Hyperbilirubinemia and Transcutaneous Bilirubinometry

Samar N. El-Beshbishi,1 Karen E. Shattuck,2 Amin A. Mohammad,3 and John R. Petersen3*

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.

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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) concentrations >221 μmol/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. 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.
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.

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**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 μmol/L. Reproduced with permission from De Luca et al. (10).
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 μmol/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 requiring phototherapy before discharge, or the number of days of treatment with phototherapy.

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 ≥75th percentile before discharge, which was associated with fewer follow-up blood tests for the evaluation of hyperbilirubinemia than visual assessment 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 ≥95th percentile or those whose TcB is increasing at a rate >3.77 μmol/L (0.22 mg/dL) per hour in the first 24 h, >2.56 μmol/L (0.15 mg/dL) per hour between 24 and 48 h, or >1.03 μmol/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 (Respircons) on a small population of 284 healthy Thai neonates. They found that neonates with a TcB >90th 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...
 bébé a été déclaré de l'hôpital.

Ces mesures, après l'exposition au soleil ou à la lumière ambiante, peuvent être plus désirables, en particulier lorsque les mesures sont prises après que les bébés sont sortis de l'hôpital et que la peau est visible, sans couture, qui est moins exposé à l'ambiance de la peau.

En outre, il a été suggéré que les mesures de TcB peuvent être utilisées sur des bébés plus âgés, bien que TcB peut être utilisé sur des nouveau-nés plus âgés, bien que les mesures de TcB peuvent être utilisées pour des bébés de moins de 10 jours. Cependant, des études préliminaires ont montré une utilisation de TcB parmi les adultes de 10 à 20 jours. Ils ont conclu que le TcB peut être utilisé sur beaucoup plus de nouveau-nés, bien que cette observation nécessite des études confirmatoires supplémentaires. Il faut également être préoccupé avec la peau qui a été couverte lors de la photothérapie. Beaucoup de ces études suggèrent que le TcB peut être utilisé sur des nouveau-nés plus âgés, bien que cette observation nécessite des études confirmatoires supplémentaires. Il faut également être préoccupé avec la peau qui a été couverte lors de la photothérapie.

Récemment, Reyes et al. (41) ont trouvé que les valeurs obtenues pour TcB utilisant BiliChek ont un biais négatif (mean bias: -29 µmol/L ou 1.7 mg/dL; 95% CI: -32 à -26.0 µmol/L) comparé à TSB, particulièrement à des niveaux plus élevés de bilirubine (>205 µmol/L (12 mg/dL)), qui serait attendu pour les nouveau-nés qui ont été évalués pour la photothérapie après le congé en maison. Ils ont conclu que BiliChek ne nous donne pas assez de précision pour surveiller de nouveau-nés à la maison après le congé en Maison. Ce désavantage peut être surmonté par des tests de peau qui ont été couverts lors de la photothérapie. Parce que du biais négatif, cependant, nombre de centres ont indiqué que les TcB valeurs >205–222 µmol/L (12–13 mg/dL) devraient être interprétées avec prudence et être confirmés avec une TSB mesure.

QUALITÉ ASSURANCE CONCERNS

Il est important que le résultat d'un TcB device soit fiable. Récemment, les inter-observateur et inter-device reproducibilités de BiliChek ont été comparées pour les TcB concentrations >137 µmol/L (8 mg/dL) et trouvé pour être 4%–5% et 7%–8%, respectivement (29). Bien que plus élevées que celles des centres hospitaliers, ces reproducibilités doivent être confirmées pour la hyperbilirubinémie. En outre, il est important que le TcB result soit documenté dans le patient’s electronic or written medical record. Curr-
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Fig. 2. Comparison of BiliChek and neonatal bilirubin concentrations (Vitros 950 and 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.

recently 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 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 μmol/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(±0.02)x + 0.6(±0.3) with r = 0.946.

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, Inc.) 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 mmol/L (<14 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 ≥300 μmol/L (17.5 mg/dL). These infants require additional bilirubin monitoring and frequently receive phototherapy.

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 not reported, they found that there were decreased

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.
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 mmol/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.
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