
• N=8,319 | • TcB measurement  
• TSB measurement | • Mean difference of TcB and TSB  
• TcB/TSB correlation | • The mean difference between TcB and TSB values was 0.84 mg/dL  
• Mean difference between TcB and TSB values was higher in African-American newborns  
• The correlation between paired TcB/TSB measurements was 0.78  
• The authors concluded that TCB measurement provided a reasonable estimate of TSB levels in...
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<tr>
<td>Afanetti, 2014</td>
<td>Preterm and term infants • N=85</td>
<td>TcB measurement (with Draeger JM-103(R) device)</td>
<td>TSB measurement</td>
<td>Correlation and agreement between TcB and TSB values</td>
<td>“TcB measurements using the Draeger JM-103(R) device correlate significantly with TSB, regardless of term and skin color. Transcutaneous bilirubinometry seems to be a safe and cost-effective screening method for severe hyperbilirubinemia in newborns of different terms and ethnic origins.”</td>
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<tr>
<td>Conceicao, 2014</td>
<td>Term newborns with no hemolytic disease • N=58</td>
<td>TcB measurement (performed on the forehead or sternum with Bilicheck(R) device)</td>
<td>TSB measurement</td>
<td>Correlation and agreement between TcB and TSB values</td>
<td>TcB measurement on the sternum was more effective than when measured on the forehead • Mean TcB values measured on the sternum corresponded well with TSB values</td>
</tr>
<tr>
<td>Mazur, 2014</td>
<td>Low-risk newborn infants with normal bilirubin levels • N=34</td>
<td>TcB measurement (with JM103 device)</td>
<td>TSB measurement</td>
<td>Differences and limits of agreement between sequential measurements</td>
<td>“We found good agreement between TcB measurements obtained sequentially by a single user and by two different users of the device, as well as between laboratory TSB values in low-risk newborn infants with normal bilirubin levels. These findings support the use of a noninvasive bilirubin meter to screen for hyperbilirubinemia, which could reduce the amount of blood obtained invasively from newborns.”</td>
</tr>
<tr>
<td>Mohamed, 2014</td>
<td>Healthy term and near-term newborns • N=141</td>
<td>Plotting TcB values on a transcutaneous nomogram (Fouzas et al. and Maisels and Kring)</td>
<td>Plotting TSB values on a TSB nomogram (Bhutani et al.)</td>
<td>Risk of developing significant hyperbilirubinemia • False negative rate • Sensitivity • Specificity • PPV and NPV</td>
<td>Plotting TcB values on a TSB nomogram was associated with higher false negative rate and decreased predictive characteristics</td>
</tr>
<tr>
<td>First Author, Year</td>
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| **Neocleous, 2014** | • Clinically jaundiced healthy-term Greek newborns  
• N=368 paired samples (from 222 infants) | • TcB measurement (with BiliCheck device) | • TSB measurement | • Level of agreement between TcB and TSB values | • TcB and TSB values did not correlate well  
• TcB tended to overestimate TSB with wide 95% limits of agreement |
| **Rylance, 2014** | • Jaundiced newborn infants  
• N=128 | • TcB measurement (from forehead and sternum) | • TSB measurement | • Correlation and agreement between TcB and TSB values  
• Sensitivity  
• Specificity | • TcB values tended to overestimate the degree of jaundice  
• A sensitivity of 91% and a specificity of 90% were observed in infants not undergoing phototherapy  
• For infants undergoing phototherapy, TcB had good sensitivity (94%), but lower specificity (36%)  
• The authors concluded TcB can be used to safely guide phototherapy in a resource-poor setting |
| **Samiee-Zafarghandy, 2014** | • Newborns of various skin colours  
• N=451 | • TcB measurement (with JM103 device) | • TSB measurement | • Association between TcB and TSB values | • TcB underestimated TSB in light and medium skin colours infants and overestimated TSB in dark skin colour  
• The authors concluded that the JM103 device was a useful screening tool to identify infants in need of TSB, regardless of their skin colour |
| **Simsek, 2014** | • Healthy Turkish neonates (gestational age ≥ 36 weeks)  
• N=250 | • TcB measurement (with JM103 device) | • TSB measurement | • Correlation between TcB and TSB values  
• Mean difference of TcB and TSB | • TcB tended to underestimate TSB, with a larger discrepancy at higher TSB values  
• The mean difference of TcB and TSB was lower in infants not requiring phototherapy than infants that required phototherapy  
• The JM-103 device is a suitable screening tool to identify jaundiced infants |
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<th>Outcomes</th>
<th>Conclusions</th>
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<tr>
<td>Srinivas, 2016</td>
<td>• Neonates admitted only to the Level 1 nursery (gestational age ≥ 37 weeks) • N=552</td>
<td>• TcB measurement (with BiliChek(R) meter)</td>
<td>• TSB measurement</td>
<td>• Correlation between TcB and TSB values • NPV • Potential cost savings</td>
<td>Correlation between TcB and TSB was estimated at 0.69 • A NPV of 99.4% was reported • TcB use was associated with a potential cost savings of $1500.00 per 100 patients • The authors concluded TcB can used as a stand-alone test until values are close to phototherapy threshold</td>
</tr>
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</table>

**Economic Evaluations**

and it may reduce the need for TSB measurements

<table>
<thead>
<tr>
<th>Reference Summarized</th>
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</table>

**Health Technology Assessments**


**Systematic Reviews and Meta-Analyses**


**Randomized Controlled Trials**


MA = meta-analysis; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; TcB: transcutaneous bilirubin; TSB = total serum bilirubin; RCT = randomized controlled trial; SR = systematic review.
Non-Randomized Studies


Economic Evaluations


Guidelines and Recommendations


Appendix — Further Information

Previous CADTH Reports


Systematic Reviews and Meta-Analyses

Alternative Population – Newborns Receiving Phototherapy


Alternative Population – Preterm Infants


Non-Randomized Studies

Alternative Population – Newborns Receiving Phototherapy


Clinical Practice Guidelines – Uncertain Methodology


Review Articles


