Predischarge Screening for Severe Neonatal Hyperbilirubinemia Identifies Infants Who Need Phototherapy

Vinod K. Bhutani, MD[1], Ann R. Stark, MD[2], Laura C. Lazzeroni, PhD[3], Ronald Poland, MD[4], Glenn R. Gourley, MD[5], Steve Kazmierczak, PhD[6], Linda Meloy, MD[7], Anthony E. Burgos, MD[8], Judith Y. Hall, RN[8], and David K. Stevenson, MD[1], on behalf of the Initial Clinical Testing Evaluation and Risk Assessment for Universal Screening for Hyperbilirubinemia Study Group*

Objective To test whether the combined use of total plasma/serum bilirubin (TSB) levels and clinical risk factors more accurately identifies infants who receive phototherapy than does the use of either method alone.

Study design We recruited healthy infants of ≥35 weeks' gestation at 6 centers that practiced universal predischarge TSB screening. Transcutaneous bilirubin (TcB) was measured at 24 hours, with TSB at 24-60 hours and at 3- to 5- and 7- to 14-day follow-up visits. Clinical risk factors were identified systematically.

Results Of 1157 infants, 1060 (92%) completed follow-up, and 982 (85%) had complete datasets for analysis. Infant characteristics included 25% were nonwhite and 55% were Hispanic/Latino; >90% were breastfed. During the first week, jaundice was documented in 84% of subjects. Predischarge TSB identified the 41 (4.2%) and 34 (3.5%) infants who received phototherapy before and after discharge, respectively. Prediction of postdischarge phototherapy was similar for combined clinical risk factors (earlier gestational age [GA], bruising, positive direct antiglobulin test, Asian race, exclusive breastfeeding, blood type incompatibility, jaundice extent) and age-adjusted TSB (area under the curve [AUC] = .86 vs .87), but combined screening was better (AUC = .95). TcB/TSB combined with GA alone was equally predictive (AUC = .95; 95% CI .93-.97).

Conclusions Jaundice is present in 4 of 5 (84%) healthy newborns. Predischarge TcB/TSB (adjusted for postnatal age) combined with specific clinical factors (especially GA) best predicts subsequent phototherapy use. Universal implementation of this strategy in the US should improve outcomes of healthy newborns discharged early. *(J Pediatr 2013;162:477-82)*.

Newborn infants require early follow-up and appropriate treatment of hyperbilirubinemia to avoid adverse outcomes such as neonatal total plasma/serum bilirubin (TSB) ≥20 mg/dL (342 μmol/L) or higher, acute bilirubin encephalopathy, sensorineural hearing loss, and possibly kernicterus.[1-11] The 2004 American Academy of Pediatrics (AAP) Clinical Practice Guideline[1] recommends that all newborn infants ≥35 weeks' gestation be assessed before discharge for the risk of developing severe neonatal hyperbilirubinemia using clinical risk factors and/or bilirubin measurements. The guideline also provides hour-specific bilirubin thresholds as a guide for intervention with intensive phototherapy according to the presence of clinical factors that may increase the risk for bilirubin neurotoxicity. In a recent update,[12,13] an expert panel suggested combining universal bilirubin measurements, using TSB or transcutaneous bilirubin (TcB), with clinical risk factors for predischarge assessment.[12] However, which risk factors are most meaningful when applied to a diverse population is uncertain.

Our goal was to identify the most effective pre-discharge assessment for the risk of developing subsequent hyperbilirubinemia. We tested the following two hypotheses in an ethnically and racially diverse US population of newborn infants ≥35 weeks' gestation: (1) that TSB or TcB, measured at age 24-60 hours, would more accurately predict severe hyperbilirubinemia than the use of clinical

AAP	American Academy of Pediatrics
AUC	Area under the curve
CAP	College of American Pathologists
DAT	Direct antiglobulin test (Coombs)
G6PD	Glucose-6-phosphate dehydrogenase
GA	Gestational age
TSB	Total plasma/serum bilirubin
TcB	Transcutaneous bilirubin

From the [1]Department of Neonatal and Developmental Medicine, Lucile Packard Children's Hospital, Department of Pediatrics, Stanford University, Stanford, CA; [2]Division of Neonatology, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN; [3]Departments of Psychiatry and Behavioral Sciences and of Pediatrics, Stanford University, Stanford, CA; [4]Department of Pediatrics, University of New Mexico, Albuquerque, NM;[5]Department of Pediatrics, University of Minnesota, Minneapolis, MN; [6]Department of Pediatrics, Oregon Health and Science University, Portland, OR; [7]Department of Pediatrics, Virginia Commonwealth University, Richmond, VA; and [8]Department of Pediatrics, Lucile Packard Children's Hospital, Stanford University, Palo Alto, CA

*A list of additional members of the ICTERUS Study Group is available at www.jpeds.com (Appendix).

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risk factors alone and (2) that the combined use of TSB or TcB with clinical risk factors would more accurately predict severe hyperbilirubinemia than would the use of either method alone.

Methods

This prospective observational multicenter cohort study was conducted in the Newborn Nurseries of the Lucile Packard Children's Hospital (Stanford, California), Ben Taub General Hospital (Baylor College of Medicine, Houston, Texas), Oregon Health and Science University (Portland, Oregon), University of New Mexico (Albuquerque, New Mexico), Medical College of Virginia (Richmond, Virginia), and University of Minnesota (Minneapolis, Minnesota). Infants were eligible for enrollment if they were managed exclusively in the newborn nursery and if they were ≥35 weeks' gestational age (GA). Infants transferred to the neonatal intensive care unit for any reason, who received parenteral antibiotics for suspected or proven sepsis for ≥48 hours, or who were unable to attend follow-up appointments in the study center were excluded from the study.

The protocol was designed to determine the relative diagnostic performance of a predischarge TSB compared with clinical risk factors to predict severe neonatal hyperbilirubinemia as defined by the use of phototherapy as recommended in the 2004 AAP guideline.[1] In addition, we determined the relative predictive performance of combined TcB/TSB and clinical risk factors compared with either alone to predict severe neonatal hyperbilirubinemia.

All participating centers had implemented the 2004 AAP guideline and routine clinical care included universal predischarge TSB screening. Institutional review boards at all participating centers approved the protocol. Informed consent was obtained from the parent(s) of each infant. TcBs were measured at age 24 ± 6 hours and before discharge (generally concurrent with metabolic screen and routine TSB measurements). Outpatient TcB was measured at age 3-5 and 7-14 days. Clinical risk factors previously associated with newborn jaundice[1] were recorded on specifically designed electronic case report forms following review of the maternal and infant medical records during the birth hospitalization. The study nurse verified specific maternal, infant, and delivery characteristics listed in Table I, scheduled the first outpatient visit, and conducted parent interviews by telephone between 14 and 30 days after birth to specifically review any adverse outcome or parental concerns.

The Kramer scale homunculus was used to record the predischarge extent of jaundice.[14,15] TcB measurements were performed on the forehead and sternum before discharge at age 24 ± 6 hours, often concurrent with routine TSB testing at the time of the metabolic screen; at the age 3- to 5-day visit; and again at the 7- to 14-day visit. TcB was measured using the BiliChek (Philips, Monroeville, Pennsylvania) device, a Food and Drug Administration–approved noninvasive bilirubinometer. Because the BiliChek may not be accurate at TcB levels above 15 mg/dL (257 μmol/L),[16-18] we verified all TcB values ≥12 mg/dL (205 μmol/L) with a TSB measurement. TcB was not performed during or after phototherapy. Predischarge TSB values used for prediction were measured at 18-60 hours after birth. We used an hour-specific nomogram[11] to assign the predischarge TSB values to risk zones (<75th percentile: low and low-intermediate; ≥75th percentile: high-intermediate and high). To ensure accuracy and to address standardization concerns regarding TSB measurements, each laboratory participated in the recommended College of American Pathologists (CAP) neonatal bilirubin and chemistry survey every 4 months.[19] Supplemental random standards were sent out by the Oregon study site (S.K.) and tested at each of the centers to compare laboratory results and to verify that sites met the CAP standards. Five separate serum pools were prepared from previously frozen patient sera. The 5 pools had total and direct bilirubin concentrations that varied from approximately 0.6 to 14.9 mg/dL (10.3-255 μmol/L) and 0.2 to 7.9 mg/dL (3.4-135 μmol/L), respectively. All therapeutic interventions (eg, formula supplementation, phototherapy, or exchange transfusion) performed during the birth or

Table I. Select maternal, perinatal, and infant characteristics of entire cohort (n = 1157)

Characteristic	n (%)
Total subjects	1157 (100)
Maternal race (self-declared)	
White	886 (76.6)
Black	100 (8.6)
Asian	67 (5.8)
American Indian/Alaskan Native	47 (4.1)
Native Hawaiian/Pacific Islander	15 (1.3)
Multiracial	14 (1.2)
Not declared	17 (1.5)
Did not know	11 (0.9)
Ethnicity	
Non-Hispanic	405 (35)
Hispanic or Latino	639 (55.2)
East Asian	39 (3.4)
Mediterranean	13 (1.1)
Multiethnic	6 (0.5)
Other	42 (3.6)
Not declared	13 (1.1)
Maternal and perinatal characteristics	
Rh-negative status	65 (5.6)
Blood type O	364 (31.5)
Diabetes mellitus	103 (8.9)
Hypertension treatment	27 (2.3)
Pitocin induction	518 (44.8)
Cesarean delivery	253 (21.9)
Assisted vaginal delivery (vacuum and/or forceps)	22 (1.9)
Infant characteristics	
Male	601 (52)
< 37 weeks' GA	70 (6.1)
37 weeks' GA	100 (8.8)
38 weeks' GA	193 (16.9)
39 weeks' GA	292 (25.6)
≥ 40 weeks' GA	457 (40.6)
Bruised at birth	75 (6.5)
Cephalohematoma	98 (8.5)
Positive DAT (18/766 tested)	18 (2.3)
Sibling with jaundice	217 (18.7)
Sibling treated with phototherapy	92 (8.0)
Exclusive breastfeeding	424 (36.6)
Breastfeeding + supplemental formula	592 (51.2)

subsequent hospitalizations were at the discretion of the health care team. The health care team also decided which phototherapy treatment threshold curve to use in determining whether an infant's TSB reached or exceeded the threshold, using the specific risk factors for bilirubin neurotoxicity defined in the AAP guideline.[1] The protocol and research team provided no clinical decision support regarding follow-up or intervention. Infants were not routinely tested for hemolysis, glucose-6-phosphate dehydrogenase (G6PD) status, or albumin level; thus, the only risk factors used by the clinicians to determine phototherapy treatment threshold curves were GA and a direct antiglobulin test (Coombs) (DAT), if available. Centers were not required to routinely test the infant's blood type, although all tested infants if the mothers were blood type O or Rh negative.

We defined the outcome of severe neonatal hyperbilirubinemia as the subsequent use of phototherapy (age ≥60 hours) as prescribed by the treating physician's interpretation and use of the hour-specific treatment thresholds recommended by 2004 AAP guideline for phototherapy.[1]

Data on maternal, infant, and delivery characteristics; designated predictor and outcome variables; mode and type of interventions; and information from the predischarge and postdischarge structured parent interview were obtained by the research team or extracted from the medical record and entered into the database. An investigator at each site audited data collected on Web-based forms, and an independent off-site investigator randomly audited 10% of the database records.

The sample size was based on an estimated rate of postdischarge hyperbilirubinemia requiring phototherapy of 4.4%.[2,11] Our sample size was based on the lower bound for the 92.5% CI around the sensitivity of the diagnostic test, which can be defined by an elevated TSB level before discharge or from the previously described clinical prediction rules.[20-22] The formula used for this estimate[23] is: sample size (n) = 1.96 [p (1 − p)]/(width of CI)^2. A lower sensitivity bound of 90% would require 49 cases of phototherapy (enrollment of 1100 infants), compared with 88 cases for a 92.5% bound for an assumed probability of .50. Based on the ongoing evaluation of the rates of TSB >95th percentile and rates of phototherapy during the course of our study, we terminated enrollment after 75 cases of phototherapy were recorded for >1100 infants.

Statistical Analyses

We used multiple logistic regression analysis to evaluate the predictive value of bilirubin measurements (TSB or TcB) and clinical factors for hyperbilirubinemia, with phototherapy use as the outcome. Although measurements at age <60 hours were considered predischarge, we restricted the analysis to bilirubin measurements at age <48 hours to preclude using as potential predictors of phototherapy bilirubin values that contributed directly to an immediate decision to initiate phototherapy. Bilirubin values used were the last observed in the window from 24 to 48 hours of age. If more than one type of bilirubin measurement was made at that time, the TSB was used. Otherwise, sternum TcB was used. We excluded from analysis infants whose phototherapy was initiated before 60 hours of age because the elevated bilirubin level might be diagnostic (rather than predictive) for use of phototherapy. Age criteria were chosen based on the data to optimize the number of infants with phototherapy available for analysis, without looking at the results of analyses including predictors. Clinical variables considered were GA, sex, presence of jaundice, jaundice progression defined according to Kramer zone, Asian race, bruising, cephalohematoma, blood type (ABO) incompatibility, maternal Rh-negative blood type, positive DAT, delivery type, and exclusive breastfeeding.[24] Blood type incompatibility was defined to be present if an infant's blood type was tested and was type A, B, or AB. Blood type and DAT data were not available for the entire study population because they were measured only when the maternal blood type was O or Rh negative or at the physician's discretion. Separate variables were considered for each type of delivery (cesarean, vaginal, or vacuum/forceps). Given the relatively small number of infants receiving phototherapy, we used forward variable selection to reduce the number of clinical variables to avoid overfitting the data. The criterion for a variable to enter the model was a Wald test result of $P \leq .05$. Forward variable selection and its reported P values do not account for the consideration of multiple variables. Thus, the use of this method gives an optimistic assessment of the predictive value of the significance of the clinical risk factors.

Comparative values of bilirubin and the combined group of selected clinical predictors were determined by likelihood ratio tests. Model effect sizes were compared in terms of the receiver-operating area under the curve (AUC), which is equivalent to the c-statistic. An additional analysis was carried out to see whether, within the 24- to 48-hour predischarge window, consideration of the age at which bilirubin was measured yielded a more accurate bilirubin-based prediction of the odds of use of phototherapy. To do this, we created a continuous interaction variable, which was the product of the bilirubin value and the postnatal age at measurement, both measured continuously. Age was standardized to equal 0 at 24 hours and 1 at 48 hours. The I interaction term was tested by Wald test of the z-statistic. All tests were 2-sided and z performed at the .05 significance level. CIs were computed at the 95% level.

Results

We enrolled 1157 infants between October 2005 and April 2007 (**Table I**). Maternal age was 26.9 ± 6.4 years and birth weight was 3310 ± 467 g (both mean ± SD). Infants were discharged at a median age of 56 hours (range, 14-780 hours). Thirteen infants were subsequently excluded from the study because they were transferred to neonatal intensive care unit (3 infants) or consent was withdrawn (10 infants). Of the remaining 1144 infants (**Figure**), all had a bilirubin measurement before discharge. Of these, 84 infants (7.3%) (who did not have phototherapy before discharge) were lost to follow-up. Eighty percent of infants returned for the

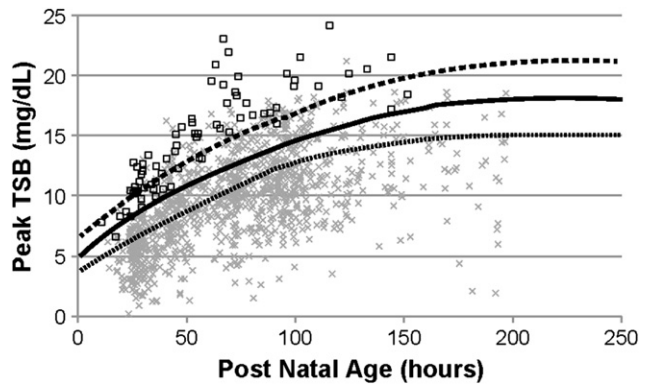

Figure. Peak bilirubin levels for all study infants. *Squares,* values before treatment in infants who received phototherapy. *Crosses,* values for infants who did not receive phototherapy. AAP Clinical Practice Guideline[1] bilirubin thresholds are shown for phototherapy use for infants at low risk (*dotted line*), moderate-risk (*solid line*), and high-risk (*dashed line*) of bilirubin neurotoxicity.

scheduled postdischarge follow-up evaluation at age 3-5 days. Approximately one-half (52%) of the study infants completed both follow-up appointments at ages 3-5 and 7-14 days that were specified in the AAP recommendations. Complete clinical (all risk factors) and postnatal age-specific bilirubin data were available for 982 infants and constitute the cohort for data analysis. Maternal, perinatal, and infant characteristics of this select cohort were similar to the entire cohort. Breastfeeding was initiated in 90.4% of infants, and exclusive formula feeding was noted in 9.6% of subjects. Maternal blood typing was available for 99.8% of study patients. Infant blood typing varied among centers and was performed in 48% of infants. DAT was tested in 67% of all infants and was reported as positive in 2.3% of infants tested. Only 4 infants in this cohort were tested for G6PD deficiency.

Phototherapy Use

We identified phototherapy use in 75 of 982 infants (7.6%), of whom 41 (4.2%) were treated during the birth hospitalization and 34 (3.5%) were treated after discharge (2 were treated at home). All infants who received neurotoxicity risk-appropriate phototherapy had predischarge hyperbilirubinemia in risk zones above the 75th percentile of the hour-specific bilirubin nomogram. Peak bilirubin levels for all study infants are shown in the Figure. Infants with postdischarge phototherapy had a repeat bilirubin measurement before treatment. In 7 of the 75 infants treated with phototherapy, clinicians began treatment within 1 to 2 mg/dL below the threshold level, possibly anticipating the trajectory for rate of bilirubin rise. Characteristics of infants treated with phototherapy were male sex, 55%; 35-37 weeks' gestation, 45%; and bruising and/or cephalohematoma, 32%. Infant blood type was determined in 69 of 75 infants treated with phototherapy. Ten infants (1.2%) had TSB levels ≥20 mg/dL (342 μmol/L) and none had levels ≥25 mg/dL (428 μmol/L). None received an exchange transfusion. Among the 907 infants not treated with phototherapy, 72 (7.9%) had ≥1 TSB level that was in the high-risk zone (>95th percentile).

Jaundice Evaluation

We identified visible jaundice in >84% of study infants during the first week after birth. Four of 130 infants (3.1%) with jaundice noted between 10 and 24 hours of age had TSB >95th percentile and were DAT positive; these infants received phototherapy within 24 hours after birth.

Resolution of Neonatal Hyperbilirubinemia. At age 7-14 days, 439 of 1157 infants who did not receive phototherapy returned for follow-up. Table II shows TSB at the 10th, 40th, 75th, 95th, and 99th percentiles. Of these, 13 infants (3.3%) had undetectable levels of bilirubin.

Clinical Risk Factors to Predict Phototherapy Use

To evaluate risk factors to predict use of phototherapy, we excluded infants who: (1) received phototherapy before 60 hours of age; (2) had no bilirubin measurement within the 24-48 hours of age window; or (3) did not have GA recorded. We included 982 babies in the logistic regression analyses, of whom 34 (3.5%) received postdischarge phototherapy. The forward selection algorithm incorporated into the model the 10 highly ranked clinical variables in decreasing order of significance: postnatal age interaction from 24 to 48 hours, GA (as a continuous variable), bruising, Asian race (mother), ABO incompatibility, cephalohematoma, exclusive breastfeeding, positive DAT (when tested), and jaundice progression (Kramer zone) (AUC = .86 ± .04 [SE], 95% CI, .79-.93; n = 982). Earlier GA (<39 weeks), bruising, Asian race (mother), ABO incompatibility, cephalohematoma, exclusive breastfeeding, positive DAT, and more extensive jaundice were associated with greater odds of phototherapy use (likelihood ratio χ^2 = 137.8 [for 10 variables], probability > χ^2 < .0001).

From these clinical risk factors, we selected those with greater odds of phototherapy use: GA <39 weeks, bruising, cephalohematoma, Asian race, blood type incompatibility, and a positive DAT test to yield predictive models (Table III). The clinical variables collectively added significant information to a model that was based on bilirubin alone (model A). Model B used combined select clinical risk factors and was also predictive. Sequence of building predictive models commenced from

Table II. Distribution of total bilirubin levels at age 7-14 days (168-336 hours) for infants screened at birth, followed, and not treated with phototherapy (n = 439)

Percentile	Bilirubin levels
10th percentile	1.6 mg/dL (27 μmol/L)
40th percentile	5.0 mg/dL (86 μmol/L)
75th percentile	9.7 mg/dL (163 μmol/L)
90th percentile	12.9 mg/dL (221 μmol/L)
95th percentile	14.4 mg/dL (246 μmol/L)
99th percentile	17.2 mg/dL (297 μmol/L)

Table III. Select clinical risk factors with and without bilirubin as predictors for subsequent use of phototherapy

	Clinical risk factor(s)	AUC	±SE	95% CI
A	TSB/TcB alone	.84	.03	.79-.90
B	Combined clinical risk factors alone	.86	.04	.79-.93
C	Combined clinical risk factors and TSB/TcB (unadjusted for age)	.93	.02	.88-.97
D	Age-adjusted (for hours) TSB/TcB	.87	.03	.82-.93
E	Combination model: clinical risk factors and age-adjusted (for hours) TSB/TcB	.95	.02	.92-.98
F	GA alone	.76	.04	.68-.84
G	Age-adjusted (for hours) TSB/TcB and GA (weeks)	.95	.03	.93-.97

AUC is calculated for different models for study sample that met analysis criteria (N = 982). Select clinical risk factors included and associated with greater odds of phototherapy were GA <39 weeks, bruising, cephalohematoma, blood type incompatibility, East Asian ancestry, and positive DAT test. Sequence of building predictive models from model (C); bilirubin data were used alone (A), excluded (B), or adjusted for age in hours (D); and the final combination model (E).

model C. Models A, B, and D had similar predictive ability. Model E, which included the select clinical risk factors with the age×bilirubin interaction term, had the best predictive ability. Model G, which included the age×bilirubin interaction term and GA alone, had equivalent predictive ability. In these interaction models, the interpretation of the effect of the bilirubin value depends on the age at which it was measured. The odds of phototherapy for a given bilirubin value at 48 hours versus 24 hours of age were estimated by the models to be 72% and 68%, respectively. When bilirubin effects are included in the model, jaundice zone and positive DAT no longer add significant information. The statistical significance of predischarge exclusive breastfeeding and cephalohematoma was also reduced.

Accuracy of Total and Direct Bilirubin Measurements

The mean results of the triplicate analyses performed at 9 study sites showed agreement with group coefficient of variance ranging from 4.6 to 5.4% for TSB <12.9 mg/dL. For TSB >14.9 mg/dL, the variance was as high as 17.5%.

Discussion

Our study provides a prospective assessment of jaundice and hyperbilirubinemia in a US population of newborn infants that was approximately one-quarter of nonwhite race and more than one-half of Hispanic or Latino ethnicity. Jaundice was detected in 84% of infants during the first week after birth and generally resolved by age 7-14 days; by this age, TSB levels >17 mg/dL (291 μmol/L) should be considered >99th percentile. Phototherapy was used in 7.6% of our study population, and with universal screening, identification, and serial monitoring, only about one-half (3.5%) of these infants were readmitted for treatment.

We have also shown in this racially and ethnically diverse cohort that the combined use of a bilirubin measurement at 24-48 hours postnatal age and GA is the best predictor for subsequent use of phototherapy. The predictability of this combination (AUC = .95; 95% CI, .93-.97) provides evidence that supports the recommendations made by the AAP Expert Panel.[12] Biochemical (bilirubin) and clinical risk factors of decreasing GA, bruising, Asian race, cephalohematoma, and blood type incompatibility optimally predicted the subsequent use of phototherapy better than either bilirubin level or clinical risk factors alone. Our prospective validation of the major clinical risk factors in this diverse population extends the prior single center observations made by Keren et al[20] and Maisels et al.[22] Importantly, the predictive role of GA as a preeminent clinical risk factor for subsequent phototherapy highlights the need for close monitoring of infants <38 weeks' GA during the first week after birth. GA has a strong impact on the prediction of severe hyperbilirubinemia, with risk decreasing continuously with each additional week of maturity. Previous reports of clinical risk factors for hyperbilirubinemia, as listed in the 2004 AAP guideline, were generally based on univariate analysis.[1-3] More recently, lower GA, breastfeeding, presence of cephalohematoma or bruising, and jaundice in the first 24 hours after birth have been distinguished from a variety of previously reported maternal, perinatal, and infant characteristics.[20-22,24-27] Our data indicate a minimal role of exclusive breastfeeding as a predischarge risk factor.

Our use of TSB level as a predictor is consistent with the known biology of increased bilirubin production and delayed bilirubin elimination due to the combined effects of hepatic excretory immaturity and increased enterohepatic circulation. Documentation and ranking of multiple clinical risk factors to quantify risk performed under study conditions are cumbersome for clinicians. Our finding that the combination of hour-specific bilirubin measurement and GA alone was as predictive of subsequent phototherapy as the hour-specific bilirubin measurement combined with multiple clinical risk factors offers this approach as more practical and easier to implement. However, the specific cause of hyperbilirubinemia should be defined if further interventions, such as use of phototherapy and/or exchange transfusion, are needed or if hyperbilirubinemia persists.

Independent of the study staff, clinicians made individual decisions to treat 7.6% of the study subjects with phototherapy. All treated infants had predischarge TSB levels in the high-risk zones (>75th percentile track on the nomogram) before receiving phototherapy. Perhaps in part because of the appropriate or early use of phototherapy, TSB level was ≥20 mg/dL (342 μmol/L) in only 1 of 98 treated infants, none had a TSB level ≥25 mg/dL (428 μmol/L), and none received an exchange transfusion. We saw no apparent intersite differences in the use of phototherapy. In the untreated infants, jaundice and hyperbilirubinemia usually resolved spontaneously by age 7-14 days. Our data also reassure the clinician that a term infant who has TcB/TSB values in the low risk zones (<75th percentile track) has the lowest predictable risk for future severe hyperbilirubinemia. The exception to this reassurance would be for infants with G6PD deficiency who remain at risk for unpredictable dramatic increase in bilirubin levels that are usually associated with hemolysis.[28]

Our study has some unavoidable limitations. First, we based our outcome of phototherapy use on a decision made by the infant's physician, and treatment was initiated at 1-2 mg/dL below the threshold level in approximately 9%. A second potential concern was the accuracy of bilirubin measurements used for screening, especially across multiple sites. Since the initiation of this study, CAP has introduced a process to improve the accuracy of bilirubin assay. Our data show good performance for TSB levels <14.9 mg/dL, with an observed variance <6% consistent with other screening tests. Third, we limited our analysis of prediction to infants treated with phototherapy after 60 hours of age and may have reduced the power to detect effects of factors potentially leading to early initiation of phototherapy, such as infants at risk for hemolytic disease. Last, use of GA as a predictor introduces an unavoidable bias. Because the AAP thresholds for phototherapy are lower at earlier GAs, late preterm infants qualify for intervention sooner than do term infants.

We were surprised that exclusive breastfeeding did not rise to a higher significance level in the predischarge predictive model, although these infants were more likely to receive phototherapy. We speculate that this may be due to good availability of lactation support during and after birth hospitalization. Unfortunately, the sample size did not allow us to detect subtle variations in our cohort or rare events such as cephalohematoma, blood type, maternal Rh-negative status, or vacuum/forceps delivery. Last, our centers did not routinely screen for G6PD deficiency syndromes and the specific cause of hyperbilirubinemia was not always available. ■

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Reprint requests: Vinod K. Bhutani, MD, FAAP, Division of Neonatal Developmental Medicine, Department of Pediatrics, Lucile Packard Children's Hospital, Stanford University, School of Medicine, 750 Welch Rd, #315, Palo Alto, CA 94304. E-mail: bhutani@stanford.edu

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Appendix

Additional members of the ICTERUS Study Group include: Carmen Garcia, Baylor College of Medicine; Carol Hartenberger, University of New Mexico; Mark Hsu, Stanford University; Erin Ruwe, Virginia Commonwealth University; Nicole Sandberg, University of Minnesota; Dena Schall, Virginia Commonwealth University; and Lisa Zindle, University of Minnesota.