Serum Bilirubin and Bilirubin/Albumin Ratio as Predictors of Bilirubin Encephalopathy

WHAT'S KNOWN ON THIS SUBJECT: Jaundiced newborns without additional risk factors rarely develop kernicterus if the total serum bilirubin is <25 mg/dL. Measuring the bilirubin/albumin ratio might improve risk assessment, but the relationships of both indicators to advancing stages of neurotoxicity are poorly documented.

WHAT THIS STUDY ADDS: Both total serum bilirubin and bilirubin/albumin ratio are strong predictors of advancing stages of acute and post-treatment auditory and neurologic impairment. However, bilirubin/albumin ratio, adjusted to the same sensitivity, does not improve prediction over total serum bilirubin alone.

abstract

BACKGROUND AND OBJECTIVE: Bilirubin/albumin ratio (B/A) may provide a better estimate of free bilirubin than total serum bilirubin (TSB), thus improving identification of newborns at risk for bilirubin encephalopathy. The objective of the study was to identify thresholds and compare specificities of TSB and B/A in detecting patients with acute and posttreatment auditory and neurologic impairment.

METHODS: A total of 193 term/near-term infants, admitted for severe jaundice to Cairo University Children's Hospital, were evaluated for neurologic status and auditory impairment (automated auditory brainstem response), both at admission and posttreatment by investigators blinded to laboratory results. The relationships of TSB and B/A to advancing stages of neurotoxicity were compared by using receiver operating characteristic curves.

RESULTS: TSB and B/A ranged from 17 to 61 mg/dL and 5.4 to 21.0 mg/g, respectively; 58 (30%) of 193 subjects developed acute bilirubin encephalopathy, leading to kernicterus in 35 infants (13 lethal). Auditory impairment was identified in 86 (49%) of 173 infants at admission and in 22 of 128 at follow-up. In the absence of clinical risk factors, no residual neurologic or hearing impairment occurred unless TSB exceeded 31 mg/dl. However, transient auditory impairment occurred at lower TSB and B/A (22.9 mg/dL and 5.7 mg/g, respectively). Intervention values of TSB and B/A set at high sensitivity to detect different stages of neurotoxicity had nearly the same specificity.

CONCLUSIONS: Both TSB and B/A are strong predictors of neurotoxicity, but B/A does not improve prediction over TSB alone. Threshold values detecting all affected patients (100% sensitivity) increase with advancing severity of neurotoxicity. *Pediatrics* 2014;134:e1330–e1339

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KEY WORDS

hyperbilirubinemia, bilirubin/albumin ratio, kernicterus, auditory impairment, bilirubin-induced neurologic dysfunction, bind score, automated auditory brainstem response

ABBREVIATIONS

AABR—automated auditory brainstem response
AAP—American Academy of Pediatrics
ABE—acute bilirubin encephalopathy
B/A—bilirubin to albumin ratio
Bf—free bilirubin
BIND—bilirubin-induced neurologic dysfunction
GA—gestational age
G6PD—glucose 6 phosphate dehydrogenase
ROC—receiver operating characteristic
RR—bilateral refer response
TSB—total serum bilirubin

Dr Iskander helped in designing the study, was responsible for training for bilirubin-induced neurologic dysfunction score examination, monitored cases while in hospital and coordinated follow-up after discharge, supervised research steps and data collection, and drafted, reviewed, and edited the manuscript until final approval; Dr Gamaleldin coordinated and supervised data collection and completion for both inpatients and follow-up and reviewed the manuscript before submission; Dr El Houchi was responsible for clinical examination at follow-up for all patients; Dr El Shenawy was responsible for the auditory assessments for infants during admission and at follow-up, as well as the diagnostic auditory procedures; Dr El Gharbawy was responsible for the laboratory coordination during admission as well as glucose 6 phosphate dehydrogenase at follow-up; Dr Abou-Youssef was responsible for data analysis as well as review and editing of the manuscript until final approval; Dr Seoud participated in study design and in designing data-collection instruments as well as supervising research till completion; Dr Aravkin carried out receiver operating characteristic analyses and edited the manuscript; and Dr Wennberg was principal investigator on the supporting National Institute of Child Health and Human Development grant, conceptualized and designed the study and data-collection tools, drafted the initial manuscript, and edited and approved the final manuscript.

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The American Academy of Pediatrics (AAP) guidelines for treating neonatal jaundice and preventing kernicterus in term/near-term infants are based on total serum bilirubin (TSB) levels adjusted for the absence or presence of clinical risk factors (eg, low gestational age [GA], sepsis, hemolytic disease).[1] Plasma free bilirubin (Bf) is thought to be a better indicator of neurotoxicity than TSB, because only Bf can cross the blood-brain barrier.[2,3] In the absence of an available assay for Bf, the bilirubin/albumin ratio (B/A) might provide a better estimate of Bf because it contains 2 of the 3 factors determining Bf (TSB, albumin, and the albumin-binding affinity).[2,3] The relationship between Bf and B/A has been studied by titration of serum samples[4] and by measuring Bf in serum of infants with varying B/A,[5] but clinical evidence comparing the relationships of TSB and B/A with outcome is sparse.[6,7] B/A is currently recommended as a safeguard to identify the rare infant at risk for neurotoxicity at low TSB because of a low serum albumin concentration.[1]

This study evaluated TSB and B/A as predictors of pretreatment and posttreatment auditory and neurologic impairment in infants with severe hyperbilirubinemia. We hypothesize that B/A is a better predictor of bilirubin toxicity than TSB. A secondary hypothesis is that advancing stages of bilirubin neurotoxicity have increasing threshold values for TSB and B/A.

METHODS

General Study Design

This prospective longitudinal observational study was performed at Cairo University Children's Hospital. Infants admitted with severe hyperbilirubinemia received serial neurologic evaluations using a standard examination for grading the severity of bilirubin-induced neurologic dysfunction (BIND score; Appendix 1).[8] Auditory function was assessed with the automated auditory brainstem response (AABR) device (Algo3i; Natus Medical, Inc, San Carlos, CA).[9] AABRs were obtained within 2 hours of admission and at discharge in most patients. Follow-up evaluation at 3 to 5 months included both a neurologic examination[10] and repeat AABR.

Treatment decisions were made by attending physicians blinded to AABR and BIND score data. Criteria for exchange transfusion were a TSB level ≥25 mg/dL, presence of neurologic signs, or a rapid rise of TSB on day 1. Investigators calculating BIND score, performing AABRs, and conducting follow-up assessments were blinded to laboratory data and were not involved in patient management.

Subjects

A total of 224 newborns were enrolled in a study evaluating risk factors for bilirubin encephalopathy between June 2009 and October 2010. Entry criteria included infants ≤14 days old with severe jaundice requiring intensive phototherapy or exchange transfusion and an estimated GA ≥34 weeks (using the New Ballard Score).[11] We analyzed a subcohort of 193 infants after excluding infants with missing albumin data (23 cases), inadequate outcome documentation (4 cases), or comorbid conditions unrelated to jaundice (4 cases). The study was approved by institutional review boards at participating universities, and parental informed consents were obtained for all infants.

Laboratory Analysis

TSB and albumin levels were determined in the clinical laboratory at Cairo University Children's Hospital. TSB was measured by the Doumas modification of the Jendrassik-Grof diazo method[12] and albumin by the bromocresol purple method[13] by using a Dimension RxL analyzer (Siemens Healthcare Diagnostics Inc, Tarrytown, NY). Quantitative glucose-6-phosphate dehydrogenase (G6PD) assay was performed at 3 to 5 months by using a G6PDH kit (Trinity Biotech, Bray, Ireland). Deficiency was defined as G6PD activity <6.4 U/g hemoglobin.

Outcome Definitions

Overt acute bilirubin encephalopathy (ABE) is defined as a BIND score of 4 to 9. The BIND score[7] describes the progression of ABE. Scores of 4 to 6 represent moderate ABE, and scores of 7 to 9 indicate severe ABE that is highly associated with kernicterus or death.[8,14–16] Infants with BIND scores of 1 to 3 are referred to as having mild neurotoxicity or mild ABE that is likely to be reversible without sequelae.

Posttreatment diagnosis of kernicterus required 1 of the following criteria: death from severe ABE, neurologic findings of kernicterus at follow-up as described by Shapiro,[10] or persistent severe encephalopathy and bilateral refer (RR) AABR at hospital discharge for infants lost to follow-up. MRI examinations were not performed.

Auditory impairment was defined as a bilateral "refer for further evaluation" result (RR AABR). Bilateral pass or unilateral pass was considered "normal." Admission AABRs were usually unsuccessful in severely affected infants due to muscle activity. If the BIND score was 6 to 9 and the infant died of kernicterus or had RR AABR at discharge, the unsuccessful admission AABR was considered to be RR for statistical analysis.

A diagnostic evaluation for auditory neuropathy[17–19] was performed if the AABR screen was RR at 3 to 5 months. Compliance with follow-up appointments was 74.5%.

Definition of Clinical Risk Factors

Hemolysis was arbitrarily defined as hematocrit ≤35% with increased reticulocytes (≥6%) in patients with possible isoimmunization. Suspected sepsis was defined as clinical deterioration in the presence of leukocytosis, leucopenia, shift to the left of neutrophils, and a positive C-reactive protein screen.[20] The accuracy of GA assessment[11] was limited by the patient's postnatal age and occasional illness at admission. Birth weights were rarely available; accuracy of GA was limited by postnatal age at admission and confounded by disease in some infants. Historically, birth weights > or ≤2500 g have been used to assess risk due to maturity.[4,21] Because birth weights were unavailable and GA often uncertain, we used admission weight (> or ≤2500 g), the only objective measure available, to assign risk related to maturity

Statistical Methods

The initial TSB and B/A were used to predict admission BIND scores and AABR results. Occasionally, blood for exchange transfusion was delayed; therefore, peak TSB and peak B/A before exchange transfusion were used to predict subsequent outcomes.

Quantitative biochemical data were not normally distributed. Data were summarized as medians, interquartile (25th–75th percentile) and total ranges, and compared by using Mann-Whitney *U* and Kruskal-Wallis tests.[22] Qualitative data were presented as frequency and percentage. Sensitivities and specificities associated with different cutoff values for TSB and B/A were evaluated by using receiver operating characteristic (ROC) curves.[23] Calculations were performed by using the IBM SPSS (version 20) program (IBM SPSS Statistics, IBM Corporation, Chicago, IL). For some analyses, subjects were stratified by the presence or absence of possible clinical risk factors.

RESULTS

Patient Characteristics

Although 87% of infants were delivered at hospitals, newborns were usually discharged several hours after birth without evaluation for jaundice or scheduled follow-up.[24] Birth weight, GA, and blood type incompatibilities were rarely documented at the birthing hospital. The median age at admission to the NICU was 4.5 days. Admission TSB was ≤25.0 mg/dL in 41 infants, 25.1 to 35.0 mg/dL in 117 infants, and >35.0 mg/dL in 35 infants. Patient characteristics are summarized in Table 1.

Clinical Risk Factors

In this cohort, 59 (30.6%) newborns had no risk factors other than severe hyperbilirubinemia. Possible clinical risk factors were present in 134 infants (69.4%), but confidence in assigning risk was often lacking. Fifty-eight infants weighed ≤2500 g, but it was sometimes unclear whether they were immature or small for GA.

A total of 103 infants had ABO incompatibility, but there was no evident relationship between incompatibility, hematocrit, reticulocyte count, direct antiglobulin test, and magnitude of hyperbilirubinemia. G6PD deficiency was identified in 10 of 134 patients tested at follow-up, but only 1 had evidence of a hemolytic crisis at admission. Blood cultures were positive in 4 of 12 infants with suspected sepsis.

Because clinical risk factors were uncertain in a large fraction of subjects, we used both nonstratified data and data dichotomized for absence or presence of possible risk factors for analyses.

Patient Management

All patients received phototherapy (irradiance <20 μW/cm^2/nm). Exchange transfusions were performed in 147 patients (76.2%), including all infants admitted with ABE (BIND scores 4–9). However, 66% of infants with no or mild ABE received exchange transfusion because of TSB >25 mg/dL. Median TSB and B/A values in infants receiving exchange transfusion were 32.2 mg/dL and 9.7 mg/g, respectively, compared with TSB 25.1 mg/dL and B/A 7.7 mg/g in those receiving only phototherapy. Blood was not available for exchange transfusion in 3 infants with TSBs 30.0 to 33.6 mg/dL, but they

TABLE 1 Patient Description (n = 193)

Characteristic	*n*		
Boys/Girls	100/93		
ABO incompatibility	103		
Rh incompatibility	22		
G6PD deficiency (< 6.4 U/g)	10/134 tested		
Suspected sepsis	12; 4 positive culture		
Exchange transfusion	147 (76%)		
	Median	1st–3rd Quartile	Range
Age, d	4.5	3.0–6.4	0.4–13.2
Admission weight, g	2830	2500–3200	1500–4500
Admission TSB, mg/dL	28.5	25.9–33.2	17.0–61.0
Admission B/A, mg/g	8.6	7.4–10.2	5.4–21.0
Albumin, g/dL	3.5	3.1–3.7	1.8–4.8
Peak TSB, mg/dL	29.6	26.4–34.4	17.0–61.0
Peak B/A, mg/g	8.9	7.6–10.5	5.4–21.0

had normal BIND scores and normal follow-up.

Most infants with mild or moderate ABE improved neurologically after exchange transfusion, but 4 infants with maximum TSBs ranging from 35 to 47 mg/dL and admission BIND scores ranging from 1 to 4 deteriorated to severe ABE and kernicterus during or after the procedure. Culture-proven sepsis was present post-exchange in 2 of these infants. A third infant had marked hemolysis from G6PD deficiency and deteriorated during the exchange transfusion.

Outcomes

At admission, 25 infants suffered moderate ABE (BIND 4–6). Among 22 of those 25 infants attending follow-up, 13 were healthy, 5 had isolated auditory neuropathy, and 4 had frank kernicterus. Severe ABE (BIND score 7–9 at admission) occurred in 33 infants. Two infants with BIND score of 7, lost to follow-up, were neurologically healthy at discharge but had RR AABR. The remaining 31 infants (94%) had adverse outcomes compared with only 9 (41%) of 22 infants with moderate encephalopathy

Kernicterus was diagnosed in 35 cases; 13 infants died with severe ABE in hospital, 17 had frank kernicterus[10] at follow-up, and 5 infants, lost to follow-up, had signs of persistent bilirubin encephalopathy at discharge. All infants with kernicterus had BIND scores of 5 to 9 while hospitalized, and all received exchange transfusion (see Appendix 2 for details).

At admission, the AABR was RR in 86 (50%) of 173 tests performed. A total of 128 surviving infants were evaluated at follow-up. Sixty percent of infants with admission RR AABR converted to bilateral pass, whereas 22 infants had persistent RR AABR confirmed to be auditory neuropathy by diagnostic audiology procedures.[17–19] All infants with maximum TSB <31 mg/dL and BIND score ≤3 had normal auditory function at follow-up.

Relationships of TSB and B/A to Outcomes

We found a clear stepwise relationship between TSB and B/A median and threshold values and the progression of acute neurotoxicity (Table 2). There was a large gap in thresholds separating mild ABE (20.0 mg/dL TSB, 5.5 mg/g B/A) and moderate ABE (27.1 mg/dL, 7.1 mg/g). A smaller increase was noted between thresholds for moderate and severe ABE. Two of 4 infants admitted at <24 hours of age with rapidly rising TSB (18.7 and 24.0 mg/dL) had refer AABRs, and 1 had a BIND score of 5. Because the response to rapidly rising bilirubin was unique in these infants, infants admitted at <1 day of age were excluded from group analyses.

Subjects were not stratified for risk factors, so results in Table 2 include patients at the highest clinical risk category defined in the AAP guidelines.[1] At all stages of toxicity, TSBs identifying 100% of diseased infants were higher than the recommended intervention guideline for high-risk infants <38 weeks' GA[1] (TSB 19.0 mg/dL), but B/A thresholds for mild neurotoxicity (BIND scores 2–3) and AABR RR at admission were lower than the AAP recommendation (6.8 mg/dL).[1] When subjects were dichotomized by the presence or absence of suspected risk factors, threshold and median values for most outcomes were nearly identical. The median and threshold values for severe ABE and kernicterus were lower in 30 patients with risk factors present (threshold 28.9 mg/dL) than in 5 infants without clinical risk factors (threshold 31 mg/dL), but the difference was not statistically significant.

ROC Analysis

We compared sensitivities and specificities of TSB and B/A in identifying acute and posttreatment outcomes by using ROC curves (Fig 1). ROC curves describe the specificity of a diagnostic test at any selected sensitivity (and vice versa). For all outcomes, the area under the curve for TSB is slightly higher than for B/A, and significantly higher for auditory impairment at admission. There is almost no crossover of ROC curves for TSB and B/A in any outcome prediction (ie, at any given sensitivity, the specificity of TSB is equal to or slightly better than B/A). Table 3 lists TSB and B/A cutoff values yielding 100% sensitivity together with specificities and confidence intervals for various stages of neurotoxicity in our study population. Calculated cutoffs are consistent with threshold values described in Table 2.

TABLE 2 Relationships of TSB and B/A to Progression of Neurotoxicity (n = 189)

Outcome	n	Median TSB[a] (Range)	Median B/A[b] (Range)
Admission AABR RR	83	33.4 (22.9[c]–61.0)	10.0 (5.7[c]–21.0)
Residual Auditory neuropathy at 3 mo	22	37.1 (31.0[c]–61.0)	11.4 (8.6[c]–21.0)
BIND 2–3 mild ABE	47	27.0 (20.0[c]–37.7)	7.6 (5.5[c]–14.4)
BIND 4–6 moderate ABE	24	32.3 (27.1[c]–43.6)[d]	10.1 (7.1[c]–13.7)[d]
BIND 7–9 severe ABE	32	38.2 (28.9[c]–61.0)[d,e]	11.3 (8.6[c]–21.1)[d,f]
Kernicterus	35	38.7 (28.9[c]–61.0)	11.5 (8.6[c]–21.0)

Four patients on admission with hyperbilirubinemia at <24 h of age are excluded.

[a] Total serum bilirubin (mg/dL), median (min–max).

[b] B/A (mg/g), median (min–max).

[c] Thresholds.

[d] $P <$ .0005 versus mild ABE.

[e] P = .003 versus moderate ABE.

[f] P = .030 versus moderate ABE.

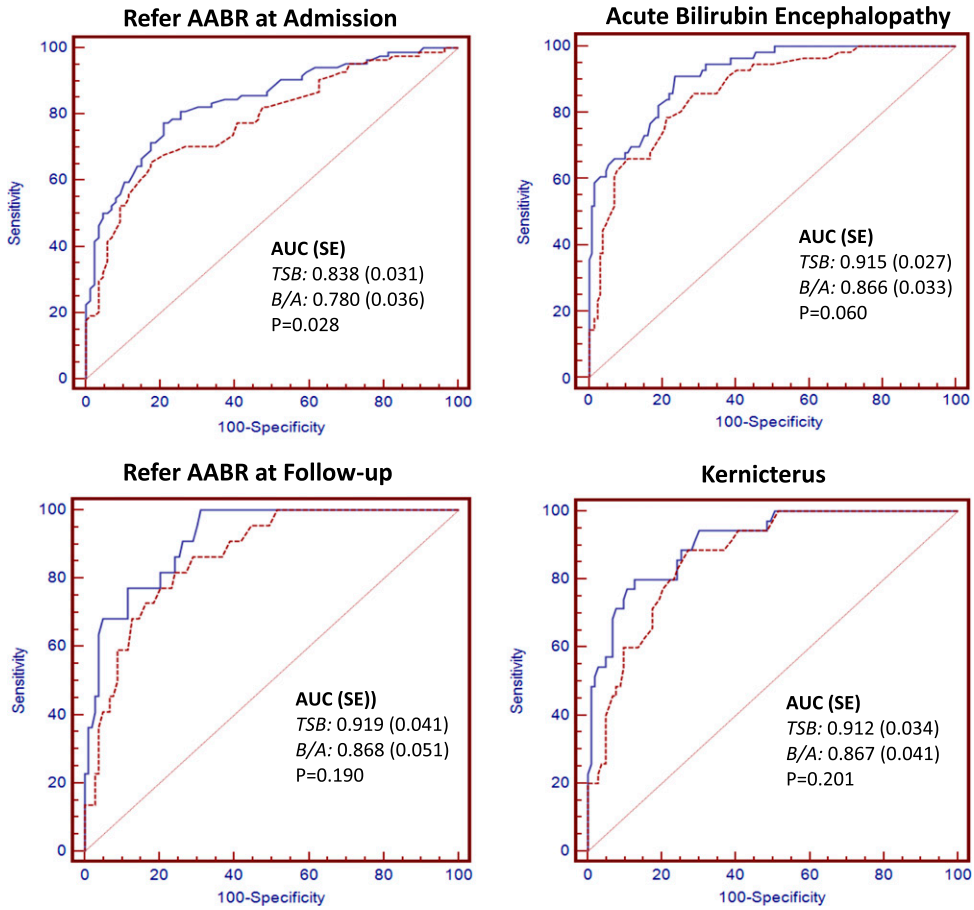

FIGURE 1

ROC curves evaluating total serum bilirubin and bilirubin/albumin as predictors of different stages of bilirubin neurotoxicity. Excludes 4 patients <24 hours of age. TSB, solid line; B/A, dashed line; AUC: area under the curve and standard error (SE) shown.

DISCUSSION

Any criterion for intervention in hyperbilirubinemia must have a high sensitivity, identifying all or nearly all infants with a possibility of permanent injury. In this study, both TSB and B/A were strong predictors of acute and residual encephalopathy, but when B/A and TSB intervention levels were selected to yield the same sensitivity, B/A did not improve discrimination of patients at risk as hypothesized. This does not mean that measuring serum albumin is unimportant. Severe hemolytic disease and capillary leak from a variety of conditions can result in plasma albumin depletion. In such infants, the risk for kernicterus may occur at TSB levels well below AAP-recommended intervention levels for sick infants,[25] but the B/A cutoff would be breeched.

Role of Risk Factors

Proposed clinical risk factors for bilirubin toxicity[1] had surprisingly little influence on either threshold or median values of TSB and BA

TABLE 3 Sensitivity and Specificity for Cutoffs Identifying All Subjects With Disease

Outcome	TSB, mg/dL			B/A, mg/g		
	Cutoff	Sensitivity (95% CI[a])	Specificity (95% CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
AABR RR at admission	22.7	100% (96–100)	9.3% (4.1–17.5)	5.6	100% (96–100)	3.5% (0.8–9.9)
ABE, maximum BIND 4–9	27.0	100% (94–100)	49.2% (40.9.2–58.1)	6.8	100% (94–100)	26.5% (19.2–34.9)
AABR RR at follow-up	30.7	100% (84–100)	68.9% (59.1–77.7)	8.5	100% (84–100)	48.5% (38.6–58.6)
Kernicterus*	28.6	100% (90–100)	49.5% (39.5–59.5)	8.5	100% (90–100)	48.5% (38.6–58.6)

CI, confidence interval. * including those who died

[a] CI Excludes 4 patients admitted at <24 h of age.

associated with disease in this study. However, Rh hemolytic disease, representing only 11% of the cohort, was responsible for 20% of kernicterus cases. Consistent with our previous study of a different cohort of 212 newborns with TSB >25 mg/dL,[26] only infants with hemolytic disease due to Rh incompatibility or with sepsis developed severe ABE below a TSB of 31 mg/dL. ABO incompatibility and G6PD deficiency (in the absence of hemolytic crisis) created minimal if any additional risk compared with idiopathic jaundice. Wolf et al[27] and Weng et al[28] reported similar results. Resistance to long-term consequences of severe hyperbilirubinemia in otherwise healthy term infants was also reported by Newman and colleagues.[29,30] This cumulative evidence strongly suggests that asymptomatic term/near-term newborns without risk factors rarely develop kernicterus or auditory neuropathy at TSB <31 mg% and/or B/A <8.6 mg/g. Given the risks of exchange transfusion,[31] intensive phototherapy and close monitoring may be a safer treatment option for those infants.

Why Did B/A Not Improve Identification of Risk in This Population?

One possible explanation is that there are wide variations in Bf transport into the brain and/or in cellular defense mechanisms. Two of 4 infants with hemolytic disease admitted on day 1 of life, had rapidly rising TSB and low thresholds for toxicity. Whether the lower thresholds are due to rate of rise of TSB, poor albumin binding, or increased brain susceptibility to Bf on day 1 of life is unknown.

A second possibility is that B/A is not a better predictor of Bf than TSB alone (ie, variations in binding ability exceed variations in albumin concentration). In contrast to premature infants who may develop ABE at B/A molar ratios <1[32–34] (where Bf is largely dependent on the quality of albumin binding), moderate to severe bilirubin toxicity in our cohort occurred only when the molar concentration of bilirubin approached or surpassed the concentration of albumin. Bf increases dramatically as TSB approaches or exceeds a B/A molar ratio of 1:1 (B/A = 8.8 mg/dL) and limitations of bilirubin solubility become a dominant issue. Several infants with no signs of toxicity had B/A molar ratios approaching 1.25, indicating that additional bilirubin-binding sites must exist in plasma.[35,36] The high likelihood of wide variations in this expanded buffering capacity reinforce the need to measure Bf directly to validate its value as a marker of infants at risk.

A third option relates to experimental design limitations. In this study, as in most published outcome studies,[15,37–38] there were no untreated controls and no serial documentation of TSB as signs of encephalopathy progressed. Fourteen patients had very low serum albumin levels, ranging from 1.8 to 2.7 g/dL, and might have benefited from considering B/A. Six of these infants had severe ABE when first seen; TSBs ranged from 32 to 44 mg/dL and B/As ranged from 14 to 20 mg/g, preventing any inference about the levels of TSB and B/A at the onset of disease.

Relationship of Thresholds to Progression of Neurotoxicity

The opportunity to evaluate AABR at admission, as well as repeated BIND scores during the first hours of admission, provided unique serial observations of auditory and neurologic events before and after therapy. This in turn allowed us to estimate threshold values for outcomes ranging from reversible neurotoxicity to irreversible injury. We observed a rather large jump in threshold values at high sensitivity between mild (BIND score 2–3) and moderate ABE, with smaller change between moderate and severe ABE. This separation in thresholds could provide guidance for intervention decisions.

Mindful that our analysis was not stratified for GA or risk factors, thresholds at 100% sensitivity included infants with highest clinical risk conditions. Cutoffs for TSB identified in this study are substantially higher than recommended intervention levels for low GA with risk factors.[1] Our findings should be confirmed because other studies have reported ABE and hearing loss at lower levels than documented here,[15,37–38] most often associated with severe hemolysis, especially from Rh hemolytic disease, sepsis, or prematurity.

Strengths and Limitations

This study was conducted at a single venue where the quality of clinical evaluation was carefully monitored. Even so, we encountered uncertainties in assigning risk factors[1] for ABE. Exchange transfusion was associated with worsening ABE and kernicterus in 4 infants, potentially confounding the relationship between admission test values and long-term outcome. Finally, the inability to administer optimal intensive phototherapy and occasional delays in receiving blood for exchange transfusion might have influenced outcomes. Notwithstanding these limitations, the ability of admission serum chemistries to predict thresholds for both acute and posttreatment outcomes was rather remarkable.

In 1988, Perlman and Frank[39] proposed a hierarchy of neurophysiological and behavioral signals leading ultimately to irreversible brain injury (kernicterus, hearing loss), but lamented that prospective cohort studies needed to determine the relative risks associated with various biochemical and clinical predictive criteria may not be available for many years. This study, conducted in an environment in which kernicterus is

not a rare event, provides a first step in achieving that goal.

CONCLUSIONS

TSB and B/A are both strong indicators of risk for acute and residual bilirubin neurotoxicity. When intervention values are adjusted to provide equal sensitivity, the specificities of TSB and B/A are nearly the same, and B/A offers no additional advantage over TSB alone in most clinical settings. TSB and B/A thresholds for disease increased with advancing severity of neurotoxicity; this should be considered when deliberating appropriate intervention guidelines.

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APPENDIX 1 BIND Score[a]

Clinical Sign (Score Most Severe Sign)	Score	Severity
Mental status		
Normal – Awake alert	0	None
Sleepy but arousable	1	Mild
Decreased feeding	1	Mild
Lethargy	2	Moderate
Poor suck and/or	2	Moderate
Irritable/jittery	2	Moderate
Unable to feed	3	Severe
Apnea	3	Severe
Seizures	3	Severe
Coma – not arousable	3	Severe
Muscle tone		
Normal flexed tone	0	None
Persistent mild hypotonia	1	Mild
Hypotonia or hypertonia depending on arousal state	2	Moderate
Bicycling	2	Moderate
Beginning nuchal rigidity and truncal arching	2	Moderate
Persistent retrocollis	3	Severe
Opisthotonos	3	Severe
Severe hypo- or hypertonia	3	Severe
Cry pattern		
Normal	0	None
High-pitched	1	Mild
Shrill	2	Moderate
Inconsolable crying or cry weak or absent	3	Severe
Total bind (ABE score)		

Tick all that apply, but total score is based on the highest in each category or 9.

Proposed interpretation:

Total BIND score 1–3: mild ABE subtle signs reversible, no apparent sequelae.

TotalBIND score 4–6: moderate ABE, signs largely reversible with aggressive treatment.

TotalBIND score 7–9: severe ABE, largely irreversible but signs may decrease with prompt treatment.

[a] Modified from Johnson L, Brown AK, Bhutani V. BIND—A clinical score for bilirubin induced neurologic dysfunction in newborns. *Pediatrics* 1999;104(suppl 4):746–747.

APPENDIX 2 Characteristics of Patients with Kernicterus

	B/A	TSB	Max. BIND	3 mo AABR	Hct.	Cause of Jaundice	Adm weight, g	Adm Age, d	Comments
1	8.6	29.1	9	ND	ND	Unknown	2250	5.3	DIED; pH 7.2 HCO_3 15 Direct Bil. 5.6
2	8.6	34.2	9	RR	33.7	Hemolysis O-A	2800	5.5	Dystonia at 3 mo
3	9.0	37	7	ND	44.0	Rh incompatibility	2250	4	DIED; Suspected sepsis
4	9.1	31	8	RR	39.7	Rh incomp. DAT neg.	2800	5.8	Severe ABE at admission; *Klebsiella* sepsis post-exchange
5	9.6	41.2	9	ND	29.2	Hemolysis[a]	3100	3.8	DIED; pH 6.97; apnea, seizures
6	9.6	37.6	8	ND	38.8	O-A incomp.	2100	7.2	Suspected sepsis
7	9.7	32	4	PR	53.7	Unknown	3000	7.6	Mild kernicterus 3 mo
8	10.2	31.7	9	RR	37.0	G6PD deficient	3200	6.5	No hemolysis, kernicterus at 3 mo
9	10.3	28.9	9	ND	24.8	Hemolysis Rh	2250	4	DIED; Suspected sepsis; pH 7.17[b]
10	10.4	31.1	5	RR	47.3	O-A incomp.	1840	3	34.5 wks SGA, high reticulocyte count, Mild kernicterus
11	10.5	43	8	ND	35.0	Unknown	2750	3.8	DIED; 2 exchange transfusions.
12	10.5	38.7	9	ND	29.4	Hemolysis[a]	2900	2	Suspected sepsis
13	10.6	35	8	ND	34.0	Hemolysis O-A	2500	3.4	DIED; *Pseudomonas* sepsis; pH 7.10[b]
14	10.8	40.02	8	ND	48.4	Rh, moderate G6PD	2750	4.5	Direct bilirubin 10.8 with no hemolysis
15	11.3	39.7	7	RR	41.9	G6PD & O-A incomp.	2030	13	Late admission, kernicterus at 3 mo
16	11.4	36.6	9	ND	45.4	Unknown	2250	8.1	pH 7.23
17	11.5	42.5	9	ND	31.1	Hemolysis O-B	3200	3.8	DIED; Suspected sepsis; seizures
18	11.5	36.7	6	RR	42.5	O-B incomp.	2250	7.7	Kernicterus at 3 mo
19	11.8	43.6	6	RR	37.0	O-A incomp.	2970	5.9	Kernicterus at 3 mo
20	12.1	35.2	9	ND	42.9	Unknown	2000	5.8	DIED; rapid deterioration after second exchange[b]
21	12.4	37	7	RR	30.0	Hemolysis O-B	2400	5	35 wk GA; hypertonic with head lag 3 mo
22	12.6	39	9	ND	37.2	O-A incomp.	2300	4.7	Suspected sepsis[b]
23	12.6	44.2	8	RR	50.9	Unknown	2400	5.4	Suspected sepsis; pH 7.33 kernicterus at 3 mo
24	12.8	39.7	8	ND	31.4	Hemolysis O-A	2760	9.8	DIED; Suspected sepsis; respiratory acidosis; apnea, seizures
25	12.8	38.5	8	RR	37.0	O-A incomp.	3150	2.3	Sustained high TSB; kernicterus at 3 mo
26	13.7	47.9	7	RR	21.7	Hemolysis G6PD def,	2800	4.9	Suspected sepsis; pH 7.30
27	14.0	36.5	7	RR	25.7	Hemolysis Rh	4000	4.2	Deterioration after second exchange[b]
28	14.9	46.2	9	ND	49.0	Unknown	2140	6.2	RR AABR and abnormal neurologically at discharge no FU
29	15.1	40.7	7	ND	ND	O-A incomp.	3000	4	DIED; classic kernicterus, seizures
30	15.1	48.3	8	RR	38.1	O-B incomp.	2930	13	Late admission; Na 157, kernicterus at 3 mo
31	15.6	42.01	8	RR	31.7	Hemolysis Rh	2450	2.2	Direct bilirubin 16, kernicterus at 3 mo
32	17.8	32	9	ND	27.9	Hemolysis O-A	2440	4.3	DIED; Suspected sepsis; pH 7.13
33	19.2	47.9	7	ND	41.5	O-B & Rh incomp.	2620	2.6	DIED; deteriorated postexchange[b]
34	20.0	44.1	9	ND	31.9	Hemolysis[a]	2850	4.1	DIED; pH 7.22 respiratory acidosis
35	21.0	61.03	7	RR	27.4	Hemolysis O-A	2900	5.1	Direct bilirubin 27.7; kernicterus at 3 mo

Ranked by increasing B/A ratio. Adm: admission Hct; hematocrit; DAT, direct antiglobulin test; incomp, blood type incompatibility without evident hemolysis. Max, maximum; ND: not done. PR: Pass refer, FU: follow up

[a] Unknown cause for hemolysis.

[b] Onset of kernicterus or worsening postexchange transfusion.