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Prediction of Hyperbilirubinemia in Near-Term and Term Infants

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ABSTRACT. *Objective.* The purpose of this study was to determine whether end-tidal carbon monoxide (CO) corrected for ambient CO (ETCOc), as a single measurement or in combination with serum total bilirubin (STB) measurements, can predict the development of hyperbilirubinemia during the first 7 days of life.

Methods. From 9 multinational clinical sites, 1370 neonates completed this cohort study from February 20, 1998, through February 22, 1999. Measurements of both ETCOc and STB were performed at 30 ± 6 hours of life; STB also was measured at 96 ± 12 hours and subsequently following a flow diagram based on a table of hours of age-specific STB. An infant was defined as hyperbilirubinemic if the hours of age-specific STB was greater than or equal to the 95th percentile as defined by the table at any time during the study.

Results. A total of 120 (8.8%) of the enrolled infants became hyperbilirubinemic. Mean STB in breastfed infants was 8.92 ± 4.37 mg/dL at 96 hours versus 7.63 ± 3.58 mg/dL in those fed formula only. The mean ETCOc at 30 ± 6 hours for the total population was 1.48 ± 0.49 ppm, whereas those of nonhyperbilirubinemic and hyperbilirubinemic infants were 1.45 ± 0.47 ppm and 1.81 ± 0.59 ppm, respectively. Seventy-six percent (92 of 120) of hyperbilirubinemic infants had ETCOc greater than the population mean. An ETCOc greater than the population mean at 30 ± 6 hours yielded a 13.0% positive predictive value (PPV) and a 95.8% negative predictive value (NPV) for STB ≥ 95 th percentile. When infants with STB >95 th percentile at <36 hours of age were excluded, the STB at 30 ± 6 hours yielded a 16.7% PPV and a 98.1% NPV for STB >75 th percentile. The combination of these 2 measurements at 30 ± 6 hours (either ETCOc more than the population mean or STB >75 th percentile) had a 6.4% PPV with a 99.0% NPV.

Conclusions. This prospective cohort study supports previous observations that measuring STB before discharge may provide some assistance in predicting an infant's risk for developing hyperbilirubinemia. The addition of an ETCOc measurement provides insight into the processes that contribute to the condition but does not materially improve the predictive ability of an hours of age-specific STB in this study population. The combination of STB and ETCOc as early as 30 ± 6 hours may identify infants with increased bilirubin production (eg, hemolysis) or decreased elimination (conjugation defects) as well as infants who require early follow-up after discharge for jaundice or other clinical problems such as late anemia. Depending on the incidence of hyperbilirubinemia within an institution, the criteria for decision making should vary according to its unique population. *Pediatrics* 2001;108:31–39; carbon monoxide, end-tidal carbon monoxide, hemolysis, hyperbilirubinemia, neonatal jaundice, prediction, serum total bilirubin.

ABBREVIATIONS. AAP, American Academy of Pediatrics; STB, serum total bilirubin; CO, carbon monoxide; ETCOc, end-tidal carbon monoxide corrected for ambient CO; NICU, neonatal intensive care unit; ETCO₂, end-tidal carbon dioxide; SD, standard deviation; ROC, receiver operator characteristic; PPV, positive predictive value; NPV, negative predictive value.

Managed care has been associated with shortened hospital stays for mothers and infants, thus curtailing the time for hospital-based professional assessment of infant feeding, instruction about breastfeeding, and the detection of jaundice.¹ In 1994, the American Academy of Pediatrics (AAP) published a practice guideline to provide pediatric practitioners with criteria for safe and early management of hyperbilirubinemia in healthy term neonates.² However, compliance with the guideline often is lacking. For example, many pediatricians do not exclude infants with hemolysis or those <37 weeks' gestation, as suggested in the guideline. This has led to the inappropriate early discharge of infants with unrecognized hemolytic disease as well as near-term infants who are having difficulty with feeding. A recent report³ reconfirmed that hyperbilirubinemia and problems related to feeding are the main reasons for hospital readmission during the first week of life.^{4–7}

The AAP practice guideline relies on the ability of the physician to recognize significant jaundice as an indication for the determination of serum total bili-

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rubin (STB) levels. Unfortunately, there is considerable variability in the accuracy of assessing the degree of jaundice among observers.^{8,9} Furthermore, with very early discharge, modest but unacceptable elevation of the STB might not be recognized clinically, thus placing the infant at risk for severe hyperbilirubinemia (STB \geq 95th percentile).¹⁰ The AAP guideline also requires that hemolysis be ruled out in infants who exhibit significant jaundice. The measurement of carbon monoxide (CO) in end-tidal breath corrected for ambient CO (ETCOc), an index of total bilirubin production, can alert the physician to possible hemolysis as well as other conditions associated with increased bilirubin production irrespective of the timing or presence of jaundice.¹¹⁻¹⁴ Moreover, the combination of hours of age-specific STB and ETCOc measurements may provide valuable insight into the dynamics of bilirubin production and elimination in individual infants. This practice also may improve the early recognition of infants who are at risk for severe hyperbilirubinemia after discharge and who may require close follow-up and/or additional diagnostic evaluation.

The objective of this study was to determine whether a measurement of ETCOc obtained at 30 ± 6 hours after birth alone or in a combination with an STB measurement obtained at the same time could predict the development of severe hyperbilirubinemia during the first 7 days (168 hours) of life with a high sensitivity and an acceptable specificity for practical clinical use.

METHODS

Participant Criteria

Infants were eligible for the study if their gestational age was ≥ 35 weeks as determined by best obstetric estimate and if enrollment could be accomplished within the first 36 hours of life during the period of February 20, 1998, through February 22, 1999. Exclusion criteria were neonates having any illness that would require admission to the neonatal intensive care unit (NICU) before 24 hours (a workup to rule out sepsis in a neonate who appeared to be well or maternal treatment with antibiotics were not exclusion criteria) or severe congenital anomalies. Also excluded were infants who were in incubators; who had pulmonary disease requiring oxygen or ventilatory assistance via hood, tent, nasal cannula, continuous positive airway pressure, or ventilator; who had significant nasal obstruction in either naris; who had a birth weight of 850 g or less; or who had respiratory rates ≤ 10 or ≥ 100 breaths per minute (operating range for the CO-Stat End-Tidal Breath Analyzer [Natus Medical Inc., San Carlos, CA]).

Study Design

This cohort study included all infants who met the eligibility criteria and for whom informed consent was obtained and had mandatory measurements of ETCOc and STB performed at 30 ± 6 hours of age and STB at 96 ± 12 hours. Additional STB measurements were performed according to a flow diagram (Fig 1) and an hourly bilirubin table (Table 1) based on a racially diverse population of 17 854 term- and near-term infants, with 15 014 neonates contributing STB values for the period of 18 to 24 hours.¹⁰ Enrollment consisted of neonates from 9 clinical sites, 4 domestic and 5 international. Each study site enrolled eligible infants serially on a schedule determined by the circumstances and restraints imposed by clinical operations and personnel limitations at the respective institutions. Each site maintained an enrollment log identifying all infants eligible to be studied and selected as well as the reasons for nonenrollment of any eligible neonate. The CO-Stat End-Tidal Breath Analyzer with single-use disposable nasal sampler was used to analyze the breath of all infants for ETCOc.^{13,14} The device

was calibrated locally every 30 days. The accuracy of the analyzer is ± 0.3 ppm (or $\mu\text{L/L}$) or 10% of the reading (whichever is greater) for respiratory rates between 10 and 60 breaths/min and ± 0.3 ppm or 15% of the reading (whichever is greater) for breathing rates >60 . In a previous bedside evaluation study of the instrument,¹³ the reproducibility and coefficient of variation of ETCOc measurements when sampling neonates and adults were determined to be better than other methods tested, such as hand sampling and semiautomatic electrochemical detection. In addition to ETCOc, other parameters measured by the device include breath CO concentration (uncorrected for ambient CO), ambient CO concentration (reflecting inhaled air), end-tidal carbon dioxide (ETCO₂), and respiratory rate. The device uses side-stream sampling to draw nasal air continuously through the sampler at 60 mL/min. The sampler is made of a clear polymer with an inner and outer diameter of 0.8 and 1.5 mm, respectively. Adhesive wings (8×5 mm) allow a maximum insertion depth of 6.0 mm before coming into contact with the lower edge of the nostril. Because participants are not required to control their breathing patterns, this device can be used with infants and others who are unable to accomplish breath control.

Blood was collected and the serum was analyzed for STB in each enrolled infant (Fig 1). Each site used its own clinical laboratory and method for all STB measurements (Hitachi 917 Spectrophotometric Analyzer [Roche-Diagnostics, Inc, Tokyo, Japan], Unistat Bilirubinometer [Reichert Jung, Vienna, Austria] at 2 sites, and the Hitachi 747 [Roche-Diagnostics, Inc] at all other sites).¹⁵ Infants were defined as hyperbilirubinemic if their hours of age-specific STB at any time during the study was ≥ 95 th percentile, as defined by Table 1. In addition, during the first 24 hours, the attending physician had the option of measuring the STB for an infant who exhibited visible jaundice. For infants whose STB was ≥ 95 th percentile, an ETCOc measurement was performed and the infant was excluded from further study. Infants who were not excluded before 24 hours had the first scheduled STB and ETCOc measurements performed at 30 ± 6 hours in coordination with state-mandated newborn screening for inborn errors of metabolism and additional required tests. Infants with STB ≥ 95 th percentile exited the study at this time. All other infants remained in the study. From 24 to 84 hours, measurements of STB were performed at the discretion of the physician. If the physician elected to perform an STB between 24 and 84 hours, then the infant exited the study if the level was ≥ 95 th percentile. If the STB was not ≥ 95 th percentile or if no STB was obtained between 24 and 84 hours, then the infant had a mandatory STB performed at 96 ± 12 hours. If the STB was ≥ 95 th percentile or <40 th percentile, then the infant exited the study. Any STB between the 40th and the 94th percentiles required a repeat STB in 24 to 48 hours based on the result. If the 96 ± 12 hour measurement was ≥ 75 th percentile and <95 th percentile, then the STB was repeated within 24 hours. If the 96 ± 12 hour measurement was >40 th percentile and <75 th percentile, then the STB was repeated within 48 hours. An infant who had an STB between the 40th and the 94th percentiles continued to have STB measured every 24 to 48 hours until the STB was ≥ 95 th percentile or <40 th percentile, the most recent STB was less than or equal to the STB result 24 to 48 hours earlier, or the infant attained 168 hours of life. At 168 hours, all infants exited the study with ongoing care provided at the discretion of the physician.

Statistical Methods

Of the 1895 participants who were enrolled in the study, 1370 completed the study. Of the excluded infants, 88 were enrolled in the study but did not participate in the testing, 272 were lost to follow-up, 131 had technical problems with preproduction samplers, 32 could not be tested with the CO-Stat device for other reasons (eg, hydrogen interference, irregular breath patterns), and 175 did not adhere to the study protocol. In addition, another 131 infants were tested at a tenth site but were excluded from analysis because measurements of STB were taken with a transcutaneous bilirubinometer rather than performed with the standard blood test. Some infants were excluded for multiple reasons.

The study was conducted in 2 phases. In phase I, 577 infants were tested with a preproduction CO-Stat nasal sampler; in phase II, 793 infants were tested with the production sampler. The ETCOc results from phase I showed a higher mean \pm standard deviation (SD) than those values from phase II (1.70 ± 0.54 vs

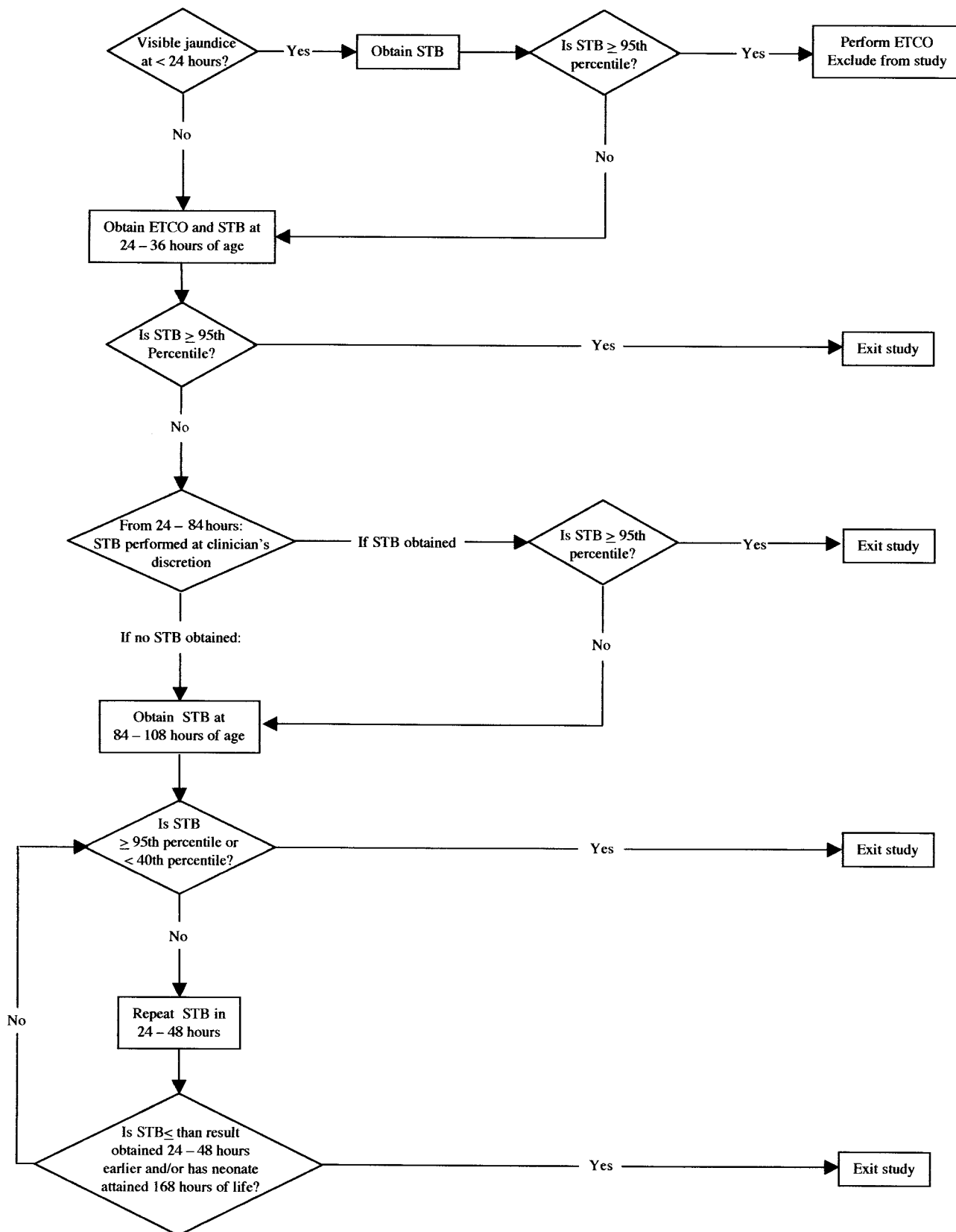


Fig 1. Study protocol decision-making flow diagram.

4.48 ± 0.49 ppm, respectively). This was attributable to a slight outgassing of CO from a material used in the preproduction sampler. The ETCOc data from the 2 phases of the study were combined and normalized by converting the measurements to Z scores (ie, standardized deviation of the measurement from the

mean, in SD units). All analyses were conducted in Z units, and the ETCOc values reported throughout this article have been converted back to ppm with the distribution having the mean and SD of phase II.

Receiver operator characteristic (ROC) analyses^{16–18} for the

TABLE 1. Hours of Age-Specific Serum Total Bilirubin (STB)*

Age (hr)	40th %tile (mg/dL)	75th %tile (mg/dL)	95th %tile (mg/dL)	Age (h)	40th %tile (mg/dL)	75th %tile (mg/dL)	95th %tile (mg/dL)	Age (h)	40th %tile (mg/dL)	75th %tile (mg/dL)	95th %tile (mg/dL)
18	4.5	5.6	6.9	69	10.8	13.2	15.7	120	13.2	15.8	17.6
19	4.6	5.7	7.2	70	10.9	13.3	15.8	121	13.2	15.8	17.6
20	4.7	5.8	7.4	71	11.1	13.3	15.9	122	13.2	15.8	17.6
21	4.8	6.0	7.5	72	11.2	13.4	15.9	123	13.2	15.7	17.6
22	4.9	6.1	7.6	73	11.2	13.5	16.0	124	13.2	15.7	17.5
23	4.9	6.3	7.7	74	11.3	13.6	16.1	125	13.2	15.7	17.5
24	5.0	6.4	7.8	75	11.3	13.7	16.1	126	13.2	15.7	17.5
25	5.2	6.6	8.1	76	11.3	13.8	16.2	127	13.2	15.7	17.5
26	5.3	6.7	8.4	77	11.4	13.9	16.3	128	13.2	15.6	17.5
27	5.5	6.9	8.6	78	11.4	14.0	16.3	129	13.2	15.6	17.5
28	5.6	7.0	8.9	79	11.4	14.1	16.4	130	13.2	15.6	17.5
29	5.8	7.2	9.2	80	11.5	14.2	16.5	131	13.2	15.6	17.4
30	6.0	7.5	9.4	81	11.5	14.3	16.5	132	13.2	15.6	17.4
31	6.1	7.7	9.7	82	11.5	14.4	16.6	133	13.2	15.5	17.4
32	6.3	8.0	10.0	83	11.6	14.5	16.6	134	13.2	15.5	17.4
33	6.5	8.2	10.3	84	11.6	14.6	16.7	135	13.2	15.5	17.4
34	6.7	8.5	10.5	85	11.7	14.7	16.8	136	13.2	15.5	17.4
35	6.9	8.7	10.8	86	11.7	14.7	16.8	137	13.2	15.5	17.4
36	7.0	8.9	11.1	87	11.8	14.8	16.9	138	13.2	15.4	17.4
37	7.2	9.2	11.4	88	11.9	14.8	16.9	139	13.2	15.4	17.3
38	7.4	9.4	11.6	89	11.9	14.9	17.0	140	13.2	15.4	17.3
39	7.6	9.7	11.9	90	12.0	14.9	17.1	141	13.2	15.4	17.3
40	7.8	9.9	12.2	91	12.1	15.0	17.1	142	13.2	15.3	17.3
41	7.9	10.0	12.3	92	12.1	15.0	17.2	143	13.2	15.3	17.3
42	7.9	10.1	12.3	93	12.2	15.1	17.2	144	13.2	15.3	17.3
43	8.0	10.1	12.4	94	12.3	15.1	17.3	145	13.2	15.3	17.3
44	8.1	10.2	12.5	95	12.3	15.2	17.3	146	13.2	15.3	17.3
45	8.2	10.4	12.7	96	12.4	15.2	17.4	147	13.2	15.3	17.4
46	8.4	10.5	12.8	97	12.4	15.2	17.4	148	13.2	15.3	17.4
47	8.5	10.7	13.0	98	12.5	15.3	17.4	149	13.3	15.3	17.5
48	8.6	10.8	13.2	99	12.5	15.3	17.4	150	13.3	15.3	17.5
49	8.7	11.0	13.3	100	12.5	15.3	17.4	151	13.3	15.3	17.5
50	8.8	11.1	13.5	101	12.6	15.3	17.4	152	13.3	15.3	17.6
51	8.9	11.3	13.7	102	12.6	15.4	17.5	153	13.3	15.3	17.6
52	8.9	11.4	13.8	103	12.7	15.4	17.5	154	13.3	15.3	17.6
53	9.0	11.6	14.0	104	12.7	15.4	17.5	155	13.3	15.4	17.7
54	9.1	11.7	14.2	105	12.7	15.4	17.5	156	13.3	15.4	17.7
55	9.2	11.9	14.3	106	12.8	15.5	17.5	157	13.3	15.4	17.7
56	9.3	12.0	14.5	107	12.8	15.5	17.5	158	13.3	15.4	17.8
57	9.4	12.2	14.7	108	12.8	15.5	17.5	159	13.4	15.4	17.8
58	9.4	12.3	14.8	109	12.9	15.5	17.5	160	13.4	15.4	17.9
59	9.5	12.5	15.0	110	12.9	15.6	17.5	161	13.4	15.4	17.9
60	9.6	12.6	15.2	111	12.9	15.6	17.5	162	13.4	15.4	17.9
61	9.7	12.7	15.2	112	13.0	15.6	17.5	163	13.4	15.4	18.0
62	9.9	12.7	15.3	113	13.0	15.6	17.5	164	13.4	15.4	18.0
63	10.0	12.8	15.4	114	13.0	15.7	17.6	165	13.4	15.4	18.0
64	10.1	12.9	15.4	115	13.1	15.7	17.6	166	13.4	15.4	18.1
65	10.3	12.9	15.5	116	13.1	15.7	17.6	167	13.4	15.4	18.1
66	10.4	13.0	15.5	117	13.1	15.7	17.6	168	13.4	15.4	18.2
67	10.5	13.1	15.6	118	13.2	15.8	17.6				
68	10.7	13.1	15.7	119	13.2	15.8	17.6				

* Adapted from Bhutani et al.¹⁰

prediction of hyperbilirubinemia were performed for 3 different parameters of predicting hyperbilirubinemia: ETCOc at 30 ± 6 hours, STB percentile (as defined by the table) at 30 ± 6 hours, and a combination of STB and ETCOc test at 30 ± 6 hours. A positive result for the combined test was defined as either an STB between the 75th and 95th percentile or an ETCOc greater than the population mean or both at 30 ± 6 hours. Infants who presented with STB ≥95th percentile at 30 ± 6 hours were excluded from the STB and combined ROC analyses because they had been found to be hyperbilirubinemic at the predicting measurement. These infants were not excluded from the ETCOc ROC analysis, because the predicting and outcome measurements were different although they occurred in the same time window.

Two stepwise logistic regression analysis models for the prediction of hyperbilirubinemia (as defined above) were performed on the data: 1 for noninvasive (ie, ETCOc) measurements and 1 for invasive measurements (ie, STB). The following variables were used in the noninvasive model: ETCOc at 30 ± 6 hours, presence of bruising, feeding type (breast milk, formula, or both), birth

weight, race (Asian, white or Hispanic, black, other), maternal diabetes, type of labor (vaginal or cesarean section), gender, infection, cephalhematoma, pregnancy-induced hypertension/pre-eclampsia, gravidity, parity, maternal blood type, and maternal Rh status.

At each step in building the first model, the variable that reduced the total squared error was added first. Two stopping rules were used: 1) the addition of the next variable reduced the overall squared error by <1%, and 2) the probability of hyperbilirubinemia was not statistically different for the candidate variable to be added to the model.

RESULTS

The distributions of STB for the total population at 30 ± 6 hours and at 96 ± 12 hours show that approximately 9% (120 of 1370) of infants had an STB ≥95th percentile. Four of 620 (0.65%, with a 95% confidence

interval of 0.02% to 1.30%) infants had an STB <40th percentile at 30 ± 6 hours but subsequently had an STB >95th percentile. Infants who were breastfed had higher mean STB levels at 96 hours (8.92 ± 4.37 mg/dL) compared with those who were fed formula exclusively (7.63 ± 3.58 mg/dL; $P < .0001$).

The distribution of ETCOc at 30 ± 6 hours is shown in Fig 2. The mean ETCOc for the total population ($N = 1370$) was 1.48 ± 0.49 ppm (range: 0.2–3.5; median: 1.5) at 30 ± 6 hours of life (Table 2). The mean ETCOc for the nonhyperbilirubinemic infants ($N = 1250$) was 1.45 ± 0.47 ppm (range: 0.1–3.1; median: 1.4) compared with 1.81 ± 0.59 ppm (range: 0.4–3.6; median: 1.9) for the hyperbilirubinemic infants ($N = 120$; $P < .0001$). Ninety-two (76%) of 120 hyperbilirubinemic participants had an ETCOc greater than the total population mean. Center variabilities of the mean ETCOc at 30 ± 6 hours of each site's total population and of infants with STB ≥ 95 th percentile are shown in Table 3.

Logistic regressions show that the following variables were found to be significant for the first stopping rule (in order of addition): ETCOc, feeding type, birth weight, race, parity, maternal diabetes, maternal blood type, and bruising. The second, more conservative, stopping rule found (in order of addition) ETCOc, feeding type, and birth weight to be the most significant variables.

The second logistic regression analysis model included the above variables as inputs as well as the STB percentiles at the 30 ± 6 hour measurement as defined by Table 1. For this analysis, the following variables were found to be significant (in order of addition): STB percentile, bruising, maternal blood type, race, maternal diabetes, feeding type, gravidity, and ETCOc. The more conservative stopping rule found that only STB percentile and bruising were significant.

ROC curves are shown in Fig 3. For the 3 param-

eters of predicting hyperbilirubinemia at a specificity of 80% ($1 - \text{specificity} = 20\%$), the sensitivity at 30 ± 6 hours ranges from approximately 50% (ETCOc alone) to approximately 65% (with 30 ± 6 hour STB). For 50% specificity, the sensitivities increase to 75% and 90%. Positive and negative predictive values (PPV and NPV, respectively) were calculated. ETCOc greater than the mean at 30 ± 6 hours yielded a 13.0% PPV with a 95.8% NPV (Table 4). STB >75th percentile at 30 ± 6 hours resulted in a 16.7% PPV with a 98.1% NPV when infants with STB >95th percentile at <36 hours of age were excluded. The combination of the 2 measurements if either ETCOc was more than the mean or STB >75th percentile yielded a 6.4% PPV with a 99.0% NPV as a result of the low prevalence of hyperbilirubinemia in the study population. With these levels of sensitivity and specificity, the PPV and NPV of early (30 ± 6 hours) measurements of ETCOc or ETCOc in combination with STB for reliable prediction of hyperbilirubinemia are not achievable.

DISCUSSION

Neonatal jaundice is a syndrome with many causes but, ultimately, is the result of an imbalance between bilirubin production and elimination. On the basis of a nomogram for hours of age-specific STB levels,¹⁰ 120 (8.8%) of 1370 infants had an STB ≥ 95 th percentile between 24 and 36 hours and 168 hours of life. Total bilirubin formation, as indexed by ETCOc, was 24.7% higher in the hyperbilirubinemic infants with the majority (76%) of these infants having an ETCOc greater than the mean of the whole population. However, it is important to note that some infants with very low bilirubin production still become hyperbilirubinemic. This strongly suggests that the elimination of bilirubin is sufficiently impaired to cause significant jaundice in approximately one quarter of the infants who develop hyperbiliru-

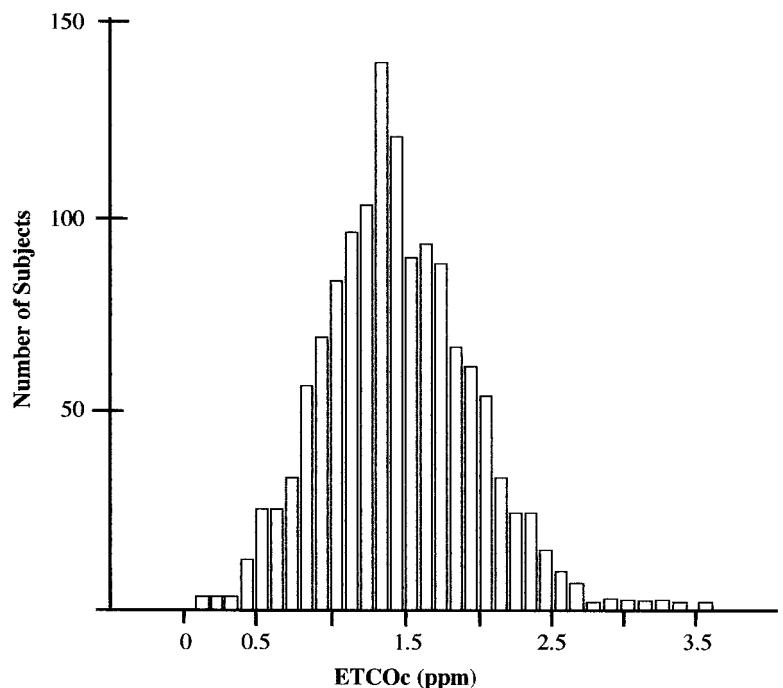


Fig 2. ETCOc, ppm, distribution at 30 ± 6 hours.

TABLE 2. Summary of the Mean ETCOc at 30 ± 6 Hours of Life (Mean ± SD) for the Total Study Population and Subcategories

Category	Subcategory	Mean ETCOc (at 30 ± 6 Hours)*				
		Total Infants		Infants With STB ≥95%		P‡
		n (%)	ETCOc	n (%)	ETCOc	
All		1370 (100)	1.48 ± 0.49	120 (8.8)	1.81 ± 0.59	≤.0001
Gender	Male	671 (49.0)	1.50 ± 0.49	63 (9.5)	1.87 ± 0.62	≤.0001
	Female	699 (51.0)	1.46 ± 0.49	57 (8.2)	1.74 ± 0.55	≤.0001
Birth weight (g)	≥mean	685 (50.0)	1.55 ± 0.50	50 (7.5)	1.99 ± 0.62	≤.0001
	<mean	685 (50.0)	1.41 ± 0.46	70 (10.2)	1.67 ± 0.53	≤.0001
Race	Asian/Pacific Islander	533 (38.9)	1.37 ± 0.50	53 (9.9)	1.71 ± 0.64	≤.0001
	Black	224 (16.4)	1.42 ± 0.44	11 (4.9)	1.80 ± 0.48	≤.0055
	Hispanic	53 (3.9)	1.56 ± 0.49	1 (1.9)	2.49	NA
	White	454 (33.1)	1.61 ± 0.46	50 (11.0)	1.92 ± 0.54	≤.0001
	Other	106 (7.7)	1.57 ± 0.51	6 (5.7)	1.62 ± 0.59	NS
Cephalhematoma		55 (4.0)	1.54 ± 0.50	9 (16.4)	1.88 ± 0.46	NS
Bruising		107 (7.8)	1.71 ± 0.55	23 (21.5)	1.85 ± 0.59	NS
Breast milk only		476 (34.7)	1.60 ± 0.47	47 (9.9)	1.87 ± 0.57	.0003
Coombs' positive		54 (3.9)	1.66 ± 0.55§	10 (18.5)	1.89 ± 0.63	NS
Coombs' negative		519 (37.9)	1.48 ± 0.51	54 (10.4)	1.89 ± 0.55	≤.0001

NA indicates not applicable; NS, not significant.

* The ETCOc values for the 577 infants measured with the preproduction sampler were adjusted to the mean ± SD of the 793 infants measured using the production sampler.

‡ Comparison of ETCOc values of infants with STB ≥ the 95th percentile with those of the total infant population in each subcategory.

§ P < .00932, when compared with the total population.

TABLE 3. Mean ETCOc at 30 ± 6 Hours (Mean ± SD) for Each Study Center Population and for the Center Participants with STB ≥ the 95th Percentile

Site	Mean ETCOc (30 ± 6 hours)			
	Total Population		Infants With STB ≥95%	
	n	ETCOc	n (%)	ETCOc
Rainbow Babies' and Children's Hospital (Cleveland, OH)	353	1.52 ± 0.45	20 (5.7)	1.84 ± 0.53
Pamela Youde Nethersole Eastern Hospital (Hong Kong, China)	303	1.39 ± 0.47	25 (8.3)	1.66 ± 0.56
Lucile Salter Packard Children's Hospital (Stanford, CA)	194	1.63 ± 0.47	19 (9.8)	1.93 ± 0.60
Queen Mary & Tsan Yuk Maternity Hospitals (Hong Kong, China)	167	1.24 ± 0.50	9 (5.4)	1.65 ± 0.60
Bikur Cholim Hospital (Jerusalem, Israel)	119	1.60 ± 0.49	9 (7.6)	1.76 ± 0.51
Women and Infants Hospital (Providence, RI)	116	1.53 ± 0.47	10 (8.6)	1.96 ± 0.54
Pennsylvania Hospital (Philadelphia, PA)	50	1.42 ± 0.45	8 (16.0)	1.75 ± 0.49
Shaare Zedek Medical Center (Jerusalem, Israel)	37	1.61 ± 0.57	8 (21.6)	2.10 ± 0.50
University of Kobe (Kobe, Japan)	31	1.53 ± 0.65	12 (38.7)	1.73 ± 0.88
Total	1370	1.48 ± 0.49	120	1.81 ± 0.59

binemia. Conversely, many infants with high bilirubin production rates do not develop significant jaundice because they can deal with this increased load. Thus, given the low prevalence of severe hyperbilirubinemia, it was unlikely that either an hours of age-specific STB or ETCOc, alone or in combination, would have a high PPV, which is what was observed in this study. Nonetheless, the combination of STB and ETCOc measurements provides insight into the underlying processes that give rise to hyperbilirubinemia but does not materially improve the predictive ability of an hours of age-specific STB in this study population. For instance, if both STB and ETCOc measurements fall below a set threshold, the least worrisome circumstance could be assumed. Thus, the absence of both an elevated hours of age-specific STB and elevated ETCOc, which has a high NPV, would support the clinical decision to limit laboratory testing and to shorten the hospital stay for such low-risk infants.

On the basis of a review of the ROC curves, a clinician might be tempted to rely on STB alone for the prediction of hyperbilirubinemia. Practically, this decision would not be unreasonable because increased bilirubin production, as indexed by ETCOc, is a major component of most hyperbilirubinemia as indicated by the proportion of infants (76%) with increased bilirubin production in the hyperbilirubinemic group. However, an ETCOc measurement in combination with the STB identifies precisely those infants who are most likely to have hemolysis versus those with conjugation incapacities, such as Gilbert's disease¹⁹⁻²¹ or the G71R missense mutation in the bilirubin glucuronosyltransferase gene.²² The added benefit of diagnosing hemolysis by measurement of the ETCOc ensures compliance with the AAP guideline that requires identification of infants with increased hemolysis.² In addition, the possibility of diagnosing conjugation defects becomes more likely among infants with a high STB and a normal or low

Fig 3. ROC curves comparing ETCOc measurements at 30 ± 6 hours (\square), STB measurements alone at 30 ± 6 hours (Δ), and combined ETCOc and STB measurements at 30 ± 6 hours (\circ) at a specificity of 80%. Dotted diagonal line = no discrimination.

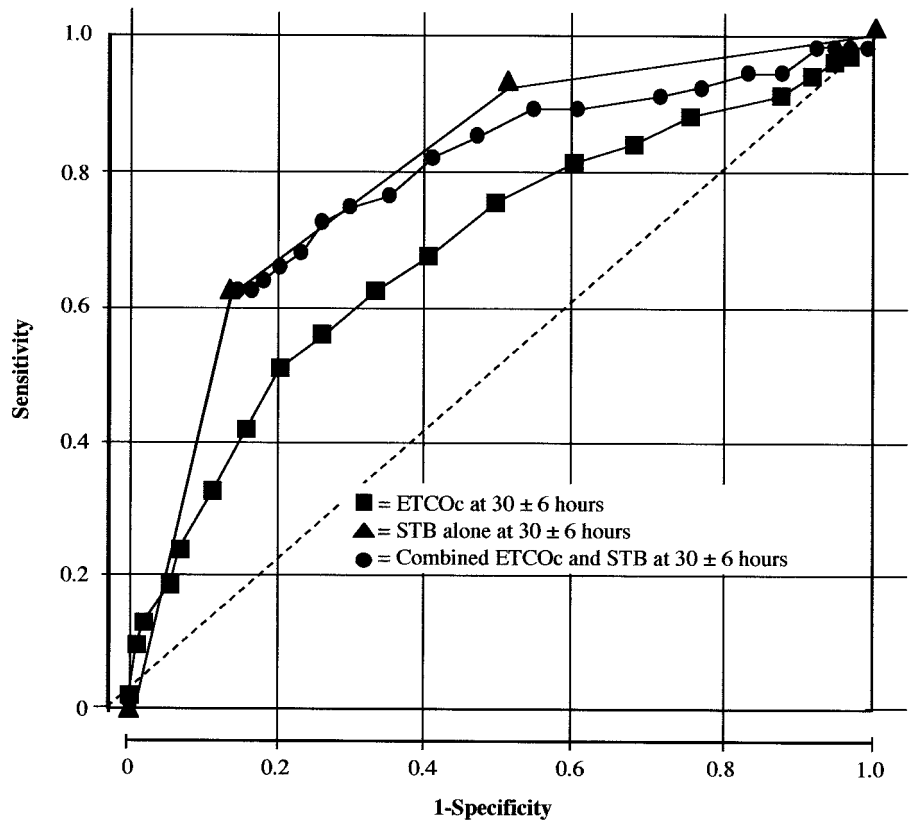


TABLE 4. Sensitivity, Specificity, PPV, and NPV for ETCOc Greater Than the Population Mean at 30 ± 6 Hours of Life (Mean \pm SD) for STB \geq 95th Percentile of the Total Study Population

Test (ETCO _c)	Disease		TP + FP (707)	PPV 92/707 = 13.0%
	Positive (120)	Negative (1250)		
Positive	True Positive (TP) (92)	False Positive (FP) (615)	TP + FP (707)	PPV 92/707 = 13.0%
Negative	False Negative (FN) (28)	True Negative (TN) (635)	FN + TN (663)	NPV 635/663 = 95.8%
	TP + FN (120)	FP + TN (1250)		
	Sensitivity 92/120 = 76.7%	Specificity 635/1250 = 50.8%		

Sensitivity = TP/TP + FN, the probability of the test finding disease among those who have the disease or the proportion of those with the disease who have a positive test result.

Specificity = TN/TN + FP, the probability of the test finding no disease among those who do not have the disease or the proportion of those free of the disease who have a negative test result.

PPV = TP/TP + FP, the percentage of people with a positive test result who actually have the disease.

NPV = TN/FN + TN, the percentage of people with a negative test result who do not have the disease.

ETCOc. Moreover, improved diagnostic differentiation of jaundiced infants might direct specific therapeutic interventions as new treatment options become available, for example, metalloporphyrin therapy for high producers of the pigment²³⁻²⁶ or gene therapy for conjugation defects.²⁷ In the meantime, high-risk infants could be targeted for close follow-up to avoid unexpected significant hyperbilirubinemia and readmission to the hospital.

In fact, logistic regression models can be used to predict later significant elevation in STB. Without using STB at 30 ± 6 hours as a predictor, the variables that are most significant are (in order of addition) ETCOc, feeding type, birth weight, race, parity, maternal diabetes, maternal blood type, and bruising. A simplified model, generated by using a rule to stop adding variables when the category of the variable was not significantly different with regard to the probability of hyperbilirubinemia, includes 3 vari-

ables: ETCOc, feeding type, and birth weight. Thus, increased bilirubin production, exclusive breastfeeding, and birth weight (a likely surrogate for gestational age in this study, which included infants with gestational ages ≥ 35 weeks) represent useful predictors for whether a particular infant develops hyperbilirubinemia. The STB percentile at 30 ± 6 hours, together with the presence of bruising (a surrogate for increased bilirubin production), provides a simplified prediction model, somewhat superior to ETCOc and the other variables available.

The common practice of using Coombs' testing as a surrogate for the identification of hemolysis is not a reliable strategy. In this study, only 18.5% (10 of 54) of infants with a positive direct Coombs' test had an STB \geq 95th percentile and mean ETCOc values of 1.89 ± 0.63 ppm ($P < .00932$ when compared with the population mean), suggesting that most infants with a positive direct Coombs' test either can handle

the bilirubin load well or do not have hemolysis. Conversely, 54 (10.4%) of 519 infants who had STB \geq 95th percentile and a mean ETCOc value of 1.89 ± 0.55 ppm had a negative direct Coombs' test, consistent with the possibility that some infants with a negative direct Coombs' test may have hemolysis. Although not all infants (only 573 of 1370, or 41.8%) had a Coombs' test performed during the course of this study, these observations suggest that an ETCOc measurement might represent a more direct way to identify noninvasively infants who do not need Coombs' testing or other laboratory tests before discharge and routine follow-up.

In addition, the guidelines for management of hyperbilirubinemia may need to vary between centers, as the percentage of infants with STB \geq 95th percentile as based on a US population varied from 5% to 39% among centers (Table 3). The propensity for jaundice in a particular population was variably related to increased ETCOc, suggesting that defects in conjugation or persistent enterohepatic circulation of bilirubin play important causative roles among infants in certain settings. The marked increased percentage of infants with STB \geq 95th percentile in Kobe, Japan, is consistent with the high proportion of infants with defective glucuronosyltransferase in this population.²² It also is interesting to note that the Chinese population in this study had a lower incidence of hyperbilirubinemia than previously reported,²⁸⁻³⁰ which suggests that there may have been changes in environmental factors. There also was a high incidence observed in the Jewish population and may be due to the small sample size of this group. Furthermore, it is interesting to note that in our total population, 4 (0.65%) of 620 infants had an STB <40th percentile at 30 ± 6 hours but nevertheless subsequently developed an STB \geq 95th percentile. In addition, the differences in the percentage of infants with STB \geq 95th percentile observed at each center also may be confounded by the known interlaboratory variability in STB measurements.¹³ This fact alone warrants the use of other measurement parameters, in concert or alone, to provide additional information for the identification and follow-up of infants who are at risk for hyperbilirubinemia.

Breastfeeding was associated with a slight increase in the STB, and, as indicated by the ETCOc, there was increased bilirubin production associated with breastfeeding. Although increased production was not observed previously in smaller studies,^{11,31} relative caloric deprivation associated with the initiation of exclusive breastfeeding perhaps could explain this phenomenon.³² More important, the possibility that increased bilirubin production compounds the effect of an increased enterohepatic circulation in exclusively breastfed infants supports further the clinical observation that breastfed-only infants have a propensity for higher STB levels after birth and suggests that the definition of physiologic jaundice should be reconsidered in this context. Furthermore, in addition to identifying infants with hemolysis or other causes of increased bilirubin production, the need to observe closely and evaluate the adequacy of breastfeeding before discharge might reduce both morbidity

and the frequency of readmission to the hospital.³³ We also confirmed that hemolysis and bruising, as expected, increased bilirubin production and the propensity for jaundice.

CONCLUSION

This prospective cohort study supports previous observations that the practice of measuring STB before discharge may provide some assistance in predicting infants who are at risk for the subsequent development of hyperbilirubinemia.^{10,34,35} However, this measurement together with an ETCOc provides insight into the processes that contribute to the condition. The combination of STB and ETCOc measurements as early as 30 ± 6 hours of life will increase the chance of identifying an infant with hemolysis or other causes of increased bilirubin production as well as infants with conjugation defects. Such combination screening could identify infants who might need early intervention with phototherapy or additional diagnostic workup and/or follow-up for jaundice after discharge. It is important to recognize that infants with increased bilirubin production, who may handle the bilirubin load well, also may have other clinical problems that require diagnosis and follow-up, such as late anemia in the presence of hemolysis. Finally, differences in the incidence of hyperbilirubinemia and its causes may vary from one center to another. Although the screening procedures might be similar across institutions, the criteria used for decision making may need to vary depending on the prevalence and unique characteristics of the particular population and practice patterns.

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REFERENCES

1. Braveman P, Egerter S, Pearl M, Marchi K, Miller C. Problems associated with early discharge of newborn infants. Early discharge of newborns and mothers: a critical review of the literature. *Pediatrics*. 1995;96:716-726
2. American Academy of Pediatrics, Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. *Pediatrics*. 1994;94:558-565 [published erratum appears in *Pediatrics*. 1995;95:458-461]
3. Brown AK, Damus K, Kim MH, et al. Factors relating to readmission of term and near-term neonates in the first two weeks of life. Early Discharge Survey Group of the Health Professional Advisory Board of the Greater New York Chapter of the March of Dimes. *J Perinat Med*. 1999;27:263-275
4. Heimler R, Shekawat P, Xy M, et al. Morbidity of newborns (NB) after nursery discharge: relationship to early discharge (ED) [abstract]. *Pediatrics*. 1996;98(suppl):576
5. Lee KS, Perlman M, Ballantyne M, Elliott I, To T. Association between duration of neonatal hospital stay and readmission rate. *J Pediatr*. 1995;127:758-766
6. Maisels MJ, Kring E. Length of stay, jaundice, and hospital readmission. *Pediatrics*. 1998;101:995-998

7. Soskolne EI, Schumacher R, Fyock C, Young ML, Schork A. The effect of early discharge and other factors on readmission rates of newborns. *Arch Pediatr Adolesc Med.* 1996;150:373–379
8. Johnson L, Bhutani VK. Guidelines for management of the jaundiced term and near-term infant. *Clin Perinatol.* 1998;25:555–574, viii
9. Moyer VA, Ahn C, Sneed S. Accuracy of clinical judgment in neonatal jaundice. *Arch Pediatr Adolesc Med.* 2000;154:391–394
10. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischARGE hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics.* 1999;103:6–14
11. Stevenson DK, Vreman HJ, Oh W, et al. Bilirubin production in healthy term infants as measured by carbon monoxide in breath. *Clin Chem.* 1994;40:1934–1939
12. Vreman HJ, Stevenson DK, Oh W, et al. Semiportable electrochemical instrument for determining carbon monoxide in breath. *Clin Chem.* 1994;40:1927–1933
13. Vreman HJ, Baxter LM, Stone RT, Stevenson DK. Evaluation of a fully automated end-tidal carbon monoxide instrument for breath analysis. *Clin Chem.* 1996;42:50–56
14. Vreman HJ, Wong RJ, Harmatz P, et al. Validation of the Natus CO-Stat End Tidal Breath Analyzer in children and adults. *J Clin Monit Comput.* 1999;15:421–427
15. Vreman HJ, Verter J, Oh W, et al. Interlaboratory variability of bilirubin measurements. *Clin Chem.* 1996;42:869–873
16. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology.* 1982;143:29–36
17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44:837–845
18. Goddard MJ, Hinberg I. Receiver operator characteristic (ROC) curves and non-normal data: an empirical study. *Stat Med.* 1990;9:325–337
19. Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med.* 1995;333:1171–1175
20. Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci U S A.* 1998;95:8170–8174
21. Kaplan M, Renbaum P, Levy-Lahad E, et al. Gilbert syndrome and glucose-6-phosphate dehydrogenase deficiency: a dose-dependent genetic interaction crucial to neonatal hyperbilirubinemia. *Proc Natl Acad Sci U S A.* 1997;94:12128–12132
22. Akaba K, Kimura T, Sasaki A, et al. Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. *Biochem Mol Biol Int.* 1998;46:21–26
23. Valaes T, Petmezaki S, Henschke C, Drummond GS, Kappas A. Control of jaundice in preterm newborns by an inhibitor of bilirubin production: studies with tin-mesoporphyrin. *Pediatrics.* 1994;93:1–11
24. Kappas A, Drummond GS, Henschke C, Valaes T. Direct comparison of Sn-mesoporphyrin, an inhibitor of bilirubin production, and phototherapy in controlling hyperbilirubinemia in term and near-term newborns. *Pediatrics.* 1995;95:468–474
25. Martinez JC, Garcia HO, Otheguy LE, Drummond GS, Kappas A. Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. *Pediatrics.* 1999;103:1–5
26. Stevenson DK, Rodgers PA, Vreman HJ. The use of metalloporphyrins for the chemoprevention of neonatal jaundice. *Am J Dis Child.* 1989;143:353–356
27. Tada K, Chowdhury NR, Neufeld D, et al. Long-term reduction of serum bilirubin levels in Gunn rats by retroviral gene transfer in vivo. *Liver Transpl Surg.* 1998;4:78–88
28. Brown WR, Boon WH. Ethnic group differences in plasma bilirubin levels in full-term, healthy Singapore newborns. *Pediatrics.* 1965;36:745–751
29. Li AM, Yeung CY, Chang WK, Soo HN. Epidemiological aspects of neonatal jaundice in Chinese infants. *Trop Geogr Med.* 1979;31:537–546
30. Fok TF, Lau SP, Hui CW. Neonatal jaundice: its prevalence in Chinese babies and associating factors. *Aust Paediatr J.* 1986;22:215–219
31. Stevenson DK, Bartoletti AL, Ostrander CR, Johnson JD. Pulmonary excretion of carbon monoxide in the human infant as an index of bilirubin production. IV. Effects of breast-feeding and caloric intake in the first postnatal week. *Pediatrics.* 1980;65:1170–1172
32. Lundh B, Johansson MB, Mercke C, Cavallin-Stahl E. Enhancement of heme catabolism by caloric restriction in man. *Scand J Clin Lab Invest.* 1972;30:421–427
33. American Academy of Pediatrics, Committee on Fetus and Newborn. Hospital stay for healthy term newborns. *Pediatrics.* 1995;96:788–790
34. Kaplan M, Hammerman C, Feldman R, Brisk R. PredischARGE bilirubin screening in glucose-6-phosphate dehydrogenase-deficient neonates. *Pediatrics.* 2000;105:533–537
35. Alpay F, Sarici SU, Tosuncuk HD, Serdar MA, Inanc N, Gokcay E. The value of first-day bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy term newborns. *Pediatrics.* 2000;106(2). URL: <http://www.pediatrics.org/cgi/content/full/106/2/e16>

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Croll E. *Endangered Daughters: Discrimination and Development in Asia.* London, United Kingdom: Routledge

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Prediction of Hyperbilirubinemia in Near-Term and Term Infants

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