ARTICLE

Bilirubin Measurement for Neonates: Comparison of 9 Frequently Used Methods

Karina Grohmann[a], Markus Roser, MD[b], Boris Rolinski, MD[c], Ingrid Kadow, MD[a], Cornelia Müller, PhD[a], Ada Goerlach-Graw, PhD[d], Matthias Nauck, MD[b], Helmut Küster, MD[a]

[a]Department of Neonatology and Pediatric Intensive Care, University Children's Hospital Greifswald, Greifswald, Germany; [b]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Greifswald, Greifswald, Germany; [c]Institute of Clinical Chemistry, Klinikum Harlaching, Munich Municipal Hospital, München, Germany; [d]Roche Diagnostics GmbH, Mannheim, Germany

Financial Disclosure: Dr Goerlach-Graw is employed by Roche Diagnostics GmbH (Mannheim, Germany).

ABSTRACT

OBJECTIVE. High blood concentrations of bilirubin are toxic to the brain and may cause kernicterus. Therefore, determination of bilirubin levels is performed for many newborns, and several different methods are available. We compared 9 frequently used methods for bilirubin determination among newborns under routine conditions, to define their sequence of use.

METHODS. In a prospective study, bilirubin concentrations were determined with 9 different methods, ie, 3 skin test devices, 3 nonchemical photometric devices (including 2 blood gas analyzers), and 3 laboratory analyzers.

RESULTS. A total of 124 samples were obtained. All 3 laboratory methods showed very strong correlations with each other, and their means were used as comparison values. To these comparison values, the skin test devices had correlation coefficients between 0.961 and 0.966, and the nonchemical photometric devices between 0.980 and 0.994. Bland-Altman plots demonstrated good agreement with the comparison values for all nonchemical photometric devices. All skin test devices and 1 nonchemical photometric device underestimated bilirubin levels, particularly at high concentrations.

CONCLUSIONS. In the routine care of newborns, the first method for bilirubin testing should be a skin test. If the skin test result exceeds 200 μmol/L and other analytes are to be determined with a nonchemical photometric device, then bilirubin can be included in this analysis and the result trusted up to 250 μmol/L. If the skin test result exceeds 200 μmol/L and only bilirubin concentrations are needed, then a standard laboratory method is the first choice, to avoid repeated blood sampling. Bilirubin concentrations from nonchemical photometric devices that exceed 250 μmol/L should be confirmed with standard laboratory methods.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-0590

doi:10.1542/peds.2005-0590

Key Words
bilirubin, hyperbilirubinemia, jaundice, neonatal, blood gas analysis, infant, newborn, diseases

Abbreviations
TcB—transcutaneous bilirubin
TB—total bilirubin
NIST—National Institute of Standards and Technology

Accepted for publication Aug 31, 2005

Address correspondence to Helmut Küster, MD, Department of Neonatology and Pediatric Intensive Care, University Children's Hospital, Soldmannstrasse 15, D-17475 Greifswald, Germany. E-mail: kuester@uni-greifswald.de

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

JAUNDICE IS A common condition among neonates, caused by the combination of increased heme catabolism and physiologic immaturity of the liver in bilirubin conjugation and excretion.[1] For most healthy term newborns, unconjugated bilirubin levels increase above 170 μmol/L (10 mg/dL) between the third and sixth days of life and decrease in the following days. Greater and more prolonged increases in bilirubin levels can be caused by hemolytic disorders (ABO or Rh factor incompatibility), glucose-6-phosphate dehydrogenase deficiency, or birth trauma.[2] Clinically relevant hyperbilirubinemia is also seen among breastfed or premature newborns.[3]

High concentrations of bilirubin are toxic to the brain and may cause a specific type of bilirubin-related encephalopathy called kernicterus. This problem has been reemerging in recent years because of an increase in the number of healthy term newborns who receive less professional medical care during their first week of life, ie, those discharged early from the hospital or born at home.[4] However, hyperbilirubinemia can be treated easily and with minimal adverse effects with phototherapy.[5]

Therefore, determination of bilirubin levels is performed for many newborns. The devices used for this purpose can essentially be grouped as (1) hand-held point-of-care devices for noninvasive reading of the skin to measure transcutaneous bilirubin (TcB) levels, (2) devices for nonchemical photometric measurement in blood samples (eg, blood gas analyzer), and (3) laboratory analyzers for photometric measurement of total bilirubin (TB) levels in serum or plasma after a chemical reaction.

A number of different methods are available for each of these 3 principal groups. Multiple investigations analyzing accuracy in bilirubin measurements with these different devices have been conducted. However, those studies usually compared only 2 or 3 devices. In addition, even routine laboratory methods for the determination of serum TB levels differ markedly.[6] On the basis of these studies, it is difficult for physicians to decide which method should be used to determine bilirubin levels and, more importantly, how to interpret the results obtained. As a consequence, frequently hospitals develop their own guidelines, but these vary substantially. Therefore, we compared 9 frequently used methods for bilirubin determination for newborns, under routine conditions, to define their sequence of use.

METHODS

Patients

The study was conducted between July 2003 and February 2004 at the Women's Hospital, University of Greifswald (Greifswald, Germany). Neonates were eligible with a gestational age of ≥32 weeks and a birth weight of ≥1500 g. Infants receiving phototherapy before blood sampling were excluded. For each infant, bilirubin concentrations were determined with 9 different devices, ie, 3 skin test devices, 3 nonchemical photometric devices, and 3 laboratory analyzers. Skin testing and blood sampling for bilirubin determinations were performed simultaneously, at the time of routine metabolic screening or if there was a clinical indication for bilirubin determination. A maximum of 1 blood sample per day and a total of 3 on consecutive days could be obtained from each individual newborn. The study was conducted according to good clinical practice guidelines and was approved by the local ethics committee. Written informed consent was obtained from the parents.

Instruments

Skin Test Devices

Bilirubin measurements were performed at the lower end of the sternum. Bilirubin concentrations were estimated by measuring the optical density of the skin at certain wavelengths. In our study, we used 3 TcB devices. To reduce variability, only 1 instrument per device type was used throughout the study period. The Biliblitz JM-102 device (Minolta, Bad Ems, Germany) gives its result as an arbitrary number; the instrument must be calibrated by the user. In our study, we retrospectively transformed the arbitrary numbers (range: 6.9–24.6; mean: 15.9) into bilirubin concentrations by using our comparison (Passing-Bablok regression analysis; TB [μmol/L] = 20.2 · [JM-102 reading] – 167.02). The Biliblitz JM-103 device (Minolta) represents an improvement by presenting the bilirubin result in micromoles per liter or milligrams per deciliter. With the BiliCheck analyzer (Medela, Eching, Germany), 5 replicate measurements must be performed to obtain a single result, given as the mean bilirubin concentration in micromoles per liter or milligrams per deciliter.

Nonchemical Photometric Devices

Twin Beam (Ginevri, Rome, Italy), ABL 735 (Radiometer, Copenhagen, Denmark), and Roche OMNI S (Roche Diagnostics, Graz, Austria) analyzers were developed to measure TB levels, with minimal blood volumes, at the point of patient care. The Twin Beam analyzer (Twin Beam Plus version) measures bilirubin levels in plasma at 455 nm and 575 nm. This necessitates centrifugation of the blood sample. The ABL 735 analyzer (software version V3.811) is a blood gas analyzer with a cooximetry module. Bilirubin levels are measured spectrophotometrically at 128 reading points between 478 nm and 672 nm, in addition to the other cooximetry parameters. The Roche OMNI S analyzer (software version 1.01–31) is also a blood gas analyzer with cooximetry. Bilirubin levels are measured at 512 reading points between 460 nm and 660 nm. The ABL 735 and Roche OMNI S analyzers both hemolyze the blood sample ultrasonically within the cooximetry module before measurement.

Laboratory Analyzers

Hitachi 912 (Roche Diagnostics), Dimension RxL (Dade Behring, Schwalbach, Germany), and Vitros 250 (Ortho Clinical Diagnostics, Neckargemünd, Germany) analyzers are clinical chemical analyzers used in core laboratories. The methods for determination of TB levels for the Hitachi 912 and Dimension RxL analyzers are diazo methods; the method for the Vitros analyzer is a direct spectrophotometric assay.

Results obtained from measurements of patients samples were used only if quality control results for the device on that day were in the declared range. Table 1 presents the principles of bilirubin measurement for all devices used.

Method Comparison

With the Biliblitz JM-102 and JM-103, 2 measurements were performed at the lower end of the sternum and the mean was obtained. With the BiliCheck, 1 (fivefold) determination was performed at the same site. For the other 6 devices, venous blood samples were obtained in 2 lithium heparin-containing microcontainers (Becton Dickinson, Heidelberg, Germany), 1 for measurements at the Children's Hospital (ABL 735 and Twin Beam) and 1 for measurements at the central laboratory (Hitachi 912, Dimension RxL, and Vitros 250). During the course of the study (October 2003), the Roche OMNI S analyzer was moved from the Women's Hospital to the Institute of Clinical Chemistry and Laboratory Medicine (Roche OMNI S at the Women's Hospital versus comparison: $y = 1.075x + 1.416$ μmol/L; $r = 0.979$; Roche OMNI S at the Institute of Clinical Chemistry and Laboratory Medicine versus comparison: $y = 1.013x - 1.818$ μmol/L; $r = 0.985$). After blood sampling, the heparin-containing microcontainers were immediately protected from light. All determinations were performed on the same day except for 11 performed with the ABL 735 and Twin Beam with delays of up to 4 days. These samples were stored protected from light.

The Vitros 250 was available on site only until September 2003. Therefore, in addition to the 29 determinations performed up to that time, bilirubin levels were measured for all samples with the identical instrument at the hospital in Prerow, Germany, in April 2004. The determinations were performed with remaining plasma that had been stored at −70°C. The difference between measurements in Greifswald and in Prerow with the Vitros 250 was within the range observed for the 3 central laboratory methods ($y = 0.967x - 0.367$ μmol/L; $n = 29$).

In our study, we used premarketing software on the Roche OMNI S analyzer (version 1.01-31). With the marketed software, results are given only for whole-blood samples with bilirubin concentrations of >51 μmol/L (>3 mg/dL).

Analytical Performance

To investigate accuracy, quality controls were prepared from certified reference material SRM 916a (98.3 ± 0.3% unconjugated bilirubin), obtained from the National Institute of Standards and Technology (NIST) (Gaithersburg, MD). Quality controls were prepared at 4 different levels (NIST levels of 0, 34, 170, and 340 μmol/L) in modified Tris buffer or in human fresh frozen plasma, as described,[7] and were immediately stored at −70°C until needed. These quality controls were also used to assess within-run imprecision (21 repetitions each at 0, 34, 170, and 340 μmol/L) and day-to-day imprecision (21 days for each of the 4 levels), according to National Committee for Clinical Laboratory Standards guidelines. In addition, NIST reference material in plasma was mixed with washed erythrocytes from umbilical cord blood and used for within-run (4 repetitions for each level with all devices) and day-to-day (16 days for each level with ABL 735 and Roche OMNI S) imprecision assessments. Linearity assessments were performed with duplicate measurements for samples at 13 levels from 0 to 340 μmol/L. In addition to these measurements, daily quality control procedures were performed for all instruments according to manufacturers' instructions.

TABLE 1 Devices Investigated, Principles of Measurement, Sample Type and Volume Needed, and Number of Samples Analyzed

Device	Principle of Measurement	Sample Volume/ Sample Type	No. of Samples
Biliblitz JM-102	Optical density of the skin at 2 wavelengths		120
Biliblitz JM-103	Optical density of the skin at 2 wavelengths		121
BiliCheck	Optical density of the skin at multiple wavelengths		122
Roche OMNI S	Multiple-wavelength photometry with whole blood	60–100 μL[a]/whole blood	109
ABL 735	Multiple-wavelength photometry with whole blood	35–95 μL[a]/whole blood	113
Twin Beam	Dual-wavelength photometry with plasma at 455/575 nm	60 μL/centrifuged blood	110
Hitachi 912	2,5-Dichlorophenyl-diazonate (DPD)	50 + 7 μL[b]/serum or plasma	122
Dimension RxL	Modified Jendrassik-Grof reaction	50 + 28 μL[b]/serum or plasma	123
Vitros 250	TB (slide of newborn bilirubin), dry chemistry/spectrophotometry	35 + 10 μL[b]/serum or plasma	118

[a] Range of sample volumes (minimum to maximum), depending on the number of analytes.

[b] Dead space volume plus volume needed for analysis.

Statistical Analyses

Data were analyzed with Microsoft Excel 2000 (Microsoft, Redmond, WA) and MedCalc (version 4.31.010) software (MedCalc Software, Mariakerke, Belgium), with Passing-Bablok regression analyses, Bland-Altman plots, and receiver operating characteristic curves.[8]

RESULTS

A total of 124 samples were obtained from 122 term or near-term infants (58 male and 64 female infants). All infants were white, with a mean gestational age of 39 weeks (range: 35–42 weeks). The mean birth weight was 3433 g (range: 2260–4510 g), and the mean age at the time of blood sampling was 3 days (range: 0–8 days). None of the infants had sepsis, respiratory distress, or cardiac or circulatory disease. Plasma bilirubin concentrations for these patients were between 9 and 388 μmol/L. Nine neonates (7%) had concentrations above 257 μmol/L (15 mg/dL).

The 3 laboratory methods met the expectations with respect to imprecision (<5%) and accuracy (<5%) with quality control material, as described above. In addition, we used 1 control serum sample from an independent manufacturer for the 3 laboratory analyzers, ie, Hitachi 912, Dimension RxL, and Vitros 250, with declared target values of 358.5, 377.5, and 335.0 μmol/L, respectively. For these 3 instruments, the means of the daily serum bilirubin determinations were 341.3 μmol/L (Hitachi 912), 349.3 μmol/L (Dimension RxL), and 337.2 μmol/L (Vitros 250).

The measurements of patient samples with the 3 standard laboratory analyzers correlated strongly with each other (Hitachi 912 versus Dimension RxL: $y = 1.019x + 3.254$ μmol/L; $r = 0.994$; Dimension RxL versus Vitros 250: $y = 0.943x - 2.629$ μmol/L; $r = 0.994$; Vitros 250 versus Hitachi 912: $y = 1.045x - 1.516$ μmol/L; $r = 0.993$ μmol/L). Therefore, and because no standard test for bilirubin determination is available, we used the mean of the Hitachi 912, Dimension RxL, and Vitros 250 measurements for comparisons with the other 6 devices. This mean is referred to as our comparison value. Results from all 3 instruments were available for all except 9 samples, for which only 2 measurements were performed.

Passing-Bablok regression analyses gave correlation coefficients for the comparison of 0.961 to 0.966 for the 3 skin test devices, of which the BiliCheck had the best result. Higher correlation coefficients were seen for all 3 nonchemical photometric devices ($r = 0.980–0.994$); of these, the Twin Beam had the best correlation coefficient (Table 2).

As shown in Fig 1, Bland-Altman plots demonstrated good agreement with the comparison values for all nonchemical photometric instruments. Slopes of the regression lines were close to 1.0 for all methods tested. Details are given in Table 2. However, all skin test devices underestimated bilirubin levels at higher concentrations. Within ±34 μmol/L (±2 mg/dL) of the comparison value were 87.5% of readings with the JM-102, 84.3% with the JM-103, and 86.9% with the BiliCheck. The maximal difference from the comparison value was −58 μmol/L (−3.4 mg/dL) for the JM-102, −55 μmol/L (−3.2 mg/dL) for the JM-103, and −39 μmol/L (−2.3 mg/dL) for the BiliCheck. These differences were found at bilirubin concentrations above 200 μmol/L (11.7 mg/dL). The Roche OMNI S overestimated TB levels by, on average, 8 μmol/L (0.5 mg/dL). The ABL 735 and the Twin Beam underestimated levels by, on average, −17 μmol/L (−1 mg/dL) (Fig 1). Within ±34 μmol/L (±2 mg/dL) of the comparison value were 89.9% of readings with the Roche OMNI S, 90.3% with the ABL 735, and 100% with the Twin Beam. The maximal difference from the comparison value was −30 μmol/L (−1.8 mg/dL) for the Roche OMNI S, −65 μmol/L (−3.8 mg/dL) for the ABL 735, and −34 μmol/L (−2.0 mg/dL) for the Twin Beam. The Twin Beam showed excellent agreement with the comparison values up to 250 μmol/L (14.6 mg/dL). However, at readings above this value, the instrument noticeably underestimated bilirubin levels, although only a few values above this threshold were seen in the study population.

In clinical practice, the most important objective is not to miss even a single infant with high bilirubin concentrations that necessitate therapeutic intervention. Therefore, the highest cutoff value that resulted in 100% sensitivity for detecting significant hyperbilirubinemia with the individual device was determined for 2 different bilirubin concentrations (222 μmol/L and 257

TABLE 2 **Passing-Bablok Regression Analysis**

Device	Range, μmol/L	Mean, μmol/L	SD, μmol/L	*r*	Slope	Slope, 95% CI	Intercept, μmol/L	Intercept, 95% CI, μmol/L
JM-102, calibrated[a]	−28 to 330	154.2	80.2	0.962	1.038	0.978–1.101	−6.391	−14.055 to +2.608
JM-103	0 to 343	143.2	76.4	0.961	0.989	0.936–1.049	−10.310	−18.419 to −1.578
BiliCheck	7 to 324	161.0	71.8	0.966	0.947	0.904–0.992	+16.088	+9.940 to +22.471
Roche OMNI S	17 to 389	159.8	82.5	0.980	1.028	0.993–1.071	+1.614	−3.080 to +4.960
ABL 735	0 to 399	136.4	81.5	0.987	1.007	0.974–1.038	−17.204	−21.767 to −11.631
Twin Beam	1 to 359	135.7	77.6	0.994	0.969	0.949–0.989	−12.688	−16.295 to −9.922

CI indicates confidence interval.

[a] The arbitrary numbers given by the JM-102 were transformed into bilirubin concentrations through regression analysis, as described in the Methods section.

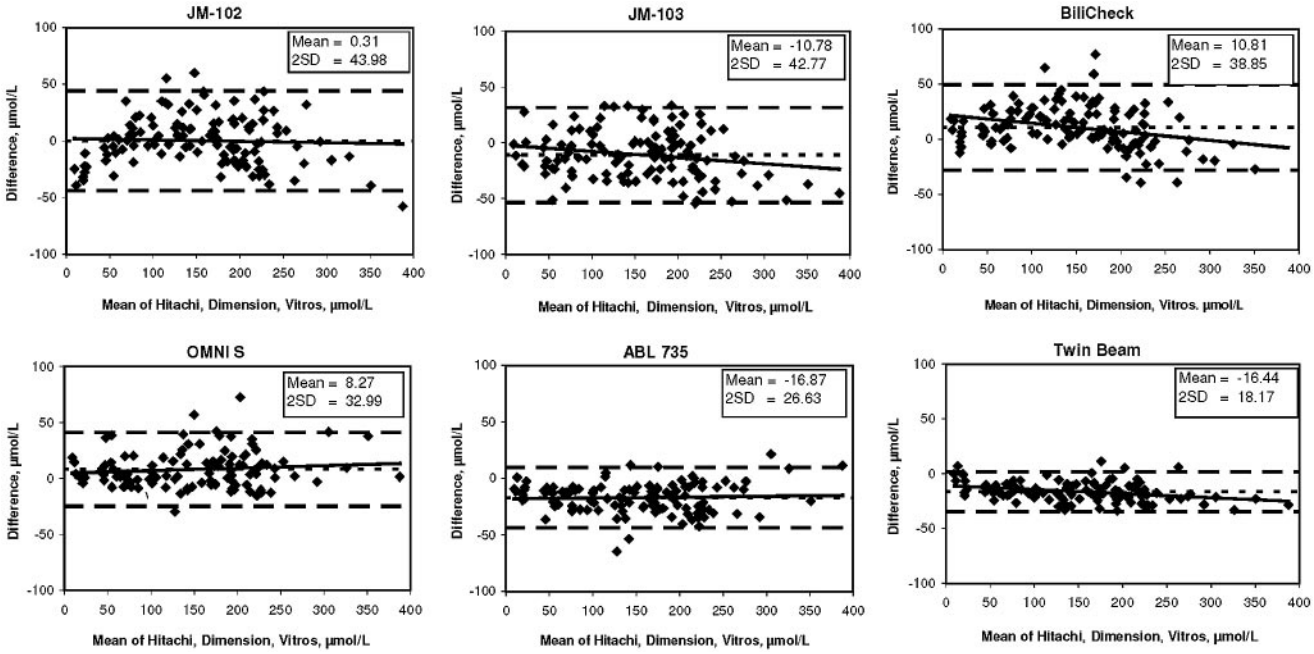

FIGURE 1

Bland-Altman plots comparing the results of the devices with the comparison values. The difference (device − comparison) values are plotted against the comparison values (mean of Hitachi 912, Dimension RxL, and Vitros 250 values). The lines drawn represent trend (solid line), mean difference (short dashes), and mean difference ± 2 SD of the difference (long dashes).

µmol/L) (Table 3 and Figs 2 and 3). Of the 3 skin test devices, the JM-102 had the highest TcB value that resulted in 100% sensitivity; if the JM-102 gave a bilirubin value of <190 µmol/L (<11.1 mg/dL), then no infant had a TB level of ≥222 µmol/L (≥13 mg/dL). Among the nonchemical photometric devices, the Roche OMNI S analyzer had the highest bilirubin value at both concentrations.

For the imprecision measurements in human plasma (within-run and day-to-day measurements), all coefficients of variation were <5%, with the exception of the 3 nonchemical photometric devices at NIST level 34. Details are presented in Table 4. It is notable that the Twin Beam measured NIST level 340 in human plasma remarkably lower, in comparison with all other devices; a deviation of −134 µmol/L (−7.8 mg/dL; −33%) was seen. All devices showed a high degree of linearity except for the Twin Beam at bilirubin levels of >135 µmol/L (>8 mg/dL). For imprecision measurements in modified Tris buffer, all coefficients of variation were <5% except for the Twin Beam at NIST level 34, for day-to-day and within-run measurements (data not shown).

DISCUSSION

Determination of serum TB levels is one of the most frequently performed laboratory tests for neonates. However, this procedure is painful, may even cause osteomyelitis if performed through heel stick, and is time and cost consuming.[9] In addition, it leads to stress for

TABLE 3 **Bilirubin Concentration That Results in 100% Sensitivity and Corresponding Specificity, Positive Predictive Value, and Area Under the Receiver Operating Characteristic Curve for Each of the Skin Test and Nonchemical Photometric Devices**

	JM-102, Calibrated	JM-103	BiliCheck	Roche OMNI S	ABL 735	Twin Beam
Cutoff value of 222 µmol/L (13 mg/dL)						
Sensitivity of 100% at level, µmol/L	190	170	180	205	179	194
Specificity, %	81	70	64	82	85	90
PPV, %	53	41	34	50	59	67
Area under the curve	0.963	0.949	0.961	0.946	0.978	0.978
Cutoff value of 257 µmol/L (15 mg/dL)						
Sensitivity of 100% at level, µmol/L	224	209	222	252	223	230
Specificity, %	91	90	89	98	98	100
PPV, %	47	45	38	75	82	100
Area under the curve	0.982	0.983	0.980	0.998	0.998	1.000

PPV indicates positive predictive value The negative predictive value was 100% for all devices.

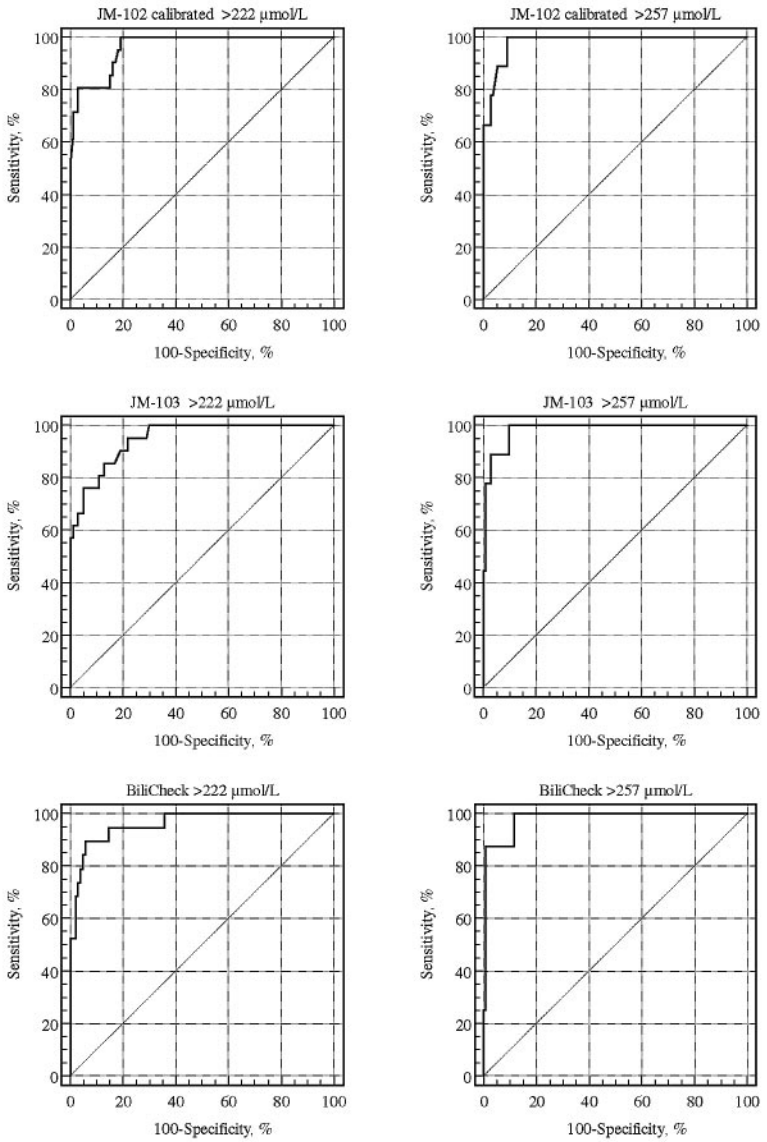

FIGURE 2
Receiver operating characteristic curves for the JM-102, JM-103, and BiliCheck at 222 μmol/L (13 mg/dL) and 257 μmol/L (15 mg/dL).

both the infant and the parents. Therefore, it is important to reduce the number of blood samples taken, as much as possible. As a consequence, a number of devices for noninvasive bilirubin determination have been developed in the past 25 years.

In 1980, Minolta/Air Shields presented a jaundice meter for noninvasive bilirubin measurements.[10] This device and its successor (JM-102) were studied extensively[11–15] and were found to have 2 major disadvantages, ie, the instrument must be calibrated by the user to convert the results given as arbitrary numbers into serum bilirubin concentrations, and readings are affected by the race and age of the infant.[16]

The JM-103 and the BiliCheck are improved devices for measuring TcB levels without an influence of skin pigmentation.[14,15,17–19] Several studies demonstrated that these skin test devices were useful in screening neonates for hyperbilirubinemia but could not replace TB measurements because of insufficient accuracy in predicting serum bilirubin concentrations.[13,20–23] However, with the use of TcB devices, blood sampling can be avoided for 66 to 80 of 100 infants.[22,24,25]

In our study, all 3 skin test devices showed good correlation with our comparison values, with the BiliCheck having the best agreement. According to the literature, skin test devices tend to underestimate bilirubin concentrations.[15,18–21,23,24] This underestimation is pronounced at high bilirubin concentrations.[20,23] Mean differences reported were up to -11.6 μmol/L for the JM-102, up to -3.3 μmol/L for the JM-103, and up to -30 μmol/L for the BiliCheck.[15,18,19,21,24] Our study found identical underestimations for the JM-102 and JM-103

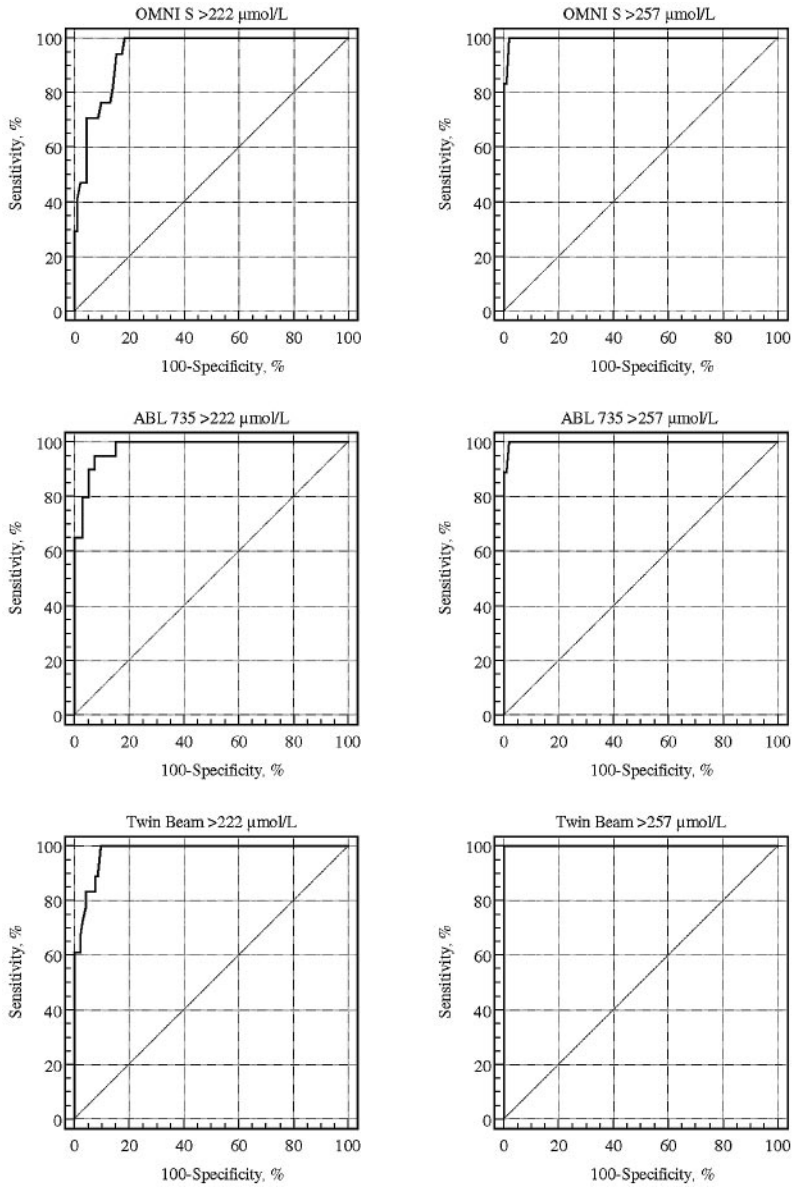

FIGURE 3
Receiver operating characteristic curves for the Roche OMNI S, ABL 735, and Twin Beam at 222 μmol/L (13 mg/dL) and 257 μmol/L (15 mg/dL).

but a slight overestimation by the BiliCheck (on average, +8.3 μmol/L). At the clinically most relevant high bilirubin concentrations above 200 to 250 μmol/L (11.7–14.6 mg/dL), all skin test devices underestimated levels, with maximal differences between −39 and −58 μmol/L (between −2.3 and −3.4 mg/dL). These results mark the limitations of these devices.

For physicians caring for neonates, it is essential to know the TcB values up to which they can trust the skin test device and avoid TB measurements without missing an infant in need of therapeutic intervention. Therefore, for clinical purposes, it is important to define a cutoff value describing the highest measurement result at which each device identifies correctly all infants with levels above a defined bilirubin concentration. For 257 μmol/L (15 mg/dL) TB, according to our comparison, these cutoff values were between 209 and 224 μmol/L (between 12.2 and 13.1 mg/dL) for the different devices. Results up to these values need not be confirmed with a laboratory test. Among the skin test devices, the JM-102 had the highest cutoff value. If no blood tests were performed below this cutoff value, then 93% of blood sampling could have been avoided for our study population. The BiliCheck had an almost identical cutoff value and the JM-103 a lower one, up to which these devices identified correctly all infants with levels of >257 μmol/L (>15 mg/dL). With those cutoff values, again 93% of blood sampling could have been avoided.

With the development of blood gas analyzers, near-patient bilirubin determinations from blood samples became available. These devices are popular because

TABLE 4 **Results of Imprecision Measurements in Plasma**

Device	NIST Level, μmol/L	Coefficient of Variation, %			
		Within-Run	Within-Run (Ery)	Day-to-Day	Day-to-Day (Ery)
Roche OMNI S	34	1.76	2.93	1.70	8.38
	170	0.49	0.54	1.29	2.49
	340	0.61	0.41	1.05	2.64
ABL 735	34	6.09	5.10	5.64	13.24
	170	0.98	0.30	1.64	3.15
	340	0.91	0.24	0.94	2.75
Twin Beam	34	6.41	12.09	7.84	ND
	170	1.92	1.96	2.65	ND
	340	0.78	0.85	2.08	ND
Hitachi 912	34	1.65	1.27	2.42	ND
	170	0.72	0.91	1.35	ND
	340	0.72	0.71	0.77	ND
Dimension RxL	34	0.41	0.15	1.34	ND
	170	0.68	0.38	0.84	ND
	340	0.44	0.46	0.71	ND
Vitros 250	34	1.69	ND	ND	ND
	170	1.00	ND	ND	ND
	340	0.55	ND	ND	ND

Because the Vitros 250 was not available throughout the whole study, precision testing of standards in plasma for this device could not be completed. There were only 4 repetitions of each level for within-run measurements and only 1 within-run measurement with erythrocytes. Within-run (Ery) indicates within-run measurements with washed erythrocytes from umbilical cord blood; day-to-day (Ery), day-to-day measurements with washed erythrocytes from umbilical cord blood; ND, not done.

multiple other clinically important analytes, such as pH, sodium levels, and calcium levels, can be determined from the same blood sample. Results are provided quickly, and the amount of blood needed is small.[26] Transport to the laboratory is no longer necessary. However, costs are usually higher and quality assurance is more difficult to control than with laboratory methods.

In our study, we used 2 different blood gas analyzers, the ABL 735 analyzer and the newly developed Roche OMNI S analyzer, which measure bilirubin levels through multiple-wavelength photometry. The Twin Beam is a bilirubinometer that measures bilirubin levels quickly and at almost no cost. As a disadvantage of this device, the sample must be centrifuged before measurement of bilirubin levels; if this is performed in a capillary tube, however, then both hematocrit and bilirubin can be measured from the same sample.

Results from all 3 nonchemical photometric devices correlated well with TB values. The Twin Beam had the highest correlation coefficient, but the device tended to underestimate bilirubin levels, particularly at high concentrations. This underestimation was especially evident in all imprecision measurements. In contrast to other authors who reported correlation coefficients of 0.76 and 0.95 for ABL 735 measurements versus TB values,[27,28] we found a higher correlation coefficient (0.987). This could be attributable to newer software implemented since those studies were performed. These software changes might also be the cause of the underestimation by, on average, −17 μmol/L (−1 mg/dL) seen in our study, compared with −3.5 μmol/L (−0.2 mg/dL) found previously.[27]

For the 3 nonchemical photometric devices also, we determined cutoff values above which blood samples should be sent to the laboratory in order not to miss an infant in need of therapeutic intervention. In our study, the Roche OMNI S analyzer had the highest cutoff value up to which all neonates were identified correctly. If no blood samples up to this cutoff value had been sent to the laboratory, then 95% of blood sample transports could have been avoided for our study population. The ABL 735 and the Twin Beam identified correctly all infants at lower cutoff values. With those cutoff values, 92% of blood sample transports could have been avoided.

Results from all 3 laboratory methods used in our study had extremely strong correlations with each other. Therefore, their mean was considered to be close to the "true" bilirubin concentration and served as a comparison value, because a true standard test for bilirubin determination has not been established. Only a proposed reference method has been published; it is neither used frequently nor accepted widely, because of its requirement for a manual procedure.[7]

Subjects in our study were white term infants. Also, bilirubin measurements were performed on the third day of life, on average. Therefore, our conclusions should be used with care for low birth weight or preterm infants, and those concerning the skin test devices might not be appropriate for nonwhite or older infants. Only

7% of our samples had bilirubin concentrations of >257 μmol/L (>15 mg/dL). Additional research should be conducted, particularly for patients with high bilirubin levels.

CONCLUSIONS

The 3 skin test devices, BiliCheck, JM-102, and JM-103, can be used as screening tools not only in the hospital but also in outpatient settings. They can help to reduce the number of blood samples taken. However, it should be noted that the JM-102 is affected by skin pigmentation, whereas the JM-103 and the BiliCheck were shown not to be influenced. The skin test devices do not replace TB measurements because of their inaccuracy and underestimation of bilirubin levels, particularly at clinically relevant high bilirubin concentrations.

Nonchemical photometric devices give more-accurate information on bilirubin concentrations than do skin test devices, but a blood sample is necessary. Among the nonchemical photometric devices, the Twin Beam presented the best results. However, readings above 250 μmol/L should be interpreted with care, because of the observed underestimation at high concentrations. Although the analysis itself is inexpensive with the Twin Beam, the requirement for sample preparation makes blood gas analyzers a more convenient choice. Their readings can be trusted up to 250 μmol/L, and they are the first choice, especially if blood gas analysis is indicated for other reasons. If skin test results exceed 200 μmol/L and only bilirubin concentrations are needed, then standard laboratory methods are the first choice, to avoid repeated blood sampling. Bilirubin concentration results from blood gas analyzers that exceed 250 μmol/L should be confirmed with standard laboratory methods.

ACKNOWLEDGMENTS

The study was supported in part by Roche Diagnostics (Mannheim, Germany).

We thank Dade Behring (Schwalbach, Germany), Ginevri (Rome, Italy), Medela (Eching, Germany), Minolta (Bad Ems, Germany), Ortho Clinical Diagnostics (Neckargemünd, Germany), and Radiometer (Copenhagen, Denmark) for providing their devices and excellent help. We are in debt to all infants and their parents who took part in this study, as well as to all nurses, doctors, and technicians for their help and support.

REFERENCES

1. Hanson TW. Bilirubin oxidation in brain. *Mol Genet Metab.* 2000;71:411–417
2. Askin DF, Diehl-Jones WL. The neonatal liver, III: pathophysiology of liver dysfunction. *Neonatal Netw.* 2003;22:5–15
3. Gourley GR. Breast-feeding, neonatal jaundice and kernicterus. *Semin Neonatol.* 2002;7:135–141
4. Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. *J Pediatr.* 2002;140:396–403
5. 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
6. Lo SF, Doumas BT, Ashwood ER. Bilirubin proficiency testing using specimens containing unconjugated bilirubin and human serum. *Arch Pathol Lab Med.* 2004;128:1219–1223
7. Doumas BT, Kwok-Cheung PP, Perry BW, et al. Candidate reference method for determination of total bilirubin in serum: development and validation. *Clin Chem.* 1985;31:1779–1789
8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1:307–310
9. Lilien LD, Harris VJ, Ramamurthy RS, Pildes RS. Neonatal osteomyelitis of the calcaneus: complication of heel puncture. *J Pediatr.* 1976;88:478–480
10. Yamanouchi I, Yamauchi Y, Igarashi I. Transcutaneous bilirubinometry: preliminary studies of noninvasive transcutaneous bilirubin meter in the Okayama National Hospital. *Pediatrics.* 1980;65:195–202
11. Maisels MJ, Conrad S. Transcutaneous bilirubin measurements in full-term infants. *Pediatrics.* 1982;70:464–467
12. Maisels MJ, Kring E. Transcutaneous bilirubinometry decreases the need for serum bilirubin measurements and saves money. *Pediatrics.* 1997;99:599–601
13. Harish R, Sharma DB. Transcutaneous bilirubinometry in neonates: evaluation of Minolta Air Shields Jaundicemeter. *Indian Pediatr.* 1998;35:264–267
14. Robertson A, Kazmierczak S, Vos P. Improved transcutaneous bilirubinometry: comparison of SpectRX BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population. *J Perinatol.* 2002;22:12–14
15. Yasuda S, Itoh S, Isobe K, et al. New transcutaneous jaundice device with two optical paths. *J Perinat Med.* 2003;31:81–88
16. Dai J, Parry DM, Krahn J. Transcutaneous bilirubinometry: its role in the assessment of neonatal jaundice. *Clin Biochem.* 1997;30:1–9
17. Maisels MJ, Ostrea EM Jr, Touch S, et al. Evaluation of a new transcutaneous bilirubinometer. *Pediatrics.* 2004;113:1628–1635
18. Bhutani VK, Gourley GR, Adler S, Kreamer B, Dalin 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(2). Available at: www.pediatrics.org/cgi/content/full/106/2/e17
19. Rubaltelli FF, Gourley GR, Loskamp N, et al. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. *Pediatrics.* 2001;107:1264–1271
20. Engle WD, Jackson GL, Sendelbach D, Manning D, Frawley WH. Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinemia in a primarily Hispanic population. *Pediatrics.* 2002;110:61–67
21. Lodha R, Deorari AK, Jatana V, Paul VK. Non-invasive estimation of total serum bilirubin by multi-wavelength spectral reflectance in neonates. *Indian Pediatr.* 2000;37:771–775
22. 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;91:203–211
23. Beck M, Kau N, Schlebusch H. Transcutaneous bilirubin measurement in newborn infants: evaluation of a new spectrophotometric method. *Arch Dis Child Fetal Neonatal Ed.* 2003;88:F350–F351
24. Yap SH, Mohammad I, Ryan CA. Avoiding painful blood sampling in neonates by transcutaneous bilirubinometry. *Ir J Med Sci.* 2002;171:188–190

25. Briscoe L, Clark S, Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies? *Arch Dis Child Fetal Neonatal Ed.* 2002;86:F190–F192
26. Peake M, Mazzachi B, Fudge A, Bais R. Bilirubin measured on a blood gas analyser: a suitable alternative for near-patient assessment of neonatal jaundice? *Ann Clin Biochem.* 2001;38: 533–540
27. Rolinski B, Küster H, Ugele B, Gruber R, Horn K. Total bilirubin measurement by photometry on a blood gas analyser: potential for use in neonatal testing at the point of care. *Clin Chem.* 2001;47:1845–1847
28. Laterza OF, Smith CH, Wilhite TR, Landt M. Accurate direct spectrophotometric bilirubin measurement combined with blood gas analysis. *Clin Chim Acta.* 2002;323:115–120

THE SECRETS OF SUCCESSFUL AGING

"Today, the average person in the United States lives for nearly 78 years. But what about those people who beat the average? Why do some men and women defy the chronological odds to live longer and in good health? Increasingly, the scientific community is shifting its focus to this elite group, these 'successful agers,' who seem to be doing a better job of getting old than the rest of us. And what they're finding isn't what you'd expect. . . . Numerous studies of rats, monkeys, nuns, British government workers and centenarians have unlocked many of the secrets of successful aging. Many of the answers were expected. People age better if they don't smoke, don't abuse alcohol, maintain a healthy weight, and get regular exercise. But one of the biggest culprits in unhealthy aging also gets the least respect from both the medical community and individuals: stress. Increasingly, researchers are viewing stress—how much stress we face in a lifetime, and how well we cope with it—as one of the most significant factors for predicting how well we age. [Consider the following] **11** — The number of additional years a 75-year-old man can expect to live; **13** — The number of additional years a 75-year-old woman can expect to live; **17** — The number of additional years a 65-year-old man can expect to live; **30** — The percentage of 80- to 102-year-old women still having sex; **40** — The waistline measurement, in inches, at which risk for heart attack increases dramatically; **63** — The percentage of 80- to 102-year-old men still having sex; **85–94** is the fastest growing age group in America."

Parker-Pope T. *Wall Street Journal.* June 20, 2005
Noted by JFL, MD