REVIEW ARTICLE

Transcutaneous Bilirubin Nomograms

A Systematic Review of Population Differences and Analysis of Bilirubin Kinetics

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Objectives: To compare available nomograms in the literature defining trends in bilirubin levels across populations with different risk factor profiles and to study a mathematical bilirubin kinetics model describing the natural course of jaundice and the bilirubin rate of rise needed to cross percentile curves.

Data Sources: We searched PubMed for publications between March 1999 and March 2009 that created transcutaneous nomograms. We performed the same search among abstracts presented in the past 2 years at meetings of the Pediatric Academic Societies or the European Society for Paediatric Research.

Study Selection: Inclusion criteria were gestational age of at least 35 weeks among study subjects, the use of an electronic transcutaneous bilirubinometer, and creation of a nomogram based on hour-specific bilirubin values. Four articles met the selection criteria.

Data Extraction: Jaundice risk factors were analyzed, and raw data were analyzed using nonlinear regression to describe trends in bilirubin levels and kinetics. The bilirubin exaggerated rate of rise needed to cross percentile curves was calculated.

Data Synthesis: Significant differences in bilirubin values exist across populations, and there is substantial variability in rates of rise. Hispanic neonates demonstrate higher rates of rise and later plateaus. Bilirubin rates of rise tend to plateau and become null (equilibrium between bilirubin production and elimination) at about 96 hours of life. Rates of rise needed to cross percentile curves decrease over time but are lower (approximately 0.11 mg/dL/h [to convert bilirubin level to micromoles per liter, multiply by 17.104]) in the first 48 hours of life than previously thought.

Conclusions: Transcutaneous bilirubin levels plateau and then decrease after about 96 hours of life in healthy neonates, with some differences across populations. A bilirubin rate of rise higher than in the previous period implies that bilirubin production exceeds elimination and indicates high risk for subsequent hyperbilirubinemia in neonates.

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As described by Bhutani et al,[1] the first bilirubin nomogram used total serum bilirubin (TSB) levels to predict subsequent hyperbilirubinemia. Nomograms are created using commercially available software.[2,3] The American Academy of Pediatrics[4] (AAP) recommends the use of an hour-specific nomogram to aid the decision-making process regarding neonatal jaundice for full-term and late-preterm neonates.

The AAP also considers the use of transcutaneous bilirubin (TcB) level as an alternative to TSB measurement, and the results of studies[4,5] have confirmed the value of transcutaneous bilirubinometry. The available literature[4,5] on this topic demonstrates a high correlation between TcB measurements obtained using 2 bilirubinometers (BiliCheck; Respironics Inc, Marietta, Georgia; and Konica-Minolta AirShields JM-103; Dräger Medical, Inc, Telford, Pennsylvania). Although these devices seem accurate, underestimation and overestimation occur based on TSB level, measurement site, and race/ethnicity.[5,6] Gestational age younger than 30 weeks may also influence agreement between measurements, but almost all investigations pooled together full-term and late-preterm neonates (≥35 weeks' gestation).[6] Generally, transcutaneous bilirubinometry is considered a valid screening method for neonatal hyperbilirubinemia, but confirmatory TSB measurement is required when specific therapy for an elevated bilirubin level is being considered.[6]

Although frequent monitoring by TcB or TSB level has provided new insights into the natural course of neonatal hyperbilirubinemia, publications describing changing trends in bilirubin levels over time have not undergone rigorous comparative analysis. The concept of bilirubin kinetics has long been used by clinicians by

means of a rate of rise, dating back to studies[7,8] of Rh incompatibility. Although bilirubin nomograms are readily available, no published study (to our knowledge) describes trends characterized by an exaggerated rate of rise (EROR) in which sequential bilirubin rates of rise cross percentile curves. This is relevant because a neonate who has a greater rate of rise is at increased risk of subsequent hyperbilirubinemia, while a neonate who is following the same percentile curve is less likely to develop severe hyperbilirubinemia.[2]

The AAP[4,9] also recommends consideration of risk factors that are significantly associated with hyperbilirubinemia. These guidelines do not differ among neonates with varying risk factors; rather, they state that the risk of severe hyperbilirubinemia is extremely low if no risk factors are present and that the risk of severe hyperbilirubinemia increases with more risk factors. These risk factors are presumed to vary across populations, and different genetic backgrounds and risk factor profiles preclude the use of a single nomogram.[5,10]

Because improvements in the accuracy of transcutaneous bilirubinometers allow successive noninvasive bilirubin evaluations, their use has led to the creation of nomograms built on TcB levels describing the natural course of jaundice in populations from different parts of the world. Nomogram creation considers risk factors that are characteristic of a particular population; depending on the nomogram used, a trend in bilirubin levels may demonstrate a natural course or may exhibit an EROR. To our knowledge, no data are available regarding variations among published percentile curves, and differences in bilirubin rates of rise needed to cross percentile curves in distinct populations have not been analyzed.

To increase the reliability of the hour-specific nomogram, the AAP[5] recognizes the need for large studies to evaluate the role of race/ethnicity and other risk factors. Our review of studies of transcutaneous bilirubinometry had the following objectives: (1) To compare available nomograms in the literature defining trends in TcB levels across populations with different risk factor profiles and (2) to study a mathematical bilirubin kinetics model describing the natural course of jaundice and the bilirubin rate of rise needed to cross percentile curves.

METHODS

SEARCH STRATEGY AND SELECTION PROCESS

We searched PubMed for publications between March 1999 and March 2009 using the following Medical Subject Heading terms: *hyperbilirubinemia*, *bilirubin*, *jaundice/neonatal*, *skin*, and *nomograms*. These terms were searched with or without the following text words: *transcutaneous bilirubinometer/bilirubinometry*, *bilirubin*, *jaundice*, *skin,* and *nomogram*. The search was limited to human subjects 1 month or younger and to English-literature publications. We performed the same search among abstracts presented in the past 2 years at meetings of the Pediatric Academic Societies or the European Society for Paediatric Research. These searches yielded 19 studies.

The following inclusion criteria were applied: (1) gestational age of at least 35 weeks among study subjects, (2) the use of an electronic transcutaneous bilirubinometer, and (3) creation of a nomogram based on hour-specific TcB values. Full-term and late-preterm neonates of at least 35 weeks' gestation were included relevant to AAP guidelines on jaundice management.[4] No limitations were applied regarding sample size, risk factors for jaundice, or type of bilirubinometer used. Four articles[11-14] met the selection criteria.

DATA EXTRACTION AND ANALYSIS

Raw data were obtained from the corresponding authors of the 4 selected studies in a format for statistical analysis (Excel; Microsoft Corporation, Redmond, Washington; or SPSS; SPSS Inc, Chicago, Illinois). Data comparisons and statistical analyses were bifurcated according to the objectives of the review.

First, we evaluated population details, enrollment criteria, and risk factors for neonatal jaundice within each individual study. Among risk factors indicated by the AAP,[4,9] we considered only those listed in the reviewed studies. Furthermore, we calculated the mean TcB rates of rise (in milligrams per deciliter per hour) for each nomogram at the following epochs that were used in 2 studies[11,12]: 12 to 24 hours, 25 to 48 hours, 49 to 72 hours, and 73 to 96 hours. We also calculated the weighted mean (pooled standard deviation) of the TcB levels and the rates of rise from all reviewed nomograms. These measures are the mean (SD) for each study, weighted for the number of neonates enrolled in each study.[15] Second, we calculated the threshold (EROR) needed to cross percentile curves for each nomogram, from the 25th to 50th percentiles and from the 50th to 75th percentiles, over the 4 epochs.

STATISTICAL ANALYSIS

Data were analyzed using statistical software (SPSS release 15.0 for Windows, SPSS Inc). χ^2 Test and 1-way analysis of variance were used for comparing proportions and continuous variables, respectively. $P < .05$ was considered statistically significant. Multiple curve estimation procedures were performed to find the best-fitting mathematical model, and quadratic regression analysis was used to describe trends in bilirubin levels over time, rate of rise, and acceleration. The quadratic regression analysis was a simple model that excluded covariates.[16] R^2 values were used to assess the model goodness of fit. R^2 is defined as the proportionate reduction in uncertainty about the strength of association between the observed and model-predicted values of the dependent variable. Larger R^2 values represent stronger relationships between variables.[16,17] The quadratic regression model was chosen because it presented the highest R^2 values.

RESULTS

Table 1 gives demographic details of the populations enrolled in the reviewed studies. Except for 1 study,[14] all nomograms were constructed using large (>2000) groups of neonates. One nomogram was constructed in a European population of white race/ethnicity,[12] while 2 other nomograms described Hispanic[13] and Thai[14] neonates. The fourth nomogram[11] comprised North American neonates, including approximately 73% of white race/ethnicity, about 10% of black race/ethnicity, and equal percentages of other races/ethnicities. For study purposes, we considered this population as a whole, designating the nomogram as North American. Gestational age differed slightly but significantly among the studies. Some jaundice risk factors were differentially distributed across the populations, while other risk factors were not always screened for (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency).

Table 1. Population Details and Jaundice Risk Factors in the 4 Reviewed Studies

Variable	Source: Maisels and Kring,[11] 2006 (n=3984)	De Luca et al,[12] 2008 (n=2198)	Engle et al,[13] 2009 (n=2005)	Sanpavat et al,[14] 2005[a] (n=284)
Gestational age, mean (SD), wk	39 (1)[b]	38.3 (1.9)[b]	39.2 (1.4)[b]	38.6 (1.2)[b]
Birth weight, mean (SD), kg	3380 (526)	3101 (549)	3403 (497)	Not available
Mode of delivery, No. (%)				
Vaginal	2386 (59.9)	1162 (52.8)	1584 (79.0)[c]	0
Cesarean section	1598 (40.1)	991 (45.2)	421 (21.0)	284 (100.0)[c]
Vacuum extractor	0	45 (2.0)	0	0
Feeding mode, No. (%)				
Breastfed	2672 (67.1)	1715 (78.0)[c]	641 (32.0)	0
Bottle fed	834 (20.9)	308 (14.0)	501 (25.0)	0
Mix	478 (12.0)	175 (8.0)	863 (43.0)	284 (100.0)[c]
Coombs-positive neonates	Included	Excluded	Included	Excluded
G6PD-deficient neonates	Not tested	Excluded	Not tested	Excluded
Discharge policy[d]	Early	Late	Early	Late

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.
[a] Birth weight was not recorded in the original data set, and an accurate estimate was unavailable. Neonates were not enrolled if they had blood type A or B with maternal blood type 0, regardless of Coombs test results.
[b] $P<.001$, analysis of variance.
[c] $P<.001$ vs the other populations.
[d] Discharge policy was defined as early if the neonate was sent home within 36 to 48 hours after birth and as late if neonate was not discharged before 72 hours after birth.

Table 2. Transcutaneous Bilirubin Levels at Different Epochs in the 4 Reviewed Populations

Hours of Life	Source, Mean (SD): Maisels and Kring,[11] 2006	De Luca et al,[12] 2008	Engle et al,[13] 2009	Sanpavat et al,[14] 2005	Weighted Mean (SD)[a]
12-24	3.0 (1.5)	4.4 (2.8)	3.3 (1.8)	2.9 (1.5)	3.4 (1.9)
25-48	5.3 (2.3)	7.2 (2.5)	5.9 (2.6)	6.0 (1.9)	5.9 (2.4)
49-72	6.4 (3.2)	9.3 (2.9)	8.1 (2.9)	8.2 (2.2)	7.6 (3.0)
73-96	6.9 (3.6)	10.4 (3.0)	9.8 (3.2)	8.7 (2.6)	8.6 (3.3)

[a] $P<.001$ for all, analysis of variance.

To test bilirubin levels, investigators used the forehead (BiliCheck) or the midsternum (Konica-Minolta AirShields JM-103). European and Thai nomograms were based on populations studied up to 96 hours of life because of a later time of discharge at their respective institutions. Hispanic and North American nomograms were developed in hospitals using an early discharge policy, and bilirubin values obtained after 48 hours of life primarily were obtained from neonates delivered by cesarean section.[11,13]

Raw mean TcB values per epoch (**Table 2**) were significantly higher for Hispanic, Asian, and, especially, European populations. These groups also had TcB levels higher than the weighted mean. All populations experienced an increase in TcB level over the first 96 hours of life.

Figure 1 shows the TcB rate of rise over time for each of the 4 reviewed studies. The rate of rise is represented by the slope of each epoch: a tendency to plateau at about 96 hours of life is evident. The trend of TcB rate of rise over time was optimally described by a quadratic equation ($R^2>0.97$). Regression lines illustrate the trend of TcB rate of rise over time for each study, and the lines were extrapolated to estimate trends beyond 96 hours of life. The TcB rate of rise generally decreased with increasing postnatal age. Based on this model and assessment of only the defined epochs, TcB rates of rise seem to plateau earlier in Thai neonates than in the other groups. The highest rate of rise seems to occur in Hispanic neonates, especially after the first 48 hours of life.

Figure 2 shows the mean TcB rate of rise, weighted for the number of neonates in each study. Based on this mathematical model, the weighted mean rate of rise is optimally described by a quadratic equation (approximate $R^2=0.99$). The model equation was then used to describe the rate of rise in the first hours of life, for which we have no data; therefore, the percentile curve was extrapolated back to time 0 (birth). The TcB rate of rise seems highest in the first hours of life (about 0.26 mg/dL/h [to convert bilirubin level to micromoles per liter, multiply by 17.104] at 1 hour of life).

Table 3 gives the TcB rate of rise needed to cross percentile curves (ie, EROR to pass from the 25th to 50th percentiles and from the 50th to 75th percentiles). EROR values are similar across studies for the same epoch. For example, between 12 and 24 hours of life, a rate of rise from 0.20 to 0.30 mg/dL/h is needed to cross percentile curves. Between 25 and 48 hours of life, EROR needed

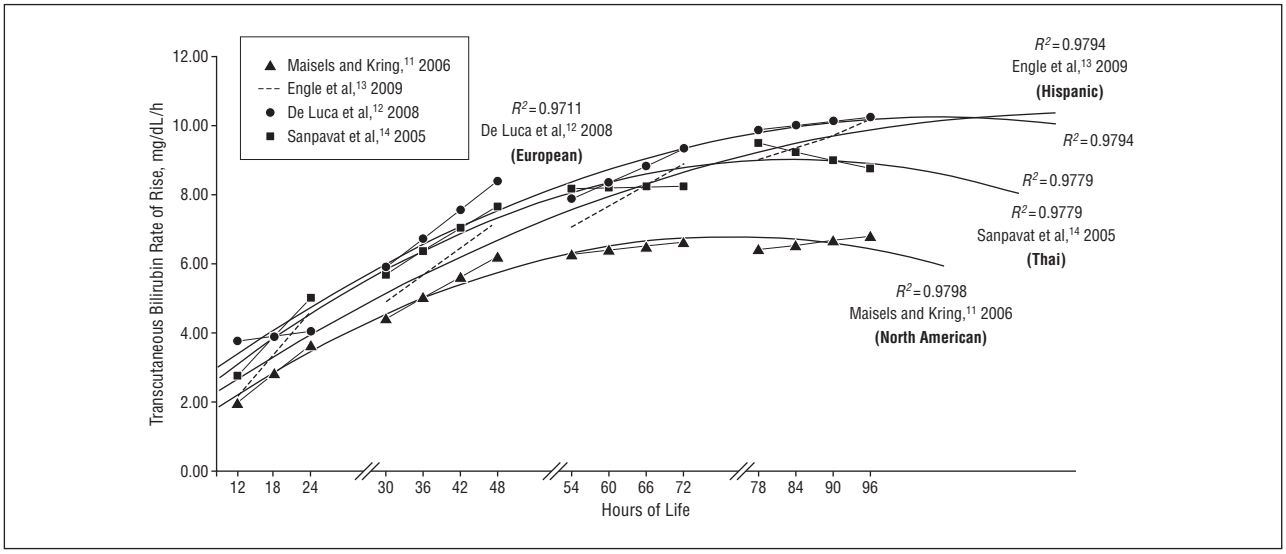

Figure 1. Mean transcutaneous bilirubin levels and rates of rise over time. Rate of rise over time is represented by the slope of each segment (short lines). Data were fitted using quadratic equations, and these are represented by percentile curves for each study. R^2 goodness of fit is indicated in the models for each study. These percentile curves demonstrate the tendency to reach a transcutaneous bilirubin plateau at about 96 hours of life. Hispanic neonates demonstrate higher rates of rise and later plateaus (>96 hours of life). The transcutaneous bilirubin levels seem to plateau earlier in Thai neonates; their rate of rise becomes negative after 72 hours of life.

to cross percentile curves is 0.14 and 0.20 mg/dL/h. ERORs decreased over time and reached a minimum of 0.05 to 0.12 mg/dL/h between 73 and 96 hours of life.

COMMENT

The availability of fast and reliable TcB measurements has led to the development of various TcB nomograms describing the natural course of jaundice. To our knowledge, a systematic comparative analysis of the available nomograms for different populations has not been performed, and this was an objective of the present study. We analyzed TcB nomograms from 4 published studies to determine whether variations in TcB levels and kinetics exist across populations and to determine the TcB rate of rise needed to cross percentile curves in each population group.

Significant differences existed across populations. Peak TcB levels occurred earliest in Thai neonates, latest in Hispanic neonates, and at intermediate epochs in European and North American populations of primarily white race/ethnicity.

Before the first description of a serum bilirubin nomogram,[1] clinical judgment based on history, physical findings, and evaluation of risk factors was the only recommended strategy to predict the course of neonatal hyperbilirubinemia.[18,19] Risk factors identified in the literature have been listed in AAP guidelines in their order of importance to guide clinicians.[4] Recent investigations seem to demonstrate the superiority of a predischarge hour-specific bilirubin evaluation compared with risk factor assessment alone, and gestational age analysis may improve reliability of the nomogram.[20-22] Several nomograms based on TSB or TcB values are now available.[11-14,23-25] Given our results, clinicians should carefully choose and interpret the "right tool" for their neonates.

Differences were noted across studies with regard to population details. The 4 reviewed nomograms included neonates of different races/ethnicities; therefore, variations in bilirubin kinetics and nomogram characteristics could be due, in part, to well-known genetic differences.[26,27] As summarized in Table 1, dissimilarities in enrollment criteria and jaundice risk factors may also explain some of the variations. We could not review the effect of some risk factors (eg, asphyxia and temperature instability) because they were not reported in the studies. Furthermore, some other risk factors (eg, G6PD deficiency) may have a significant role in the develop-

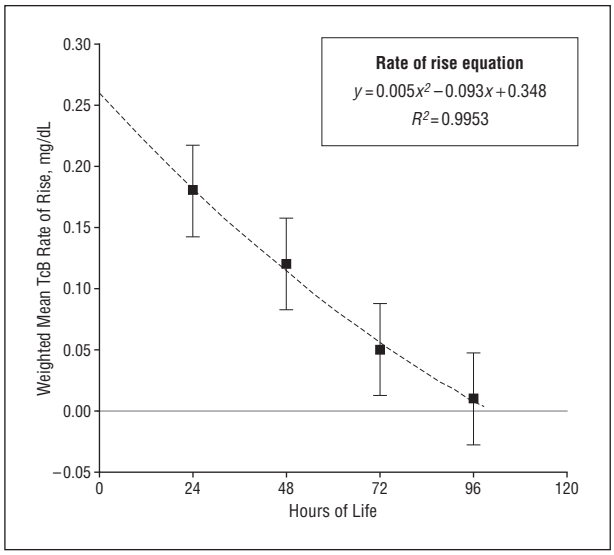

Figure 2. Weighted mean transcutaneous bilirubin (TcB) rate of rise, calculated by averaging the rates of rise and weighting them by the number of neonates in each study. Data were fitted using quadratic regression analysis: the equation and R^2 goodness of fit are shown. The regression line is represented by the hatched line, which was extrapolated to describe the hypothetical trend in the first hours of life. Vertical bars represent the standard deviation. Weighted mean TcB rates of rise are 0.17 mg/dL/h at 24 hours of life, 0.12 mg/dL/h at 48 hours of life, 0.05 mg/dL/h at 72 hours of life, and 0.02 mg/dL/h at 96 hours of life.

Table 3. Transcutaneous Bilirubin Exaggerated Rate of Rise (EROR) Needed to Cross the Percentile Curves From the 25th to 50th Percentiles and From the 50th to 75th Percentiles

	Transcutaneous Bilirubin EROR Needed, mg/dL/h[a]							
	12-24 Hours of Life		25-48 Hours of Life		49-72 Hours of Life		73-96 Hours of Life	
Source	25th to 50th Percentiles	50th to 75th Percentiles	25th to 50th Percentiles	50th to 75th Percentiles	25th to 50th Percentiles	50th to 75th Percentiles	25th to 50th Percentiles	50th to 75th Percentiles
Maisels and Kring,[11] 2006	0.23	0.23	0.15	0.17	0.11	0.12	0.12	0.09
De Luca et al,[12] 2008	0.23	0.30	0.17	0.15	0.17	0.17	0.11	0.12
Engle et al,[13] 2009	0.26	0.28	0.16	0.20	0.11	0.11	0.05	0.09
Sanpavat et al,[14] 2005	0.20	0.21	0.14	0.17	0.10	0.09	0.07	0.07

[a] EROR needed to reach the higher percentile is expressed in milligrams per deciliter per hour.

ment of jaundice,[28,29] but these data were unavailable for 2 studies.[11,13]

The TcB rate of rise decreased over time in all population groups. This suggests that TcB levels tend to reach a plateau that is attained at different postnatal ages in various populations. Extrapolation of the data shown in Figure 1 suggests that Thai neonates reach a plateau earliest at approximately 72 hours of life, the neonates of primarily white race/ethnicity between 73 and 96 hours of life, followed by Hispanic neonates after 96 hours of life. The plateau point should be conceptualized as the postnatal age when rates of bilirubin production and excretion are equal. Combining the entire population of all 4 studies and describing it using a mean rate of rise weighted for the number of neonates, the plateau point was reached at about 96 hours on average. Hispanic neonates have the highest TcB rate of rise at all epochs.[13]

Because our analysis considered the data from 4 studies, this allowed us to build a mathematical model to study the natural course of jaundice and its kinetics among a population of more than 8400 neonates. The TcB rate of rise was best described by a quadratic equation. This analysis depicted the bilirubin rate of rise during the natural course of physiologic jaundice. Although difficult to define, the term *physiologic jaundice* refers to the occurrence of jaundice in a neonate in whom the bilirubin rate of rise does not cross percentile curves and in whom peak bilirubin levels are below the 95th percentile for age. Therefore, the TcB rate of rise should decrease over time. We showed that the rate of rise generally decreases with increasing postnatal age. Up to 48 hours of life, the rate of rise is decreasing, and, after 48 hours of life, the rate of rise tends to reach a plateau, and acceleration gradually returns to zero. This point may indicate equilibrium between bilirubin production and elimination.[2]

In contrast, Maisels and Kring[30] recently demonstrated a steady increment in bilirubin production in neonates who appear very jaundiced (>75th percentile according to Bhutani et al[1]) in the first 96 hours of life, while this was not evident in neonates without jaundice. Their study illustrates the disparity between infants with exaggerated hyperbilirubinemia and the percentile curves in the present study, which are based on large, presumably healthy, populations. When an increase in the bilirubin rate of rise is noted, other causes for jaundice should be considered.[1,31] This had been assumed in the past, but our mathematical model provides further evidence that EROR should be considered worrisome, as it is absent in healthy populations during the natural course of neonatal bilirubinemia.

Our study provides values needed to detect EROR in different populations. The AAP has suggested that a rate of rise of 0.25 mg/dL/h should raise concern.[4,31] However, a rate of rise of 0.20 mg/dL/h seems excessive in our Thai population, and EROR thresholds are lower (approximately 0.11 mg/dL/h) in general in the first 48 hours of life. EROR thresholds further decrease with increasing postnatal age. During the first 48 hours of life, bilirubin "physiologically" increases more rapidly than in the subsequent hours of life. To be worrisome, a bilirubin rate of rise must be very high in the first hours of life, so early hyperbilirubinemia is generally of more concern.

Some limitations of our analysis should be mentioned. Caution must be used when extrapolating our findings to Asian neonates because they represent the smallest proportion of the reviewed populations. Moreover, our TcB analysis should not be directly applied to serum bilirubin measurements. Transcutaneous bilirubin and serum bilirubin level are correlated but are basically distinct.[32] Several studies[33-35] have investigated the passage of bilirubin from vessels to the skin, but this remains an area for further research. Although multiple studies[4,5] analyzing transcutaneous bilirubinometry exist, we focused only on studies with a visually represented nomogram. Studies without nomograms typically do not provide the time of individual sampling; therefore, it would be difficult to perform a combined analysis. Finally, other studies that provided nomograms based on TSB values were excluded because our focus was on TcB.[23-25]

CONCLUSIONS

Transcutaneous bilirubin rates of rise reach a plateau and then decrease after 73 to 96 hours of life in healthy neonates. Differences were noted among the diverse populations studied, and some racial/ethnic groups exhibit a higher TcB rate of rise and a later TcB peak.

Most important, a bilirubin rate of rise higher than in the previous period implies that bilirubin production exceeds elimination. EROR is the result of this imbalance, and EROR thresholds decrease as postnatal age in-

creases. EROR indicates high risk for subsequent hyperbilirubinemia in neonates and should lead to close monitoring. This is of conceptual relevance for future research investigating similar patterns of trends in serum bilirubin levels and the passage of bilirubin to the skin.

This study is of practical usefulness for those who care for late-preterm and term neonates in whom TcB rates of rise are measured. The nomogram used should reflect the population that most closely represents the neonate under evaluation. Development of additional nomograms for other populations should further enhance the care of neonates with jaundice.

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