

Hyperbilirubinemia and Transcutaneous Bilirubinometry

Samar N. El-Beshbishi,¹ Karen E. Shattuck,² Amin A. Mohammad,³ and John R. Petersen^{3*}

BACKGROUND: Neonatal jaundice or hyperbilirubinemia is a common occurrence in newborns. Although most cases of neonatal jaundice have a benign course, severe hyperbilirubinemia can lead to kernicterus, which is preventable if the hyperbilirubinemia is identified early and treated appropriately.

CONTENT: This review discusses neonatal jaundice and the use of transcutaneous bilirubin (TcB) measurements for identification of neonates at risk of severe hyperbilirubinemia. Such a practice requires appropriate serial testing and result interpretation according to risk level from a nomogram that provides bilirubin concentrations specific for the age of the neonate in hours. In this context, we have evaluated the potential impact on clinical outcome and limitations of TcB methods in current use.

SUMMARY: TcB measurement is a viable option in screening neonates to determine if they are at risk for clinically significant hyperbilirubinemia. Total serum bilirubin should be measured by a clinical laboratory if a newborn is shown to be at higher risk for clinically significant hyperbilirubinemia. In addition, external quality assessment to identify biases and operator training issues should be part of any TcB monitoring program.

© 2009 American Association for Clinical Chemistry

Neonatal hyperbilirubinemia (jaundice) occurs in more than 60% of late preterm and term newborns, peaking at 3–5 days of life and usually resolving by 2 weeks of age (1). This common clinical finding is the result of an imbalance between production and elimination of bilirubin, a breakdown product of hemoglobin. Bilirubin formation in newborns is 2 to 3 times greater than in adults owing to the shorter life span of fetal hemoglobin compared to adult hemoglobin. The developmentally immature liver and gastrointestinal tracts of newborns are unable to excrete bilirubin as

quickly as it is produced. When bilirubin accumulates in blood and body tissues, skin and eyes exhibit the yellow color characteristic of jaundice. Severe neonatal hyperbilirubinemia, defined as total serum bilirubin (TSB)⁴ concentrations >221 $\mu\text{mol/L}$ (12.9 mg/dL), has been estimated to occur in up to 10% of newborns (2, 3). The major risk factors for severe hyperbilirubinemia are prematurity (gestation <38 weeks), breastfeeding, family history of significant jaundice in a sibling, Rh/ABO incompatibility, or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Jaundice is typically noticed first on the baby's face, progressing to the trunk and extremities as the serum bilirubin concentration increases. Since most term newborns go home with their mothers by 1–2 days of age, jaundice may not be apparent at the time of hospital discharge. Although usually a benign condition, hyperbilirubinemia when severe is associated with lethargy, poor feeding, inconsolability, high-pitched crying, fever, and apnea. The worst-case scenario is development of kernicterus, a term used to describe the irreversible brain damage associated with staining of the basal ganglia. Kernicterus is preventable by appropriate management of hyperbilirubinemia in newborns. Infants who are sick or preterm are at risk of developing kernicterus at lower TSB concentrations compared to the term neonate (4).

Hyperbilirubinemia and the American Academy of Pediatrics Recommendation

Kernicterus associated with jaundice has been recognized for centuries and has been associated with significant morbidity. With the development of laboratory testing for TSB, phototherapy, and exchange transfusion techniques, however, the condition had almost disappeared by the 1970s in term newborns. Unfortunately, largely because of shorter lengths of hospital stays for newborns, a resurgence of this preventable disorder has been reported over the last 15 years (5). In response to the reappearance of kernicterus, updated practice guidelines were published in 2004 by the American Academy of Pediatrics (6) and more recently by the American Academy of Pediatrics and European

¹ Department of Medical Parasitology, Mansoura University, Mansoura, Egypt; ² Department of Pediatrics; and ³ Department of Pathology, University of Texas Medical Branch, Galveston, TX.

* Address correspondence to this author at: Department of Pathology, University of Texas Medical Branch, 301 University Blvd., Rm. 5.156, JSA, Galveston, TX 77555-0551. Fax 409-772-1350; e-mail jrpeters@utmb.edu.

Received December 9, 2008; accepted April 16, 2009.

Previously published online at DOI: 10.1373/clinchem.2008.121889

⁴ Nonstandard abbreviations: TSB, total serum bilirubin; G6PD, glucose-6-phosphate dehydrogenase; JCo, Joint Commission on Accreditation of Hospitals; TcB, transcutaneous bilirubin.

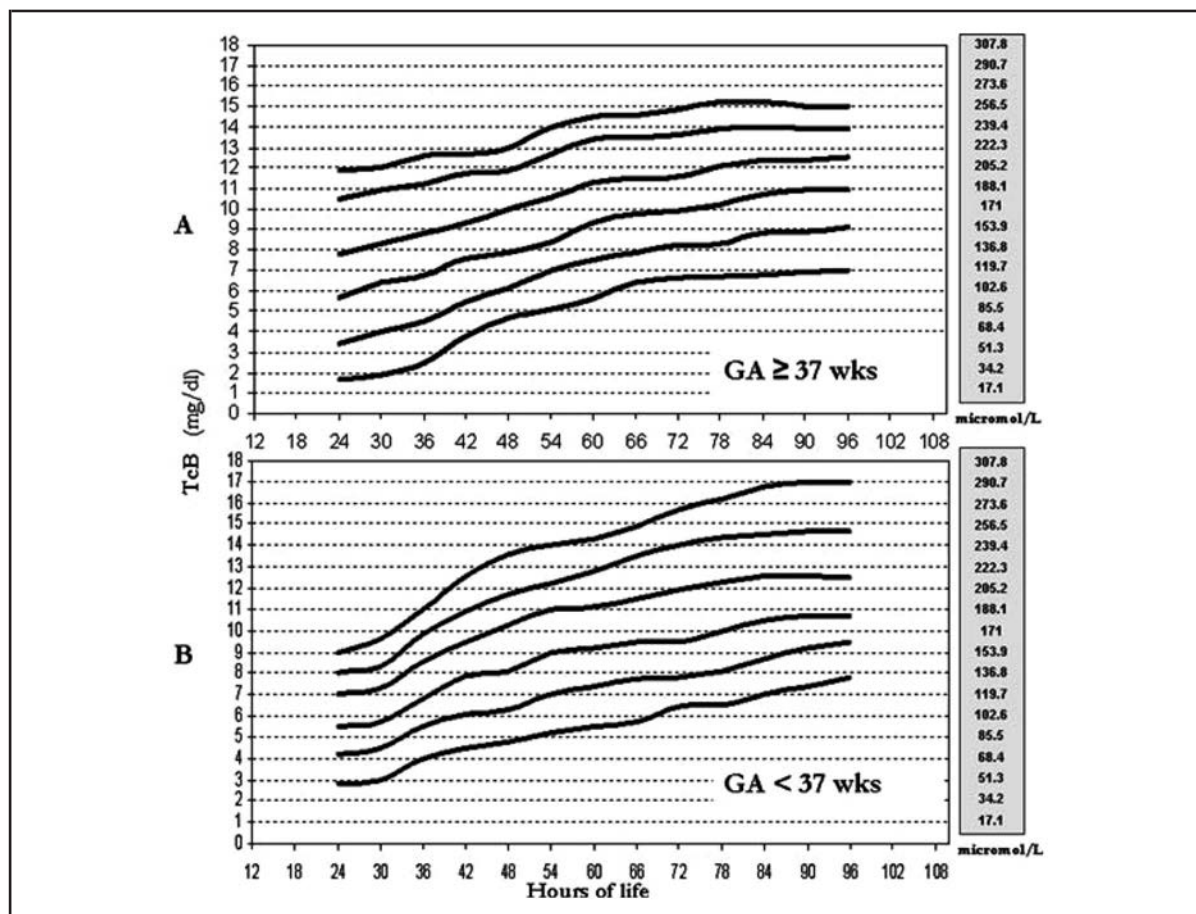


Fig. 1. Nomograms of TcB from healthy newborns.

Nomograms showing curves of the 10th, 25th, 50th, 75th, 90th, and 95th percentiles for TcB (BiliChek) in 2198 healthy normal European neonates ≥ 35 weeks of gestation. (A) and (B) show nomograms for term (≥ 37 weeks) and near-term (≥ 35 but < 37 weeks) babies, respectively. Bilirubin values on the left are expressed in mg/dL and on the right (grey boxes) in $\mu\text{mol/L}$. Reprinted with permission from Blackwell Publishing [De Luca et al. (10)].

Society for Pediatric Research in 2008 (7). In addition, many other professional and clinical organizations, including National Association of Neonatal Nurses, *Morbidity and Mortality Weekly Report*, and the Joint Commission on Accreditation of Hospitals (JCo), have issued practice guidelines, position statements, and sentinel alerts regarding kernicterus and its prevention. All recommend assessment of the risk of hyperbilirubinemia of all newborns before nursery discharge. This may be done by universal bilirubin measurement, either serum or transcutaneous, and/or assessment of clinical risk factors in individual infants with follow-up bilirubin testing of those at increased risk. In the past, visual inspection of babies was relied on much more extensively than as is the case today.

The sentinel alert by the JCo has been a major factor for many hospitals, ours included, for the increased use of TSB or transcutaneous bilirubin (TcB) before

release from the hospital. By using an hour-based risk assessment nomogram such as developed by Bhutani et al. (2), newborns may be discharged with follow-up as an outpatient in 1–2 days, started on phototherapy in the hospital, or receive phototherapy at home. Several nomograms using TcB have been developed since (8–10). See Fig. 1 for an hour-specific nomogram using TcB. Using such a nomogram to interpret serial measurements of bilirubin concentrations is necessary to assess the need for phototherapy and to determine when to terminate treatment.

TcB Impact on Length of Stay and Readmission Rate

Estimation of serum bilirubin by visual inspection of the skin or sclera is rapid and cost-free but not sufficiently accurate, especially when applied to newborns of mixed ethnicity or diverse racial backgrounds

(6, 7, 11). Another technique for estimating serum bilirubin that is noninvasive, fast, and relatively inexpensive is the use of transcutaneous spectrophotometric measurement or TcB (4, 12). TcB testing has become more popular than visual assessment because of the known limitations of visual identification of hyperbilirubinemia, especially in nonwhite babies. Although a linear relationship exists between TcB and TSB ($r = 0.87-0.96$), at TSB concentrations $>257 \mu\text{mol/L}$ (15 mg/dL) the accuracy of TcB has been questioned (13). When used properly, however, TcB measurement appears to be reliable in identification of hyperbilirubinemia in neonates from variety of ethnic backgrounds (3, 14-16).

Although it has been speculated that TcB measurements may influence length of stay, clinical outcome, and readmission rates, prospective studies addressing these issues are lacking. In a retrospective study, Petersen et al. (17) reviewed 6603 newborns over a time period of 8 months before and after implementation of TcB measurements. These investigators found that availability of TcB measurements was not associated with a decrease in the mean length of stay for normal newborns, the number of newborns with hyperbilirubinemia requiring phototherapy before discharge, or the number of days of treatment with phototherapy. However, Petersen et al. did note a significant reduction in the number of hospital readmissions per 1000 newborns for clinically significant hyperbilirubinemia, from a mean (SD) of 4.5 (2.4) to 1.8 (1.7), and a statistically significant increase in the monthly incidence of phototherapy treatment before discharge from 5.9% (1.3%) to 7.7% (1.3%) after implementation of TcB measurements. They speculated that the convenience and rapid turnaround time of TcB testing may have encouraged more effective screening and identification of newborns with clinically significant hyperbilirubinemia before discharge.

TcB and Clinical Outcome

Measurement of TSB concentrations is a frequent reason for collection of blood from newborns, especially preterm infants (18). For newborns, the majority of the samples are taken by heelstick, which can be painful and involves other potential complications of blood collection, including infection and possibly osteomyelitis (19). Studies suggest that a 20% to 50% reduction in samples collected for bilirubin analysis could be achieved after implementation of TcB measurements (20-22) in preterm babies >34 weeks of age. Kaplan et al. (23) concluded that TcB measurement was a practical method for detection of neonates with plasma total bilirubin ≥ 75 th percentile before discharge, which was associated with fewer follow-up blood tests for the evaluation of hyperbilirubinemia than visual assess-

ment alone. Because of the reduced number of blood draws, the implementation of TcB measurements would be expected to decrease the incidence of infection and osteomyelitis; however, a large population study would be needed to address this question because of the low baseline incidence of these complications.

Not all studies have found TcB testing to be associated with a reduction in blood testing. Petersen et al. (17) found that the mean number of TSB measurements did not change after the introduction of TcB testing. In fact, babies had more bilirubin testing done after TcB monitoring was introduced. When both TSB and TcB measurements were considered, the number of bilirubin measurements (TSB plus TcB) per newborn increased from 0.37 (0.08) to 0.61 (0.13). A possible explanation is that because more neonates were identified to have hyperbilirubinemia, more ended up being monitored.

TcB Reference Nomograms

Predischarge TcB measurements, together with gestational age and age in hours, are useful for predicting the risk of subsequent hyperbilirubinemia (24) in late preterm babies as well as in term babies. As recently pointed out, a nomogram based on TSB may not be appropriate in identifying neonates at risk of hyperbilirubinemia when using TcB meters (25). Unless method bias was corrected, an increased number of false negatives were found for the 2 TcB meters studied (6% for Bilichek and 62% for JM-103). In this regard, Maisels and Kring (8) published a nomogram based on 3984 healthy North Americans neonates (gestational age ≥ 35 weeks) from 6 to 96 h of age using the Draeger Air-Shields JM-103 transcutaneous jaundice meter (Dräger Medical). They found that infants requiring additional monitoring were those whose TcB concentrations were ≥ 95 th percentile or those whose TcB is increasing at a rate $>3.77 \mu\text{mol/L}$ (0.22 mg/dL) per hour in the first 24 h, $>2.56 \mu\text{mol/L}$ (0.15 mg/dL) per hour between 24 and 48 h, or $>1.03 \mu\text{mol/L}$ (0.06 mg/dL) per hour after 48 h. Similarly, Sanpavat et al. (9) developed an hour-specific nomogram from 4 to 96 h using BiliChek (Respironics) on a small population of 284 healthy Thai neonates. They found that neonates with a TcB >90 th percentile were identified as being at high risk of subsequent hyperbilirubinemia with diagnostic sensitivity, specificity, and positive and negative predictive values of 96.9%, 78.8%, 29.1%, and 99%, respectively. A good summary of the diagnostic sensitivity, specificity, and positive and negative predictive values from various studies has been recently published by Carceller-Blanchard et al. (26). More recently, De Luca et al. (10) defined expected bilirubin concentrations in healthy European neonates (gestational age

≥ 35 weeks) in the first 24–96 h of life along with the natural bilirubin rate of increase using BiliChek (Fig. 1). They found that bilirubin increases linearly with an average increase of $2.29 \mu\text{mol/L}$ (0.14 mg/dL) per hour in the first 48 h; less rapidly from 48 to 72 h, with an average increase of $1.37 \mu\text{mol/L}$ (0.08 mg/dL) per hour; and a minimal increase after 72 h, $<0.68 \mu\text{mol/L}$ ($<0.04 \text{ mg/dL}$) per hour.

Effect of Site on the Quality of TcB Results

The body site (forehead, sternum, back, knee, or foot) used for TcB measurement has also been shown to have an effect on the accuracy of the results, with measurements made on the forehead and sternum having the best correlation with TSB (27–29). Randeberg et al. (30) found that TcB measurements on neonates taken from the heel, back, or thigh did not correlate as well with TSB as those taken from the forehead. Maisels et al. (13), however, found better correlation with TSB when TcB measurements were performed on the sternum ($r = 0.953$) compared with the forehead ($r = 0.914$). In addition, they suggested that measurements from the sternum, which is less likely to be exposed to sunlight or ambient light, may be more desirable, especially when measurements are taken after infants have been discharged from the hospital.

Accuracy of TcB Measurements and Serum Bilirubin Testing

In the majority of studies evaluating TcB measurements, TSB was measured by laboratory instruments using diazo-based methods (31) that have interferences with hemoglobin and other intracellular compounds (32). Because blood collected from newborns is often hemolysed, this could affect the accuracy of the clinical laboratory methods. Several studies have evaluated the accuracy and precision of TcB measurements compared to HPLC measurements; the HPLC measurement approach, unlike routine laboratory-based methods, is not subject to interference from hemolysis or lipemia (30, 33). These studies suggest that TcB measurements may be used not only as a screening device but also as a reliable substitute for clinical laboratory-based serum bilirubin measurements. This is in line with the recent National Academy of Clinical Biochemistry laboratory medicine practice guidelines, which concluded that the TcB meters currently available for clinical use in the US (BiliChek and JM-103) provide results comparable to laboratory TSB (34, 35). When comparing TcB and TSB measurements, it is also important to remember that the 2 methods of measurement may be evaluating different physiologic entities. Rubaltelli et al. (29) suggested that TcB methods measure the amount of bilirubin that has moved

from the serum into the tissue, possibly mimicking the movement of bilirubin across the blood–brain barrier and into brain issue, whereas laboratory-based methods measure only bilirubin that is circulating in the blood. Thus, TcB may actually offer additional information not provided by TSB measurements, although this hypothesis remains to be proven.

Limitations of TcB Measurements

Although TcB measurements have been shown to correlate well with TSB, TcB can be affected by a variety of factors, such as phototherapy and exposure to sunlight (28, 36, 37). The algorithms that transform the TcB measurements into a bilirubin concentration use estimates of hemoglobin concentrations, which decrease approximately 10% in the first week of life, along with dermal thickness and the melanin content of the skin, both of which are known to impact TcB measurements (38, 39). This has led most facilities to limit the use of TcB to infants <10 days old. However, preliminary studies on the use of TcB to identify adults at risk of liver dysfunction by Harbrecht et al. (40) suggest that TcB may be used on much older newborns, although this observation will require additional confirmatory studies. Care must also be taken to avoid testing skin that is bruised, has a birthmark, or is covered with hair.

Recently, Reyes et al. (41) found that the values obtained for TcB using BiliChek have a negative bias (mean bias $-29 \mu\text{mol/L}$ or 1.7 mg/dL ; 95% CI -32 to $-26.0 \mu\text{mol/L}$) compared with TSB, particularly at higher bilirubin concentrations [$>205 \mu\text{mol/L}$ (12 mg/dL)], which would be expected for newborns being evaluated for phototherapy after discharge to home. They concluded that BiliChek does not provide sufficient accuracy for monitoring newborns on home phototherapy or ascertaining when to discontinue treatment. This disadvantage may be overcome by testing skin that has been covered during phototherapy. Because of the negative bias, however, many facilities have indicated that TcB values >205 – $222 \mu\text{mol/L}$ (12 – 13 mg/dL) should be interpreted with caution and be confirmed with a TSB measurement.

Quality Assurance Concerns

It is important that the result from a TcB device be reproducible. Recently, the interobserver and interdevice reproducibilities of BiliChek were evaluated for TcB concentrations $>137 \mu\text{mol/L}$ (8 mg/dL) and found to be 4%–5% and 7%–8%, respectively (29). Although higher than those of central laboratory measurements, these reproducibilities should allow adequate identification of neonates requiring further evaluation for hyperbilirubinemia. In addition, it is

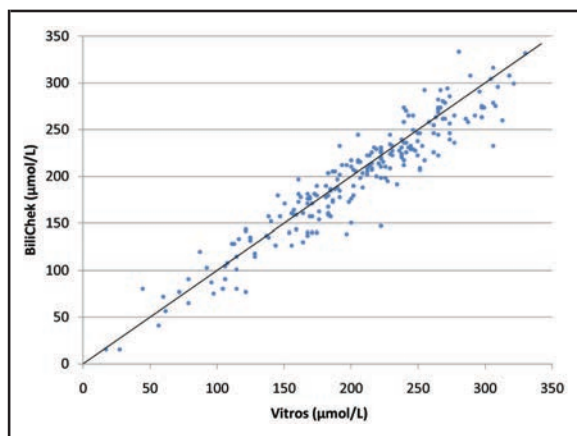


Fig. 2. Comparison of BiliChek and neonatal bilirubin concentrations (Vitros 950 and Vitros 5,1 FS) over a 3-year time period.

The babies were being evaluated for hyperbilirubinemia in the newborn nursery or outpatient clinics after release from the hospital. As part of a routine quality assurance project to monitor acceptability of transcutaneous bilirubin results, a TcB was obtained monthly on a baby who was having a routine sample drawn or for follow-up due to suspicion of hyperbilirubinemia. A TSB was ordered and, along with the TcB, reported via a website developed for this purpose. Due to the negative bias, values $>222 \mu\text{mol/L}$ (13 mg/dL) should be interpreted with caution and should be confirmed with a TSB measurement. The solid line assumes a 1:1 relationship between BiliChek and Vitros. The regression equation is $y = 0.92(\pm 0.02)x + 0.6(\pm 0.3)$ with $r = 0.946$.

important that the TcB result be documented in the patient's electronic or written medical record. Currently this is a manual process but, hopefully, newer generations of TcB meters will have the capability to interface with the appropriate information system to eliminate the errors inherent with manual entry.

As with any test that is performed at the point of care, continuing assessment of the competency of the personnel using the device is extremely important. Clearly, this is a major issue not only with TcB meters but with point-of-care testing in general. When nurses or other healthcare professionals perform the testing, it can be difficult to identify which operators require additional training or what instruments are not functioning properly. To monitor the numerous sites that use TcB, including those at a distance of 5–100 miles from the main hospital, we instituted a proficiency program that requires monthly comparisons to be made between simultaneously measured TcB and TSB (see Fig. 2 for 3 years of comparison data). When a sample is being drawn on a newborn for routine screening or for follow-up owing to suspicion of hyperbilirubinemia, a

TcB is obtained. A TSB is then ordered and both the TcB and TSB results are reported via a website developed for this purpose. In addition to allowing monitoring of potential shifts in the TcB values due to instrument problems, this process also allows identification of operators that require additional training.

Instruments for Measuring TcB

Among the first of the devices used for noninvasive bilirubin measurement was the ColorMate III (Chromatics Color Sciences International Inc). This transcutaneous bilirubinometer used a xenon flash tube and light sensors to measure wavelengths from 400 to 700 nm. A major drawback of this device was the requirement for a baseline TSB reading on each neonate shortly after birth. The Minolta Jaundice Meter (Konica Minolta Holdings) uses 2 wavelengths (460 and 550 nm) along with a dual optical path system to measure bilirubin transcutaneously. The original Jaundice Meter and the JM-102 model gave readings as a numerical index that required an initial correlation to the TSB. It was also necessary to account for gestational age and race, as both parameters affected the results. Recent studies with the newest version of the meter, JM-103 (see Fig. 3 for a schematic of how the instrument works), show much better correlation with TSB than the earlier JM-101 and JM-102 models (13).

More recently a transcutaneous meter (BiliChek) was developed that uses reflectance data from multiple wavelength readings (see Fig. 4 for a schematic of how the instrument works). The use of multiple wavelength (400 to 760 nm) readings allows correction for differences in skin pigmentation and hemoglobin, eliminating the need for a patient-specific baseline reading. Compared to HPLC, the BiliChek device was shown to be more accurate than clinical laboratory bilirubin measurements (29). Although BiliChek was recognized as a significant improvement over the older transcutaneous devices (12), a clean, disposable tip is required for each measurement, substantially increasing the cost of the test.

Recently, Leite et al. (42) found that TcB measurements using BiliChek gave the same information as a capillary plasma bilirubin if the TcB concentration was $<240 \mu\text{mol/L}$ ($<14 \text{ mg/dL}$). Above this concentration, they believed that the BiliChek device should be considered only as a screen and samples should be sent to a central laboratory for confirmation. Conversely, Boo and Ishak (43) stated that BiliChek should not be considered a substitute for TSB, although they found that TcB was useful in the identification of infants with a TSB $\geq 300 \mu\text{mol/L}$ (17.5 mg/dL). These infants require additional bilirubin monitoring and frequently receive phototherapy.

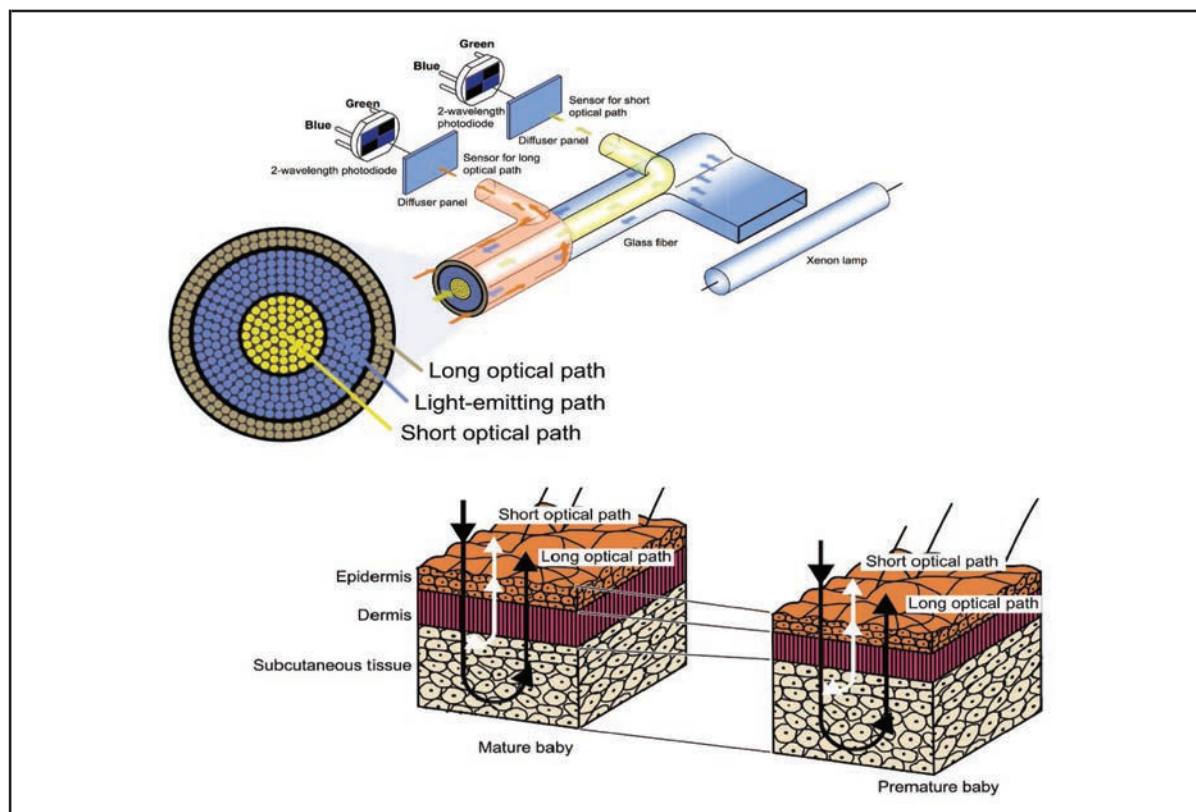


Fig. 3. Measurement principle of JM-103.

The JM-103 determines the yellowness (bilirubin) of the subcutaneous tissue of a neonate by measuring the difference in the optical densities of reflected light at 450 and 550 nm by the newborn skin. With this method, 2 optical paths are incorporated into a measuring probe that minimizes the interference due to melanin or skin maturity. When the light returns to the fiber, it is scattered from shallow areas of subcutaneous tissue and passes through the inner core (short optical path) of the fiber, whereas the light scattered from deep areas of subcutaneous tissue pass through the outer core (long optical path). The reflected light is then collected by photodiodes. Because there is a linear correlation with TSB and the difference in the absorbance, the TSB can be estimated. Reproduced with the permission of Draeger Medical Systems, Inc., Telford, PA.

The Bilitest BB77 (Bertocchi SRL Elettromedicali), a new device for TcB measurements, was compared by Bertini et al. (44) with a standard clinical laboratory TSB method. They found that while the Bilitest correlated well with TSB and may be less expensive than the BiliChek because it does not require additional consumables, it underestimated TSB concentrations ≥ 206 mmol/l (12 mg/dL). Thus a TSB is still required when phototherapy or exchange transfusion is being considered. Recently, a new transcutaneous meter, BiliMed (Medick SA) was evaluated by De Luca et al. (45). Despite the potential practical advantages of BiliMed, such as use of diode technology and no additional disposables, it is less accurate than the BiliChek and was not be recommended for current clinical practice.

Whereas multiple instruments have been studied, only 2, BiliChek and JM-103, are currently cleared by the US Food and Drug Administration for clinical

use in the US. Although these instruments use slightly different methods of measurement and different algorithms, both appear to compare favorably to TSB results and have been recommended for use in the clinical setting (34, 35), although the use of nomograms specific to the TcB meter may be warranted (25).

Cost-Effectiveness of TcB Measurements

Currently, no studies have been published to determine the costs associated with the use of TcB measurements in clinical practice. A number of studies have suggested that the increased cost of TcB measurements is offset by a decreased requirement for serum bilirubin measurements (8, 22, 29). Similarly, Petersen et al. (17) attempted to evaluate the costs associated with TcB by estimating the impact of TcB measurements on hospital charges. Although data about actual costs was

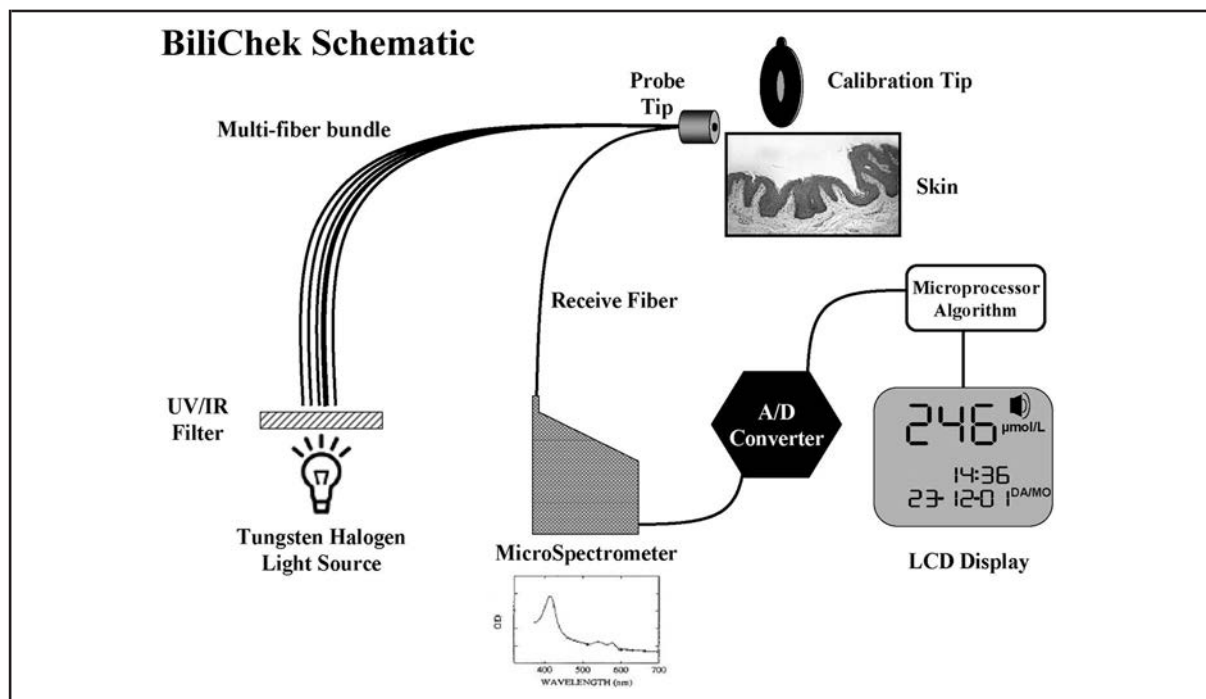


Fig. 4. Measurement principle of BiliChek.

Schematic of the reflection of light emitted by a tungsten halogen lamp by the newborn skin. A proprietary algorithm is used to analyze the collected light. The device measures the bilirubin transcutaneously by using visible light (380–760 nm) reflected by the skin. The light absorption of interfering factors, such as hemoglobin, melanin, and dermal thickness, is mathematically subtracted to estimate the bilirubin concentration in the capillary beds and subcutaneous tissue. IR, infrared; A/D, analog-to-digital; DA/MO, days/months; LCD, liquid crystal display; OD, optical density (A, absorbance). Reproduced with the permission of Philips/Children's Medical Ventures, Monroeville, PA.

not reported, they found that there were decreased charges as a result of fewer readmissions of newborns because of hyperbilirubinemia. However, the decrease in readmissions was offset by increased charges associated with TcB measurements and increased number of newborns treated by phototherapy. The net result was a small but statistically insignificant increase in charges after the introduction of TcB measurements.

Recommendation

Although measurement of TSB remains the gold standard for assessment of neonatal jaundice, TcB is a viable option for universal screening. If screening by TcB indicates that a neonate is at increased risk for clinically significant hyperbilirubinemia, TSB should be measured by the clinical laboratory. It is also important to be aware that TcB appears to underestimate bilirubin concentrations >206–240 μmol/L (12–14 mg/dL) and at the clinician's discretion should be confirmed by the clinical laboratory.

As with any test that is done at the point of care, continuing assessment of the competency of the personnel using the device is extremely important. Because of the absence of commercial proficiency programs, requiring comparisons between simultaneously measured TcB and TSB is a valuable approach to monitor potential shifts in the TcB values (instrument problems) or to identify operators that require additional training.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

- Cabra MA, Whitfield JM. The challenge of preventing neonatal bilirubin encephalopathy: a new nursing protocol in the well newborn nursery. *Proceedings (Bayl Univ Med Cent)* 2005;18:217–9.
- Bhutani VK, Johnson L, Sivieri EM. Predictive ability of predischarge hour specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and new-term newborns. *Pediatrics* 1999;103:6–14.
- Bhutani VK, Gourley GR, Adler S, Kreamer B, Dolin C, Johnson LH. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. *Pediatrics* 2000;106:E17.
- Kaplan M, Hammerman C. Understanding and preventing severe neonatal hyperbilirubinemia; is bilirubin neurotoxicity really a concern in the developed world? *Clin Perinatol* 2004;31:555–75.
- Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Kernicterus threatens healthy newborns. *Sentinel Event Alert* 2001;18:1–2. <http://www.jointcommission.org/Sentinel/Events/Sentinel/EventAlert/sea-18.htm> (Accessed September 2007).
- American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114:297–316.
- Bhutani VK, Maisels MJ, Stark AR, Buonocore G. Management of jaundice and prevention of severe neonatal hyperbilirubinemia in infants ≥ 35 weeks gestation. *Neonatology* 2008;94:63–7.
- Maisels MJ, Kring E. Transcutaneous bilirubin level in the first 96 hours in a normal newborn population of ≥ 35 weeks' gestation. *Pediatrics* 2006;117:1169–73.
- Sanpavat S, Nuchprayoon I, Smathakane C, Hansuebsai R. Nomogram for prediction of the risk of neonatal hyperbilirubinemia, using transcutaneous bilirubin. *J Med Assoc Thai* 2005;88:1187–93.
- De Luca D, Romagnoli C, Tiberi E, Zuppa AA, Zecca E. Skin bilirubin nomogram for the first 96 hours of life in a European normal healthy newborn population, obtained with multiwave length transcutaneous bilirubinometry. *Acta Paediatr* 2008;97:146–50.
- Maisels MJ, Kring E. Length of stay, jaundice, and hospital admission. *Pediatr* 1998;101:995–8.
- Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glick S, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. *Pediatrics* 2004;114:e130–53.
- Maisels MJ, Ostrea EM Jr, Touch S, Clune SE, Cepeda E, Kring E, et al. Evaluation of a new transcutaneous bilirubinometer. *Pediatrics* 2004;113:1628–35.
- Slusher TM, Angyo IA, Bode-Thomas F, Akor F, Pam SD, Adetunji AA, et al. Transcutaneous bilirubin measurements and serum total bilirubin levels in indigenous African infants. *Pediatrics* 2004;113:1636–41.
- Janjindamai W, Tansantiwong T. Accuracy of transcutaneous bilirubinometer estimates using BiliCheck in Thai neonates. *J Med Assoc Thai* 2005;88:187–90.
- Kolman KB, Mathieson KM, Frias C. A comparison of transcutaneous and total serum bilirubin in newborn Hispanic infants at 35 or more weeks of gestation. *J Am Board Fam Med* 2007;20:266–71.
- Petersen JR, Okorodudu AO, Mohammad AA, Fernando A, Shattuck KE. Association of transcutaneous bilirubin testing in hospital with decreased readmission rate for hyperbilirubinemia. *Clin Chem* 2005;51:540–4.
- Madsen LP, Rasmussen MK, Bjerregaard LL, Nohr SB, Ebbesen F. Impact of blood sampling in very preterm infants. *Scand J Clin Lab Invest* 2000;60:125–32.
- Lilien LD, Harris VJ, Ramamurthy RS, Pildes RS. Neonatal osteomyelitis of the calcaneus: complication of heel puncture. *J Paediatr* 1976;88:478–80.
- Tayaba R, Gribetz D, Gribetz I, Holtzman IR. Noninvasive estimation of serum bilirubin. *Pediatrics* 1998;102:e28.
- Stevenson DK, Wong RJ, Vreman HJ, McDonagh AF, Maisels MJ, Lightner DA. NICHD conference on kernicterus: research on prevention of bilirubin-induced brain injury and kernicterus: bench-to-bedside: diagnostic methods and prevention and treatment strategies. *J Perinatol* 2004;24:521–5.
- Maisels MJ. Transcutaneous bilirubinometry. *NeoReviews* 2006;7:e217–25.
- Kaplan M, Shchors I, Algor N, Bromiker R, Schimmel MS, Hammerman C. Visual screening versus transcutaneous bilirubinometry for predischarge jaundice assessment. *Acta Paediatr* 2008;97:759–63.
- Keren R, Luan X, Friedman S, Saddlemire S, Cnnan A, Bhutani VK. A comparison of alternative risk-assessment strategies for predicting significant neonatal hyperbilirubinemia in term and near-term infants. *Pediatrics* 2008;121:e170–9.
- Rodríguez-Capote K, Kim K, Paes B, Turner D, Grey V. Clinical implication of the difference between transcutaneous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinemia. *Clin Biochem* 2009;42:176–9.
- Carceller-Blanchard A, Cousineau J, Delvin EE. Point of care testing: transcutaneous bilirubinometry in neonates. *Clin Biochem* 2009;42:143–9.
- Ebbesen F, Rasmussen LM, Wimberley PD. A new transcutaneous bilirubinometer, BiliCheck, used in the neonatal intensive care unit and the maternity ward. *Acta Paediatr* 2002;91:203–11.
- Tan KL, Dong F. Transcutaneous bilirubinometry during and after phototherapy. *Acta Paediatr* 2003;92:327–31.
- Rubaltelli FF, Gourley GR, Loskamp N, Modi N, Roth-Kleiner AM, Sender A, Vert P. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. *Pediatrics* 2001;107:1264–71.
- Randeberg LL, Roll EB, Nilsen LTN, Christensen T, Svaasand LO. In vivo spectroscopy of jaundiced newborn skin reveals more than a bilirubin index. *Acta Paediatr* 2005;94:65–71.
- Lo S, Doumas BT, Ashwood E. Performance of bilirubin determinations in US laboratories—revisited. *Clin Chem* 2004;50:190–4.
- Kazmierczak SC, Robertson AF, Briley KP. Comparison of hemolysis in blood samples collected using an automatic incision device and a manual lance. *Arch Pediatr Adolesc Med* 2002;156:1072–4.
- Kazmierczak SC, Robertson AF, Briley KP, Kreamer B, Gourley GR. Transcutaneous measurement of bilirubin in newborns: comparison with an automated Jendrassik-Grof procedure and HPLC. *Clin Chem* 2004;50:433–5.
- Nichols JH, Christenson RH, Clarke W, Gronowski A, Hammett-Stabler CA, Jacobs E, et al. Executive summary. The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline: evidence-based practice for point-of-care testing. *Clin Chim Acta* 2007;379:14–28.
- Kazmierczak S, Bhutani V, Gourley G, Kerr S, Lo S, Robertson A, Sena SF. Transcutaneous bilirubin testing. In: *Laboratory medicine practice guideline: evidence-based practice for point-of-care testing*. AACC Press 2007;5–12. <http://www.aacc.org/SiteCollectionDocuments/NACB/LMPG/POCTLMPG.pdf>. (Accessed March 2009).
- Knüpfer M, Pulzer F, Braun L, Heilmann A, Robel-Tillig E, Vogtmann C. Transcutaneous bilirubinometry in preterm infants. *Acta Paediatr* 2001;90:899–903.
- Ozkan H, Oren H, Duman N, Duman M. Dermal bilirubin kinetics during phototherapy in term neonates. *Acta Paediatr* 2003;92:577–81.
- Yamanouchi I, Yamauchi Y. Transcutaneous bilirubinometry: effect of postnatal age. *Acta Paediatr Jpn* 1991;33:663–7.
- Onks D, Silverman L, Robertson A. Effect of melatonin, oxyhemoglobin, and bilirubin on transcutaneous bilirubinometry. *Acta Paediatr* 1993;82:19–21.
- Harbrecht BG, Rosengart MR, Bukauskas K, Zenati MS, Marsh JW Jr, Geller DA. Assessment of transcutaneous bilirubinometry in hospitalized adults. *J Am Coll Surg* 2008;206:1129–36.
- Reyes CA, Stednitz DR, Hahn C, Mutchie KD, McCullough SR, Kronberg K. Evaluation of the BiliCheck being used on hyperbilirubinemic newborns undergoing home phototherapy. *Arch Pathol Lab Med* 2008;132:684–9.
- Leite M, Granto V, Facchini F, Marba S. Comparison of transcutaneous and plasma bilirubin measurements. *J Pediatr (Rio J)* 2007;83:283–6.
- Boo N, Ishak S. Prediction of severe hyperbilirubinemia using the BiliCheck transcutaneous bilirubinometer. *J Paediatr Child Health* 2007;43:297–302.
- Bertini G, Pratesi S, Cosenza E, Dani C. Transcutaneous bilirubin measurement: evaluation of Bilitest. *Neonatology* 2008;93:101–5.
- De Luca D, Zecca E, Corsello M, Tiberi E, Semeraro C, Romagnoli C. Attempt to improve transcutaneous bilirubinometry: a double-blind study of Medick BiliMed versus Respironics BiliCheck. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F135–9.