Risk Factors for Neurotoxicity in Newborns With Severe Neonatal Hyperbilirubinemia

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KEY WORDS

kernicterus, neonatal hyperbilirubinemia, bilirubin encephalopathy, acute bilirubin encephalopathy, BIND score, risk factors for kernicterus

ABBREVIATIONS

AAP—American Academy of Pediatrics
TSB—total serum bilirubin
BE—bilirubin encephalopathy
ABE—acute bilirubin encephalopathy
BIND—bilirubin-induced neurologic dysfunction
OR—odds ratio
PPV—positive predictive value
ROC—receiver operator characteristic
FPR—false-positive rate

Dr Gamaleldin participated in the plan and follow-up of the study, formulated and tabulated data, participated in the initial analysis, and wrote the initial and edited drafts; Dr Iskander participated in the study plan, data monitoring, and initial data analysis and reviewed and edited the manuscript; Dr Seoud initiated the project idea, supervised Dr Aboraya, monitored results, and reviewed and edited drafts; Dr Aboraya performed data acquisition and the BIND examinations on most subjects as part of a doctoral thesis; Dr Aravkin organized the database and performed statistical analysis; Dr Sampson supervised the final statistical analysis and wrote the statistics section; and Dr Wennberg edited initial drafts and recommended approaches to analyzing and presenting data and collated the final draft in consultation with all coauthors.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-0206

doi:10.1542/peds.2011-0206

Accepted for publication Jun 21, 2011

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Funded by the National Institutes of Health (NIH).

WHAT'S KNOWN ON THIS SUBJECT: Hemolytic disease, sepsis, and low gestational age are thought to increase the risk for bilirubin encephalopathy in term/near-term newborns with severe hyperbilirubinemia, but data describing relative risks of these factors are lacking.

WHAT THIS STUDY ADDS: Infants with no neurotoxicity risk factors may tolerate high bilirubin levels without adverse effects (≥31 mg/dL in this study). Beyond a threshold bilirubin of ≤25 mg/dL, the risk for encephalopathy in infants with Rh hemolytic disease or sepsis depends primarily on unidentified modifying factors.

abstract

OBJECTIVE: To evaluate the importance of total serum bilirubin (TSB) and neurotoxicity risk factors in predicting acute bilirubin encephalopathy (ABE) at admission or posttreatment bilirubin encephalopathy (BE) in infants with severe hyperbilirubinemia.

METHODS: We analyzed the interaction of TSB and risk factors as determinants of ABE and BE in 249 newborns admitted with a TSB level of ≥25 mg/dL (427 μmol/L) to Cairo University Children's Hospital during a 12-month period.

RESULTS: Admission TSB values ranged from 25 to 76.4 mg/dL. Forty-four newborns had moderate or severe ABE at admission; 35 of 249 infants (14%) had evidence of BE at the time of discharge or death. Rh incompatibility (odds ratio [OR]: 48.6) and sepsis (OR: 20.6) greatly increased the risk for ABE/BE, but TSB levels correlated poorly with the presence or absence of ABE or BE in these patients. The OR for ABO incompatibility with anemia (1.8) was not statistically significant. Low admission weight (OR: 0.83 per 100 g) increased the risk for BE, especially when other risk factors were present. The threshold TSB level that identified 90% of infants with ABE/BE was 25.4 mg/dL when neurotoxicity risk factors were present. In contrast, neurotoxicity was first observed at a TSB level of >31.5 mg/dL in 111 infants without risk factors.

CONCLUSIONS: Newborns without risk factors for neurotoxicity have a higher tolerance for hyperbilirubinemia than recognized in management guidelines. The risk for BE in hemolytic disease varies with etiology. The great variation in response to TSB indicates that biological factors other than TSB values are important in the pathogenesis of BE. *Pediatrics* 2011;128:e925–e931

Management guidelines of the American Academy of Pediatrics (AAP) for jaundiced term and near-term infants to prevent kernicterus are based on the premise that total serum bilirubin concentration (TSB), modified by several "risk factors for neurotoxicity," is the best available predictor of risk for kernicterus.[1] Exchange transfusion is indicated when phototherapy fails to reduce the bilirubin load to <25 mg/dL in healthy term infants or to lower thresholds in the presence of neurotoxicity risk factors. These consensus-generated risk factors include: prematurity, isoimmune hemolytic anemia, glucose-6-phosphate dehydrogenase deficiency, significant lethargy, sepsis, acidosis, asphyxia, temperature instability, and hypoalbuminemia (<3 g/dL). There are limited data to rank the risk factors. In healthy term infants without risk factors, admission or peak TSB between 25 and 30 mg/dL (428–513 μmol/L) is associated with little risk of developing bilirubin encephalopathy (BE).[2–12]

This study reports the predictive relationships of TSB obtained at admission and several risk factors for (1) acute bilirubin encephalopathy (ABE) at admission and/or (2) evidence of residual BE after treatment (ie, at time of discharge or death) in 249 term and late-preterm infants with TSB levels of ≥25 mg/dL.

METHODS

We examined the early outcomes of newborns with severe neonatal hyperbilirubinemia admitted to the NICU of Cairo University Children's Hospital during a 12-month period from January 1, 2008, to December 31, 2008. The study was approved by the ethics committee of the Pediatrics Department, Cairo University. Inclusion criteria included infants with estimated gestational age >34 weeks or admission weight of >2000 g, postnatal age of 14 days or younger, and TSB level of ≥25 mg/dL. The entry TSB level was not adjusted to accommodate risk factors. All patients were born at outside birthing facilities, and early discharge, failure to screen for blood type incompatibility, and no scheduled postdischarge follow-up contributed to delayed diagnosis of hyperbilirubinemia. After admission, patients were managed according to the unit protocol based on the recommendations of the AAP for the management of severe neonatal jaundice.[1]

A neurologic evaluation was performed within 12 hours of admission by using the bilirubin-induced neurologic dysfunction protocol (BIND score)[4,13] based on clinical signs characteristic of ABE.[14,15] The examiner was blinded to the admission TSB value. The BIND score is used to evaluate changes in mental state, muscle tone, and cry; a score of 0 to 3 was assigned to each category, yielding a total score ranging from 0 to 9. A total BIND score of 1 to 3 suggests subtle, normally reversible, toxic effects of bilirubin. Scores of 4 to 6 are thought to reflect moderate but potentially reversible ABE, whereas scores of 7 to 9 indicate severe ABE likely to result in long-term disability from kernicterus.[9,13]

Test variables included admission TSB level, admission weight, Rh incompatibility, ABO incompatibility, and presence of sepsis. An admission weight of ≤2700 g was used as a surrogate for <38 weeks' gestational age (identified as a risk transition by the AAP[1]). Perinatal documentation of gestation and birth weights was rarely available. The direct antiglobulin test was not reliable, so analysis of Rh and ABO incompatibility was stratified for associated anemia (hematocrit < 35%). A diagnosis of sepsis required clinical signs of sepsis associated with (1) a positive blood culture result and/or (2) an elevated C-reactive protein level, total leukocyte count of >25 000 or <5000, an immature-to-total neutrophil ratio of >0.2, or a band count of >10%. In our outcome analysis, we defined ABE as a BIND score of 4 to 9 on admission (pretreatment), and BE as neurologic evidence of bilirubin encephalopathy[14,15] at the time of death or discharge.

We used multiple logistic regression to examine the effects of TSB, and neurotoxicity risk variables on adverse effects/outcomes (ABE, BE) in our defined cohort (TSB ≥25 mg/dL). Coefficients of the predictors in the logistic regression models can be directly interpreted as odds ratios (ORs) for specified outcomes, adjusting for effects of other predictors. The positive predictive value (PPV) of TSB levels 25 mg/dL in subcohorts stratified for neurotoxicity risk factors was calculated. The interaction of risk factors with TSB level was examined using TSB values dichotomized at ≥30 mg/dL and by receiver operator characteristic (ROC) curve analysis. Using ROC analysis, we estimated the threshold values of TSB that identified 90% of patients with ABE or BE in each risk category and determined the false-positive rate (FPR) (1-specificity). Confidence intervals for thresholds and FPR were calculated by bootstrapping using 1000 replications.[16] The R statistics program was used to run the analyses,[17] and the ROCR package was used to generate the ROC figures (R Foundation for Statistical Computing, Vienna, Austria).[18]

RESULTS

Cohort Description

Demographic characteristics and admission TSB are summarized in Table 1. A total of 121 patients had TSB levels ranging between 25 and 29.9 mg/dL (median: 27 mg/dL), and 128 patients had TSB levels ranging between 30 and 76.4 mg/dL (median: 34 mg/dL). Gestational age and birth weights were not documented, but admission weights

TABLE 1 Subject Characteristics

Characteristic	*n*	%
Gender		
Male	135	54.2
Female	114	45.8
Mode of delivery		
Vaginal	182	73.3
Cesarean	67	26.7
Positive consanguinity (first cousins)	59	23.7
Positive history in siblings	23	9.24
Total bilirubin, mg/dL		
25–29.9	121	48.6
30–34.9	71	28.5
35–39.9	33	13.3
40–54.9	20	8.0
≥55	4	1.6

TABLE 2 Suspected Causes of Hyperbilirubinemia

Suspected Cause	*n*	%
Rh incompatibility (*n* with hematocrit ≤ 35%)	25 (22)	8.8
ABO incompatibility (*n* with hematocrit ≤ 35%)	71 (59)	23.7
Combined Rh and ABO (*n* with hematocrit > 35%)	9 (6)	2.4
Glucose-6-phosphate dehydrogenase deficiency (tested in 86)	7	2.8 (8.1% of tested)
Cephalohematoma/bruising	3	1.2
Sepsis	4[a]	1.6
Polycythemia		
Congenital heart disease	1	0.4
IUGR	2	0.8
Twin (IUGR)	1	0.4
Unidentified cause	2	0.8
Unidentified	124	49.79

IUGR indicates intrauterine growth restriction.
[a] Seven additional sepsis cases were hospital acquired or unrecognized at admission.

TABLE 3 BIND Score as a Predictor of BE

Admission BIND Score	*n*	Resolved	Survived + BE	Death + BE	Total Bilirubin, Median (Range)
0 (normal)	150	NA	0	0	28.3 (25.0–59.0)
1–3 (subtle)	55	36	2	1	33.0 (25.1–57.0)
4–6 (moderate ABE)	25	11	5	9	32.0 (25.0–76.4)
7–9 (severe ABE)	19	1	2	16	36.5 (25.0–51.0)
Total	249	49	9	26	30.0 (25.0–76.4)

ranged from 1600 to 4200 g; 133 of 249 (53%) weighed <3000 g. Postnatal age at admission ranged from 2 to 14 days (mean [SD]: 5.3 [2.0] days). Suspected etiologies of hyperbilirubinemia are listed in Table 2. Fifty percent of infants had no identifiable cause of jaundice. All patients were treated with phototherapy, and 207 infants (83%) received exchange transfusions. At the time of admission, 44 infants (18%) had moderate or severe ABE (BIND score 4–9), 55 infants had subtle evidence of neurotoxicity (BIND 1–3), and 150 infants (60%) had no evidence of ABE (Table 3). Thirty-five patients (14%) had evidence of BE at time of discharge (9 [3.6%]) or death (26 [10.4%]). All deaths were associated with signs of kernicterus.

Relationship of Admission BIND Score to Hospital Outcome

The BIND score codifies the progression of neurologic signs observed in bilirubin neurotoxicity[13–15] and may serve both to document physical findings (acute outcome) and to predict ultimate outcome.[7,9] In our study, no infant with BIND scores of 0 to 1 on admission ($N = 166$) developed later signs of BE. Fourteen of 25 patients with moderate ABE (BIND score of 4–6) and 18 of 19 with severe ABE (BIND score 7–9) had persistent evidence of BE at the time of death or discharge. However, 3 of the 35 cases with BE had a BIND score of only 3 on admission. Of these, 1 patient with a TSB level 55.5 mg/dL, direct fraction 16 mg/dL, had minimal signs of toxicity on admission but rapidly deteriorated thereafter. One infant developed sepsis and BE, and 1 with Rh hemolytic disease progressed from subtle signs on admission to frank BE at discharge. The unexpected adverse outcomes in these infants may be due in part to the duration of observation because signs of ABE can be intermittent and sometimes elicited only by stimulation.[9] In general, a pretreatment BIND score was a very good predictor of outcome; BIND scores of ≥6 anticipated an adverse outcome in 22 of 25 patients (88%).

Relationship of TSB Level to ABE and BE

Admission TSB level bore little relationship to the presence or severity of ABE in our nonstratified cohort. The median TSB level in patients with no clinical signs of ABE on admission (28.3 mg/dL) was lower than the median TSB level for patients with subtle toxicity, moderate ABE, and severe ABE (33, 32, and 36.5 mg/dL, respectively), but the range of TSB levels in all groups was similar (Table 3). The range and median TSB level in patients who developed BE (median: 35 mg/dL) was similar to values in those with ABE who had normal outcome (median: 33 mg/dL). Of the 26 infants who died with evidence of BE, 19 had a TSB level of ≥30 mg/dL and 7 had TSB levels of <30 mg/dL. All 7 patients with lower TSB level had evidence of severe hemolysis (median hemoglobin: 8.8 g/dL; median reticulocyte count: 14.9%) including 6 with Rh incompatibility. Among 9 infants who survived with persistent evidence of BE at time of discharge, 6 had TSB levels of >30 mg/dL and 3 had TSB levels of <30 mg/dL (2 with sepsis and 1 with Rh hemolytic disease).

Influence of Risk Factors for Neurotoxicity on Outcome

The AAP guidelines, as well as the aforementioned observations, suggest

TABLE 4 Odds of Having ABE at Admission and/or BE at Discharge or Death

Variable	BIND 4+ or BE	
	OR (95% CI)	*P*
TSB (per mg/dL)	1.09 (1.03–1.16)	<.005
Admission weight (100 g)	0.83 (0.74–0.93)	<.001
Rh incompatible (hematocrit < 35%)	48.6 (14–168)	<1e-9
Sepsis	20.6 (4.9–87.5)	<.0001
ABO incompatible (hematocrit < 35%)	1.8 (0.8–4.5)	.17

that certain risk factors may potentiate bilirubin toxicity. We first performed multiple logistic regression analysis to evaluate the effects of TSB and other risk factors on moderate or severe ABE (BIND score 4–9). ORs for each effect in logistic models, with 95% confidence intervals, are shown in Table 4. Except for higher admission weight, which decreased risk, all factors evaluated increased the odds of an adverse outcome. The presence of sepsis and Rh hemolytic disease greatly increased the risk for BE (20.6 and 48.6 times, respectively), in contrast to ABO hemolytic disease, for which the estimated OR was only 1.8 ($P = .17$). TSB level (in a cohort in which all TSB levels are ≥25 mg/dL) was a relatively weak predictor of outcome in logistic regression (OR: 1.54 per 5 mg/dL increase). Nearly identical results (not shown) were found when outcome was limited to BE.

Risk Factors and PPV of 25 mg/dL

The PPV varied greatly with different risk factors (Table 5). Twenty-four of 38 infants with Rh hemolytic disease and/or sepsis (63%) developed ABE or BE. In contrast, <5% of 111 infants without risk factors developed signs of ABE. The PPV increased greatly when hemolytic disease was associated with lower admission weight or sepsis and was 1.0 when 3 risk factors coexisted.

Relationship of TSB Level to ABE/BE in Stratified Risk Groups

As with nonstratified patients, the presence or absence of ABE and/or BE in infants with sepsis or Rh incompatibility was unrelated to TSB value when evaluated as a binary distribution of infants having TSB levels 25 to 29.9 vs ≥30 mg/dL (Table 6). Six of 11 infants (55%) with evidence of sepsis developed signs of BE, and 4 of these 6 infants had a TSB level of <30 mg/dL. Sixteen of 28 infants with Rh (or Rh/ABO) incompatibility (57%) developed BE, and 6 of these infants had TSB levels of <30 mg/dL; 13 of 16 died. In contrast, only 1 of 19 infants with ABO hemolytic disease as the only risk factor and TSB level of >30 mg/dL developed BE.

Clinical judgment is most challenged in otherwise normal term newborns with idiopathic severe hyperbilirubinemia and no signs of ABE. We stratified subjects to exclude all risk factors tested above and to include only infants with an admission weight of >2700 g (as a surrogate for ≥38 weeks' gestation). A total of 111 infants meeting these criteria on admission had TSB values ranging from 25 to 59 mg/dL. Three of 47 infants with TSB levels of >30 mg/dL developed moderate ABE (TSB: 31.8, 33, and 34.5 mg/dL) that resolved with treatment. Two infants with undiagnosed cause for jaundice (TSBs 41 and 44 mg/dL) died of BE.

TABLE 5 Risk Factors and PPV at 25 mg/dL

Risk Factor	*n*	No ABE/BE	ABE or BE	PPV
No risk factors	111	106	5	0.05
Subtotal: 1 risk factor	103	81	22	0.21
ABO incompatibility (hematocrit < 35%)	38	34	4	0.10
Admission weight ≤ 2700 g	45	38	7	0.16
Rh incompatibility (hematocrit < 35%)	16	6	10	0.63
Sepsis	4	3	1	0.25
Subtotal: 2 risk factors	30	18	12	0.4
Rh and ABO	4	2	2	0.5
Rh and admission weight ≤ 2700 g	5	1	4	0.8
ABO and sepsis	2	1	1	0.5
ABO and admission weight ≤ 2700 g	17	13	4	0.24
Admission weight ≤ 2700 g and sepsis	2	1	1	0.5
Subtotal: 3 risk factors	5	0	5	1.0
Admission weight, sepsis, and ABO	2	0	2	1
Admission weight, sepsis, and Rh	1	0	1	1
Admission weight, Rh, and ABO	2	0	1	1
Total	249	205	44	0.18

PPV indicates number of ABE or BE/total number identified to be at risk.

TABLE 6 Effect of Risk Factors and TSB on Neurotoxicity

Risk Factor	*n*	No ABE/BE	ABE Only	BE
No risk factors, TSB < 30 mg/dL	64	64	0	0
No risk factors, TSB ≥ 30 mg/dL	47	42	3	2
No risk factors, total	111	106	3	2
ABO, TSB < 30 mg/dL	19	18	1	0
ABO, TSB ≥ 30 mg/dL	19	16	2	1
ABO, total[a]	38	34	3	1
Sepsis/Rh, TSB < 30 mg/dL	16	3	3	10
Sepsis/Rh, TSB ≥ 30 mg/dL	22	8	3	11
Sepsis/Rh, total[b]	38	11	6	21

[a] Includes ABO incompatibility with hematocrit <35% and no other risk factors.

[b] Includes all patients with sepsis or Rh incompatibility with or without other risk factors.

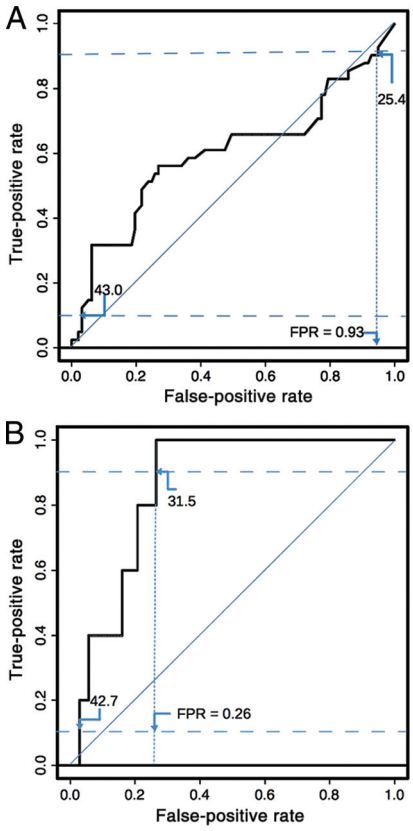

FIGURE 1

A, ROC analysis of risk for ABE or BE (BIND score 4–9) in 138 infants with recognized risk factors; threshold TSB and FPRs at 90% sensitivity and TSB at 10% sensitivity are indicated. The subcohort excludes infants charted in B and includes infants with Rh and ABO incompatibility with evidence of hemolysis, sepsis, and/or an admission weight of ≤2700 g. Many patients had >1 risk factor. The area under the curve was 0.595 (0.533 when ABO incompatibility was excluded). B, ROC analysis of risk for ABE or BE (BIND score 4–9) in 111 infants with no recognized risk factors; threshold TSB and FPRs at 90% sensitivity and TSB at 10% sensitivity are indicated. The subcohort excludes patients with ABO incompatibility with hematocrit at ≤35%, Rh incompatibility, weight of ≤2700 g, and evidence of sepsis. Only 3 of 111 infants developed ABE (TSB: 31.8–34.5 mg/dL). Two patients had severe BE (TSB: 41.8 and 43.2 mg/dL). The area under the curve was 0.857.

The sensitivities and FPRs of TSB levels for predicting outcomes in infants with and without risk factors are illustrated in the ROC curves of Figure 1. In contrast to PPV, we assumed no a priori threshold for intervention but selected a TSB value that identified 90% of patients with disease out of the study population. In the presence of risk factors (Fig 1A), a threshold of 25.4 mg/dL identified 90% of affected infants, but 93% of the 94 infants without disease also had a TSB level greater than this threshold (FPR: 93%). Ten percent of infants with disease had a TSB level of ≥43 mg/dL. The area under the curve was only 0.595 and was further reduced to 0.533 when ABO incompatibility was eliminated, indicating no demonstrable association between TSB value and disease over the range of 25 to 43 mg/dL.

In the absence of risk factors (Fig 1B), the minimum TSB value used to identify all 5 affected infants was 31.5 mg/dL; of 106 infants who were disease free, 74% had TSB levels ranging 25 to 31.5 mg/dL, and 26% (the FPR) had a TSB level of >31.5 mg/dL. The TSB level at 10% sensitivity was nearly identical in infants with and without risk factors present. Despite the difference in thresholds and FPR, the confidence intervals were inconclusive because, in the first case, the threshold was close to the study entry criterion of 25 mg/dL, suggesting that the true threshold for outcomes is likely to be lower and, in the latter case, the number of affected infants was small (5 with ABE or BE). Notwithstanding these limitations, the difference in the ROC curves for infants with and without risk factors to TSB is striking.

DISCUSSION

In the absence of risk factors for neurotoxicity, we observed no cases of ABE below a TSB level of 31.8 mg/dL and no evidence of BE at discharge despite TSB levels of >30 mg/dL in 25 infants. Longer-term outcome studies by Newman et al[10,11] also indicate that healthy term infants have a greater tolerance for severe hyperbilirubinemia. Physicians treating an asymptomatic infant with no risk factors and a TSB level in the range of 25 to ≥30 mg/dL are faced with a dilemma of whether to use intensive phototherapy or perform the more risky exchange transfusion, as currently recommended. In some environments, the risk of exchange transfusion[19–21] may exceed the risk of BE in this group of patients.

The AAP guidelines do not rank the risk of hemolytic disease according to etiology or severity, but logistic regression indicated that ABO with associated anemia (the direct antiglobulin test was unreliable) had far less influence on outcome than Rh incompatibility. The TSB threshold for severe disease was higher in ABO (33.7 mg/dL) than in Rh incompatibility (25.4 mg/dL), again indicating that the magnitude of risk for BE in hemolytic disease depends more on the etiology of hemolysis than on the severity of hyperbilirubinemia. On occasion, ABO hemolytic disease can present as overt erythroblastosis fetalis with severe hemolysis. This was not documented in our patients but might lower the TSB threshold for neurotoxicity.

Infants with sepsis or Rh hemolytic disease had a low group threshold for disease, but above 25 mg/dL, up to 43 mg/dL, the TSB value had no apparent relationship to outcome (Fig 1A). This surprising observation suggests that the threshold of 25 mg/dL is permissive of neurotoxicity, but above this threshold, the major determinants of neurotoxicity involve unidentified plasma and/or host defense variables that are altered by neurotoxicity risk factors. The sample size precluded determining specific thresholds for intervention in infants with and without risk factors, and the study entry level of TSB ≥25 likely concealed the true threshold for infants with sepsis and Rh hemolytic disease.[22]

The reason for the variation in susceptibility of infants to a given TSB level is unknown. Erythroblastosis fetalis will produce a more rapid rate of rise in TSB with a higher rate of bilirubin pro-

duction that might alter distribution of bilirubin between plasma and alternative body compartments, including the brain. Similar intolerance to a rapid load of bilirubin has been observed in hemolytic crises from glucose-6-phosphate dehydrogenase deficiency.[23] Low serum albumin levels, lower serum binding affinity for bilirubin, immaturity or alteration of the blood–brain barrier, and decreased cellular defense systems may also modify risk in severe hemolytic disease.[8,24–27] Although plasma binding of bilirubin has not been systematically evaluated in term/near-term infants or in patients with Rh isoimmune disease, there is good evidence that sick newborns with acidosis or sepsis, especially premature infants, have both poor binding and an increased risk for kernicterus.[24,25] Equally intriguing in this study is the observation that several infants with very high TSB levels were free of disease. Although free bilirubin levels were not measured, the high level of TSB in these infants would most probably require bilirubin binding to sites other than the primary site on albumin, implying that free bilirubin will be high and that resistance or susceptibility to neurotoxicity is not solely controlled by plasma factors.[26,27]

This study has several important limitations. Birth histories were not available, and documentation of birth weight and gestational age was rarely available for the population studied. Separating the effects of gestational age and fetal growth retardation was usually impossible. The diagnosis of hemolytic disease was compromised by an unreliable direct antiglobulin test, and we did not routinely screen for glucose-6-phosphate dehydrogenase deficiency. Thresholds for neurotoxicity in patients with Rh incompatibility and suspected sepsis were at or only slightly higher than the subject entry criterion of 25 mg/dL. The delay in evaluating blood types and other risk factors after admission precluded stratifying TSB entry criteria. Bilirubin/albumin ratios were not measured, and the roles of free bilirubin and plasma binding as mediators of risk factors (eg, in sepsis, Rh hemolytic disease) or as independent risk factors were not studied. We did not evaluate auditory pathway toxicity as an adverse outcome. Alterations in brainstem auditory evoked potentials are common and may be the only manifestation of bilirubin-induced brain injury.[28,29] These changes may resolve as transient expressions of mild ABE or progress to severe neurosensory hearing loss or auditory neuropathy/auditory dysynchrony.[8,28,29] Longer term follow-up might reveal more subtle expressions of BE or resolution of neurologic signs persisting at discharge.

Strengths of the current study include a short time frame to achieve targeted recruitment, consistency in treatment protocol using a single institution, consistent neurologic assessment because a single investigator (Dr Aboraya) performed BIND evaluations in the majority of patients, and consistency in TSB assays performed at a single hospital laboratory. In contrast to problems encountered in multicenter outcome studies required in countries having a low incidence of severe hyperbilirubinemia,[30,31] we were able to conduct a large systematic evaluation of neurotoxicity in patients with extremely high TSB levels within a single referral institution. With >250 newborns with severe hyperbilirubinemia admitted for care each year, Cairo University Children's Hospital provides a unique venue to evaluate variables that place jaundiced infants at risk for BE.

CONCLUSIONS

In the absence of neurotoxicity risk factors, newborns tolerate bilirubin levels of 25 to 30 mg/dL with low risk for ABE/BE; the TSB threshold for ABE was 31.5 mg/dL in 111 infants who had no risk factors identified. The risk for BE increased markedly in infants with Rh hemolytic disease and sepsis but only slightly with ABO incompatibility, suggesting that the magnitude of risk for BE in hemolytic disease greatly depends on etiology. When risk factors were present, the predictive relationship of TSB (beyond 25 mg/dL) to ABE/BE was poor in the population studied. This wide variation in response to TSB indicates that the pathogenesis of BE involves critical plasma and/or host defense variables not measured in this study.

ACKNOWLEDGMENTS

This research was supported in part by National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development award R21HD060901 and the American Recovery and Reinvestment Act of 2009.

We are grateful to Vinod K. Bhutani, MD, for constructive criticism that improved the focus and presentation of this study.

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