

ORIGINAL ARTICLE

Transcutaneous bilirubin levels in newborns < 35 weeks' gestation

MJ Maisels¹, MP Coffey² and E Kring¹

OBJECTIVE: In infants < 35 weeks' gestation, we sought to define the transcutaneous bilirubin (TcB) levels at which a total serum bilirubin (TSB) level suggesting the need for phototherapy is unlikely to occur and a TSB measurement can, therefore, be avoided.

STUDY DESIGN: Nursing staff performed 896 TcB measurements within 1 h of a TSB on 225 neonates 26 0/7–34 6/7 weeks' postmenstrual age (PMA). Generalized linear models were fit with generalized estimating equations (GEEs) to model the probability of having a TSB level at or above the phototherapy initiation cutpoint as a function of the TcB; these methods allow for multiple tests per infant.

RESULTS: The mean difference between TcB and TSB measurements was < 1 mg dl⁻¹ for each PMA category. When the TcB was at least 3 mg dl⁻¹ below the TSB cutpoint for phototherapy, there was a ≥98% probability that the TSB was not at, or above, the recommended phototherapy level. The single exception to this was a phototherapy level of 6 mg dl⁻¹ for infants of 28 0/7–29 6/7 weeks' PMA, where a TcB of 4 mg dl⁻¹ below the phototherapy level (ie a TcB ≤ 2 mg dl⁻¹) was necessary to achieve ≥98% probability.

CONCLUSION: Our data support the use of routine TcB screening for infants 28–34 6/7 weeks' gestation. TcB screening in the neonatal intensive care unit can identify infants who require a TSB to confirm or exclude the need for phototherapy.

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INTRODUCTION

Multiple studies have documented the relationship between transcutaneous bilirubin (TcB) and total serum bilirubin (TSB) levels and the utility of TcB measurements in the care of term and late preterm infants is now well established.¹ Several studies have also evaluated the relationship between TSB and TcB in preterm infants.^{1,2} In a systematic review of 22 studies, Nagar *et al.*² concluded that '...TcB devices reliably estimated bilirubin levels in preterm infants and could be used in clinical practice to reduce blood sampling' but these authors do not provide specific guidelines for the use of TcB measurements in this population. The primary purpose of screening newborns with TcB measurements is to help the clinician to decide when to obtain a TSB measurement that, in turn, might suggest the need for phototherapy. Using recently recommended levels for initiating phototherapy at different postmenstrual ages, (PMA)³ we sought to define the TcB levels at which a TSB level suggesting the need for phototherapy³ is unlikely to occur and a TSB measurement (and heel stick) can, therefore, be avoided.

METHODS

Between 1 October 2011 and 13 October 2012 the nursing staff in our neonatal intensive care unit (NICU) performed 896 TcB measurements on 225 neonates at 26 0/7–34 6/7 weeks PMA. TcB measurements were obtained from the lower sternum within 1 h of a TSB measurement that had been obtained in the course of routine clinical care. TSB measurements were performed in the hospital clinical laboratory with the Synchron

Diazo method (Beckman Coulter, Fullerton, CA, USA). All TcB measurements were obtained using the Konica Minolta Dräger Air-Shields transcutaneous jaundice meter, model JM-103 (Draeger Medical, Telford, PA, USA). Three independent measurements were obtained, a maximum of the three values was recorded and used as the TcB measurement in this study. TcB measurements were discontinued if phototherapy was instituted. The study was approved by the hospital's Human Investigation Committee and, because of the noninvasive nature of this measurement, the committee approved a waiver of consent.

STATISTICAL METHODS

Because many infants had multiple bilirubin measurements, we estimated means and s.d. of the differences between TcB and TSB using a random effects model with infants as a random effect. We grouped infants by PMA and performed separate analyses for different recommended TSB cutpoint levels for initiation of phototherapy for each PMA group. To include a specific TSB cutpoint, we required at least five TSB readings at or above that cutpoint. Generalized linear models were fit with generalized estimating equations to model the probability of having a TSB level at or above the phototherapy initiation cutpoint as a function of the TcB; these methods allow for multiple tests per infant. Model fit was assessed through plots of cumulative residuals. If the model fit was satisfactory, probabilities and confidence intervals for the probability of TSB levels at or above the cutpoint for a given TcB level were obtained. The SAS System (SAS Institute, Cary, NC, USA) for Windows version 9.3 and StatXact release 10 (Cytel, Cambridge, MA, USA) were used for statistical analysis.

¹Department of Pediatrics, Oakland University William Beaumont School of Medicine, Beaumont Children's Hospital, Royal Oak, MI, USA and ²Department of Biostatistics, William Beaumont Hospital Research Institute, Royal Oak, MI, USA. Correspondence: Dr MJ Maisels, Department of Pediatrics, Oakland University William Beaumont School of Medicine, Beaumont Children's Hospital, Royal Oak 48073-6769, MI, USA.

E-mail: jmaisels@beaumont.edu

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RESULTS

The population consisted of 62% white, 18% African-American, 6% Asian, 4% Hispanic, 10% unknown and 54% male. The infant's age at testing ranged from day 1 to day 29 of the hospital stay. Table 1 shows the data for measurements according to the infants' PMA. Other than in infants < 28 weeks, where we obtained only 15 samples, the correlation between TcB and TSB was good. The Pearson correlation coefficient (r) was 0.85 for the total population and ranged from 0.77–0.83 for each postmenstrual category (Figure 1). The mean difference between TcB and TSB measurements was small, $0.47 \pm 1.55 \text{ mg dl}^{-1}$ (s.d.), and was $< 1 \text{ mg dl}^{-1}$ for each PMA (Table 1). The day-to-day variability in the differences between repeat TcB and TSB measurements in individual infants (using the square root of the one-way ANOVA estimate of variance) was slightly smaller than the s.d. of these measurements between infants in the corresponding PMA groups, ranging from 0.59–1.44 mg dl^{-1} . The s.d. shown in Table 1 incorporate both within infant and between infant variability.

Figure 1 provides linear regression analysis for the total population and for each PMA category. Figure 2 illustrates the effect of increasing TSB on the difference between TcB and TSB. Contrary to our findings in infants of ≥ 35 weeks,⁴ there is a weak and clinically reassuring positive relationship between increasing TSB levels and the difference between TcB and TSB for the total population and most PMA categories. There was no greater tendency for the TcB to underestimate the TSB as TSB levels increase, although, because of the preterm population studied, very few TSB levels were $> 13 \text{ mg dl}^{-1}$ and none were $> 15 \text{ mg dl}^{-1}$ (Tables 1 and 2). Table 2 shows the number of recorded observations (not infants) above each phototherapy level for each PMA group. Figure 3 illustrates that the age of the infant at the time of measurement also had a mild positive but clinically unimportant effect on the difference between TcB and TSB ($r=0.266$). Table 3 shows the probability of having a TSB

level at or above the phototherapy initiation cutpoint as a function of the TcB level and Table 4 provides the data derived from Table 3 but presented in a more user friendly format for the clinician.

DISCUSSION

The primary purpose of TcB measurements is to identify when a TSB should be measured, and when used to screen both term and preterm infants in this manner TcB has been shown to be a reliable and effective tool.^{1,2}

In addition to reducing the need for heel sticks in tiny infants, it is important that screening with TcB should avoid missing a TSB that might indicate the need for phototherapy. To minimize this possibility, we have always used the highest of three independent TcB measurements as the level used for screening purposes and have shown that, compared with the average of three measurements, using the highest value will reduce the number of false negative TcB's by about 50% but increase false positives by a similar amount.⁴ Using the TSB phototherapy levels that have recently been recommended for infants of < 35 weeks of gestation,³ we provide TcB levels that permit screening of infants in the NICU with some degree of confidence while saving the need for a heel stick TSB measurement in many infants. Among all 896 TcB measurements on 225 infants, the TcB was $\geq 3 \text{ mg dl}^{-1}$ below the TSB in only 13 measurements from 11 infants. In only 1 infant could this difference possibly have misled the clinician with regard to the need for phototherapy (a 33 1/7wk PMA infant whose TcB was 7.2 mg dl^{-1} and TSB 10.7 mg dl^{-1}). If we include this single example among the total population of 226 infants, we can calculate a 95% confidence interval of 0.0002–0.023 for the probability of being 'led astray' in an infant by at least one TcB measurement. But if we measure TcB levels daily, both the estimate of the probability and the upper bound of the

Table 1. TcB and TSB values for each postmenstrual age group

Postmenstrual age	n		TcB (mg dl^{-1})	TSB (mg dl^{-1})	TcB-TSB (mg dl^{-1})	Age at testing	
	Samples	Infants				Hours	Days
All < 35 weeks	896	225					
Mean (\pm s.d.)			7.3 ± 2.9	6.9 ± 2.2	0.5 ± 1.6	131 ± 108	5.6 ± 4.5
Median			7.3	6.7	0.4	105	4.2
Range			0–18.6	0.8–14.7	–6.6–6	0.7–692	0.03–18.6
< 28 weeks	15	10					
Mean (\pm s.d.)			4.5 ± 2.1	4.9 ± 0.9	-0.3 ± 1.5	96 ± 93.1	4.0 ± 3.8
Median			4.1	4.9	–0.7	76	3.2
Range			2.3–10.5	3.7–7.2	–2.2–3.3	12.3–322	0.6–13.4
28–29 6/7 weeks	74	33					
Mean (\pm s.d.)			4.6 ± 2.3	4.8 ± 1.4	-0.2 ± 1.4	167 ± 113.2	7.0 ± 4.7
Median			4.7	4.75	–0.2	175	7.3
Range			0–10.2	0.8–7.9	–3.1–4.7	8.0–436	0.33–18.2
30–31 6/7 weeks	184	62					
Mean (\pm s.d.)			6.1 ± 2.3	6.0 ± 1.5	0.2 ± 1.5	147 ± 116	6.1 ± 4.8
Median			6.3	6.1	0.2	128	4.81
Range			0–12.2	1.6–9.5	–5.3–3.6	1.4–492.4	0.06–20.5
32–33 6/7 weeks	299	98					
Mean (\pm s.d.)			7.2 ± 2.4	6.8 ± 1.8	0.4 ± 1.4	154 ± 122.2	6.4 ± 5.1
Median			7.4	6.9	0.3	131	5.48
Range			1.2–13.6	1.5–11.3	–3.5–5.1	0.7–692	0.03–28.8
34–34 6/7 weeks	324	112					
Mean (\pm s.d.)			8.8 ± 2.9	8.0 ± 2.4	0.8 ± 1.7	95 ± 75.6	4.0 ± 3.2
Median			9	8.3	0.8	71	3
Range			2.3–18.6	2.9–14.7	–6.6–6	8.0–426	0.32–17.8

Abbreviations: NICU, neonatal intensive care unit; TcB, transcutaneous bilirubin; TSB, total serum bilirubin. Note: As infants were sampled more than once during their NICU stay, data from one infant can appear in more than one age group. Mean and s.d. estimated using a random effects model.

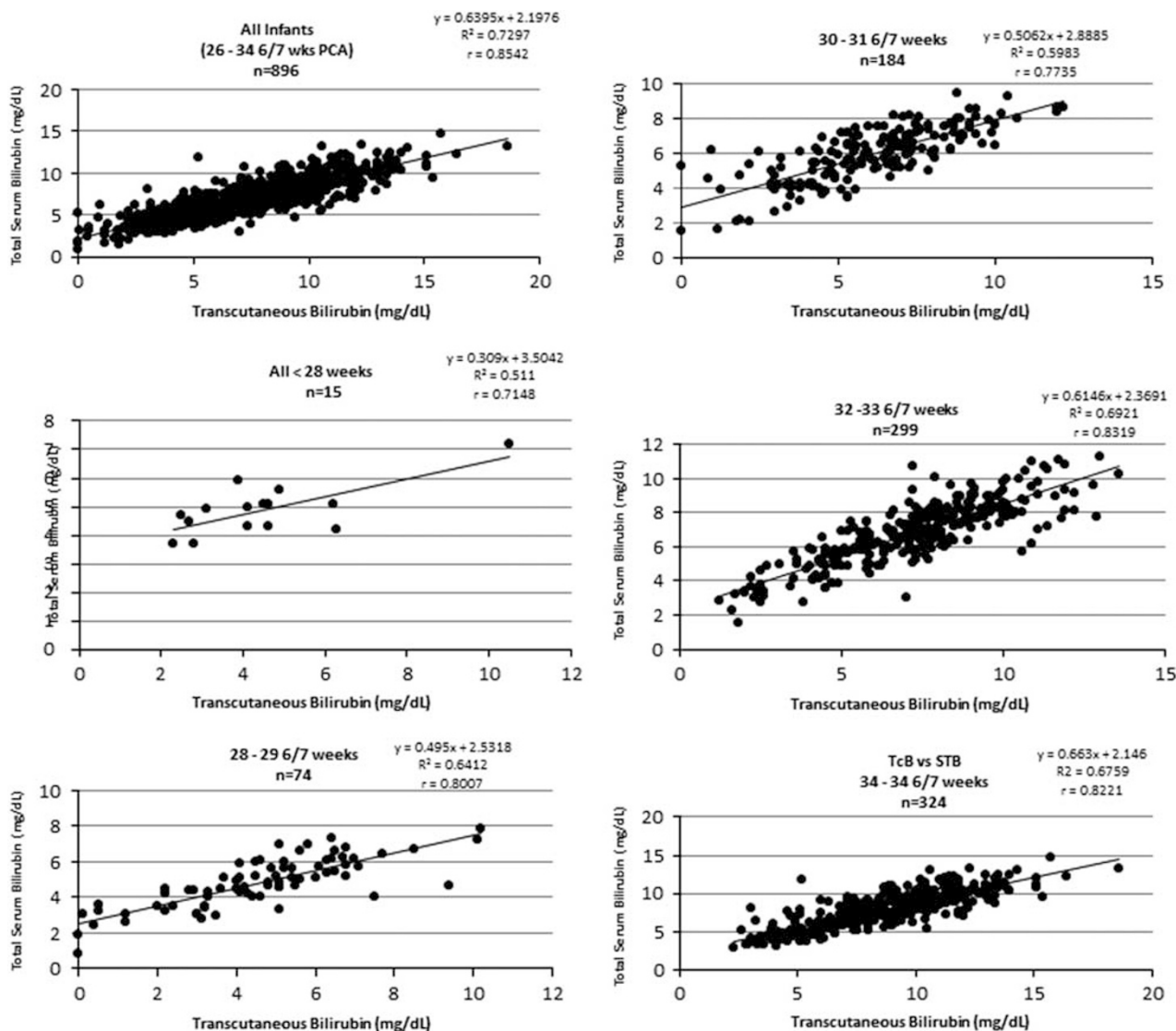


Figure 1. Linear regression plot of JM-103 TcB versus TSB measurements in the total study population and for each postmenstrual age group. TSB, total serum bilirubin.

confidence interval of 2.3/100 are likely an over estimate of the risk of not measuring the TSB in a particular infant who has an elevated TSB. With daily measurements, there is a high probability that if the TSB remains at a level suggesting the need for phototherapy a subsequent TcB measurement within a day or two will identify the need for a TSB measurement and, perhaps, phototherapy. Our data do suggest a useful 'rule of thumb:' when the TcB is at least 3 U below the TSB cutpoint for phototherapy, there is a high probability that the TSB is not at or above the recommended phototherapy level and a heel stick can be avoided. The single exception to this is the phototherapy level of 6 mg dl⁻¹ in the 28 0/7–29 6/7 week PMA category (Table 3) where a TcB of 4 mg dl⁻¹ below the phototherapy level (that is, a TcB ≤ 2 mg dl⁻¹) was necessary to achieve > 98% probability. As only one infant had a TSB that exceeded the upper recommended limits for phototherapy for the PMA group (Table 2), we do not know if this rule of thumb applies to those elevated levels.

Other investigators have studied similar populations in the US and elsewhere and provided TcB values that predicted different TSB levels^{2,5,6} or used a TcB level of 70% of the recommended phototherapy level in that country as the criterion for measuring the TSB.^{7,8} Using these and other cutoffs investigators have,

without exception, documented the clinical utility and acceptable accuracy of TcB measurements and shown that they can reduce blood sampling and spare the need for multiple heel sticks in this fragile population.² TcB measurements in these studies have been obtained from the forehead and sternum. In our first study of infants ≥ 35 weeks with the JM-103 device,⁹ we found a better correlation between TcB and TSB when TcB was measured at the sternum, a finding that has been subsequently confirmed by others.² In a recent study of 24–34 week neonates, however, Yaser *et al.*¹⁰ found that measurements of TcB in the interscapular area provided fewer false negatives than measurements from the forehead or sternum for the prediction of TSB levels that suggested the need for phototherapy.

A strength of our study is the relatively large number of infants studied and the number of TcB levels obtained. In addition, all measurements were made by our regular nursing staff during the course of routine NICU care, rather than by research staff, thus providing data that should have application to other similar units. This is also the first study, to our knowledge, that has examined the effect of chronological age on TcB measurements in a preterm population. Tables 3 and 4 provide, for the first time, confidence intervals for the probability of a TcB predicting a TSB that meets

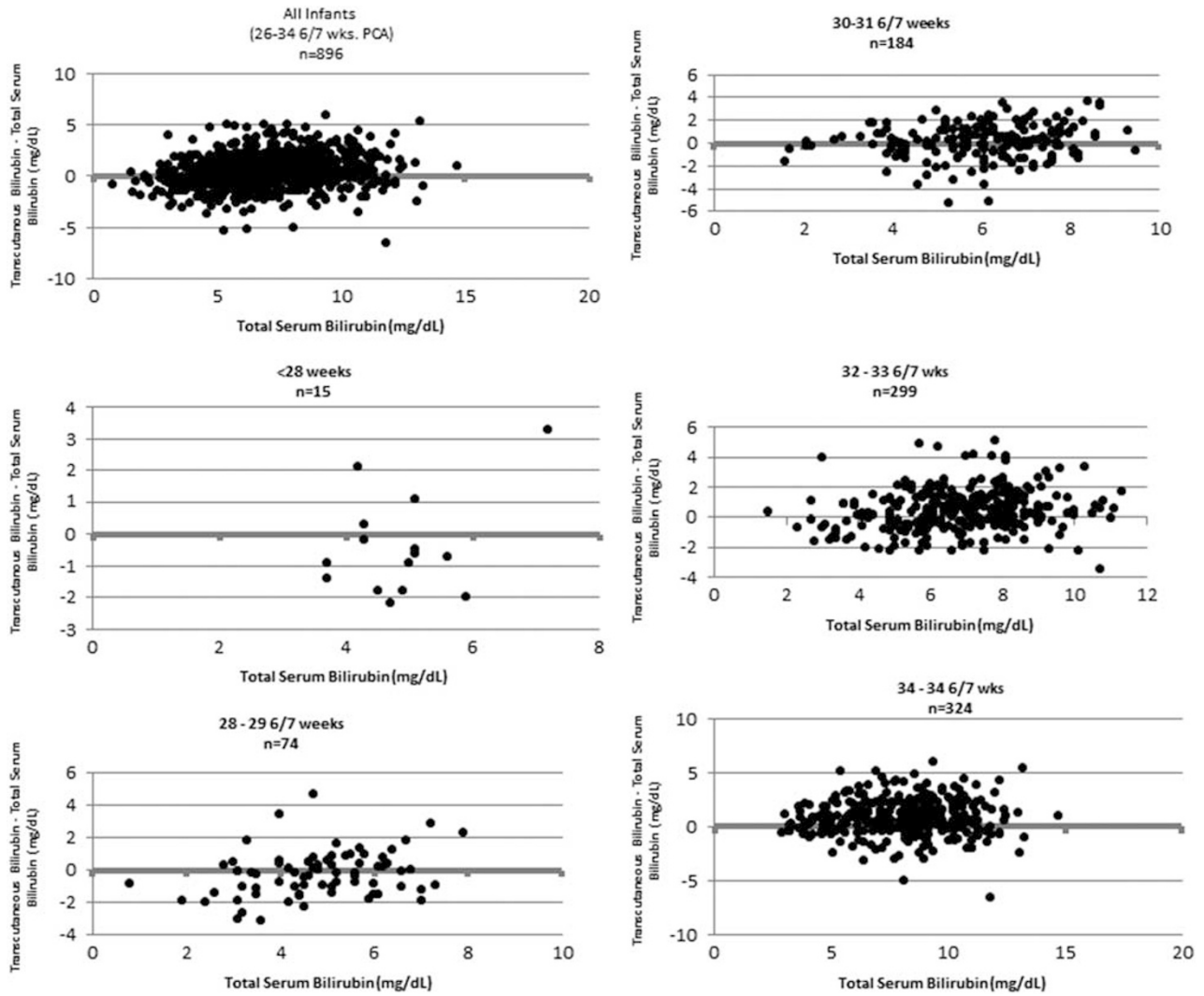


Figure 2. Plot of total serum bilirubin (TSB) versus the difference between the TcB and TSB in the total study population and for each postmenstrual age group. TcB, transcutaneous bilirubin.

Table 2. The number of TSBs (number of observations, not number of infants) above each phototherapy level for each PMA group

Postmenstrual age	TcB/TSB levels (n)	Recommended TSB phototherapy level (mg dl ⁻¹)	Number of observations above phototherapy level
26 0/7–27 6/7	15	6	1
28 0/7–29 6/7	74	6	17
		7	5
		8	0
30 0/7–31 6/7	184	8	17
		9	2
		10	0
32 0/7–33 6/7	299	10	12
		11	3
		12	0
34 0/7–34 6/7	324	12	12
		13	5
		14	1

Abbreviations: TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

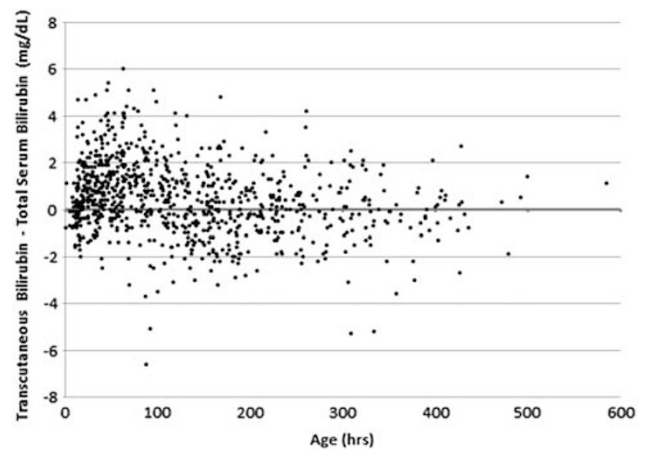


Figure 3. Plot of the infant's chronologic age at the time of measurement versus the difference between the TcB and TSB. TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

Table 3. Probability of having a TSB level at or above the phototherapy initiation cutpoint as a function of the transcutaneous bilirubin level

Postmenstrual age (week)	Infants (n)	TcB/TSB levels (n)	Recommended TSB phototherapy level (mg dl ⁻¹)	TcB (mg dl ⁻¹) ^a	Estimated probability	95% CI for estimated probability
26 0/7–27 6/7	10	15			Insufficient data ^b	
28 0/7–29 6/7	34	74	6	≤2	0.019	0.004, 0.100
				≤3	0.044	0.012, 0.144
				≤4	0.093	0.038, 0.210
			7	≤5	0.188	0.103, 0.318
				≤3	0.009	0.001, 0.070
				≤4	0.018	0.003, 0.096
				≤5	0.036	0.009, 0.134
30 0/7–31 6/7	62	184	8		Insufficient data ^b	
			8	≤5	0.004	0.001, 0.022
				≤6	0.013	0.004, 0.045
				≤7	0.040	0.016, 0.096
32 0/7–33 6/7	102	299	9, 10		Insufficient data ^b	
			10	≤6	0.003	0.001, 0.014
				≤7	0.006	0.002, 0.025
				≤8	0.015	0.005, 0.044
				≤9	0.036	0.016, 0.079
34–34 6/7	114	324	11, 12		Insufficient data ^b	
			12	≤9	0.004	0.001, 0.017
				≤10	0.010	0.003, 0.031
				≤11	0.024	0.010, 0.060
			13	≤10	0.005	0.001, 0.027
				≤11	0.010	0.002, 0.041
				≤12	0.022	0.007, 0.066
			14		Insufficient data ^b	

Abbreviations: CI, confidence interval; TcB, transcutaneous bilirubin; TSB, total serum bilirubin. ^aProbability of TSB ≥ phototherapy level for that postmenstrual age computed at the upper endpoint of the range (probabilities are smaller below the upper endpoint) ^bFewer than five TSB levels at or above the cutpoint(s)

Table 4. TcB cutpoints that provide ≥98–99% probability that the TSB is below the phototherapy level for each PMA category

Postmenstrual age	TcB mg dl ⁻¹	Phototherapy level mg dl ⁻¹	Probability (confidence interval)
28 0/7–29 6/7	≤2	6	98.1 (90.0–99.6)
	≤3	7	99.1 (93.0–99.9)
	≤4	7	98.2 (90.4–99.7)
30 0/7–31 6/7	≤5	8	99.6 (97.8–99.9)
	≤6	8	98.7 (95.5–99.6)
32 0/7–33 0/7	≤7	10	99.4 (97.5–99.8)
	≤8	10	98.5 (95.6–99.5)
34–34 0/7	≤10	12	99.0(96.9–99.7)
	≤10	13	99.5 (97.3–99.9)
	≤11	13	99.0 (95.9–99.8)

Abbreviation: TcB, transcutaneous bilirubin.

criteria for initiating phototherapy according to recently published guidelines,³ and Table 4 shows the probability of avoiding a false negative TcB. A weakness is the potential bias that resulted from the initiation of phototherapy at levels similar to those recommended³ by the neonatologists caring for these infants. As a result, infants with higher TSB levels relative to PMA were already receiving phototherapy and could not be included in the study and this prevented us from calculating the predictive confidence of TcB measurements for the higher range of phototherapy TSB levels.³

CONCLUSION

Routine screening with TcB measurements in a level III NICU can identify infants who do or do not require a TSB to rule in or out the

need for phototherapy and can eliminate the need for many heel stick blood samples. With the single exception of infants with a PMA of 28 0/7–29 6/7 weeks and a phototherapy level of 6–mg dl⁻¹, if the TcB is at least 3 mg dl⁻¹ below the TSB cutpoint for phototherapy, there is a high probability that the TSB is not at or above the recommended phototherapy level. Together with the data already published, our data now provide sufficient information to support the use of routine TcB screening for infants of < 35 weeks but at least of 28 weeks' gestation.

CONFLICT OF INTEREST

Dr. Maisels is an unpaid consultant to Draeger Medical Inc., the US supplier of the JM-103. The other authors declare no conflict of interest.

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