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A neurologic dysfunction scoring protocol for jaundiced neonates requiring exchange transfusion

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Abstract

Aim: To evaluate the performance of a neurologic assessment protocol among jaundiced infants requiring exchange transfusion (ET).

Methods: We identified infants in a referral children's hospital who received ET and those who met the American Academy of Pediatrics (AAP) criteria for ET based on total serum bilirubin (TSB) levels. The performance of a bilirubin-induced neurologic dysfunction (BIND-M) scoring protocol for acute bilirubin encephalopathy (ABE) in detecting infants treated with ET in both groups was investigated by logistic regression analysis and c-statistic.

Results: A total of 438 late-preterm and term infants were enrolled, out of which 141 (32.2%) received ET, and 155 (35.4%) met AAP criteria for ET. Infants with BIND-M scores of 3–6 (intermediate ABE) or 7–12 (advanced ABE) were significantly associated with ET in both groups, but not scores of 1–2 (mild ABE), with or without adjustment for confounding neurotoxicity risk factors. However, the discriminatory ability of BIND-M regression models was modestly satisfactory (c-statistic range: 0.693 to 0.791).

Conclusions: Our findings suggest that BIND-M is a potentially useful decision-making tool for ET and support current recommendation for immediate ET for infants with intermediate-to-advanced stages of ABE regardless of the TSB levels.

Keywords

acute bilirubin encephalopathy; neurological examination; newborn care; exchange transfusion; late presentation

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Author contributions: BOO conceived and designed the study, analyzed the data and drafted the manuscript. FBO, AAA, OEA, AAO participated in the completion of the BIND-M protocol and data collection. SMO was the laboratory scientist for the study. AAE supervised data collection and participated in the interpretation of the data. All authors reviewed and approved the final version for submission.

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Introduction

Neonatal jaundice is a leading illness in newborns and a frequent reason for hospital readmission in the first week of life worldwide [1–3]. Phototherapy and exchange transfusion (ET) are the mainstays of treatment to prevent kernicterus or bilirubin-related mortality [4–6]. In most cases, timely detection and treatment with intensive phototherapy is effective in reducing the need for the invasive, painful, and time-consuming ET procedure [7]. ET usually becomes a priority when phototherapy proves ineffective in averting the risk of bilirubin neurotoxicity or when the neurological signs of acute bilirubin encephalopathy (ABE) are evident [4–6]. Most practice guidelines recommend ET based on prescribed age-specific thresholds for total serum bilirubin (TSB), and/or clinical signs of ABE [4,5]. However, the assessment of ABE is frequently based on subjective physical examinations, and the outcome typically variable, possibly resulting in under- or over-treatment [8,9].

A standardized scoring protocol has been proposed and used to provide a systematic and structured assessment of the generally accepted clinical signs associated with ABE or bilirubin-induced neurologic dysfunctions (BIND) [10–13]. This is conceptually similar to the Apgar score, or the optimality score pioneered by Dubowitz et al for neurological examination of newborns [14,15]. The simplicity of this scoring algorithm makes it an attractive tool for minimizing bias in clinical diagnosis of ABE in newborns. However, it is unclear how such a tool can independently optimize decision-making for ET, especially in resource-constrained settings where timely determination of TSB levels cannot be assured, and late presentation of infants with severe hyperbilirubinemia is common [16]. This study set out to evaluate the usefulness of a scoring protocol for ABE in identifying infants who may require ET in a referral hospital setting.

Methods

This cross-sectional study was conducted at Massey Street Children's Hospital (MSCH), the first children's specialist hospital in Nigeria. It is a 100-bed, state-owned referral hospital that provides critical pediatric care to several private and public hospitals within and outside its catchment area. The study was approved by the Lagos State Health Service Commission. Participants were drawn from a sampling frame of infants recruited for a substantive research project on the prevalence of ABE in Lagos from January 2013 to December 2014.

Late preterm and term infants (gestational age ≥35 weeks or birthweight >2.2 kg) who presented with, or while on admission in the emergency unit for any other illness developed clinically severe jaundice (evidenced by generalized icterus extending to the palms and soles, or clinical features of ABE) were enrolled for this study. Phototherapy was commonly initiated at approximately TSB ≥12mg/dL (204 μmol/L) in otherwise healthy normal weight (≥2500g) infants. This level was widely used because of the high prevalence of glucose 6-phospho-dehydrogenase (G6PD) deficiency in this population [17]. During the study period, TSB was measured from venous blood samples collected by the attending physicians using the Advanced Bilirubin Stat-Analyzer (Model BR 2) (Advanced Instruments Inc, Norwood, CA). Irradiance levels of phototherapy devices were routinely monitored by a research technician using a duly calibrated BiliBlanket® II Meter (General Electric, Fairfield, CT) to

ensure that they were within recommended therapeutic range for conventional and intensive phototherapy. Double-volume ET with fresh whole blood, was typically initiated at TSB ≥20mg/dL (340 μmol/L) in apparently healthy late preterm and term infants, with or without clinical features of ABE.

Prior to TSB determination, enrolled infants were evaluated for signs of ABE using a modified and previously validated bilirubin-induced neurologic dysfunction (BIND-M) scoring protocol by pediatric residents who had received prior training on the use of the protocol [13]. The residents were simply required to indicate the observed neurologic signs on a standard form that included measures of mental status, muscle tone, cry pattern and oculomotor/eye movements (Supplementary Figure S1). Scores of 0 – 3 were independently assigned to the outcomes of the examination in each of the four domains by the lead author (BOO) to derive a total BIND-M score of between 0 and 12 for each infant. A total BIND-M score of 1–2 was considered as indicative of mild ABE, 3–6 for moderate (or intermediate) ABE, and 7–12, severe (or advanced) ABE [13]. These scores were computed at the end of the study period and were not considered in the decision-making for ET by the attending physicians. All infants included in this analysis were tested for G6PD activity.

Statistical analysis

The performance of BIND-M was evaluated with respect to two measures: infants who received ET during the study period and those who would have required ET strictly based on the AAP age-specific TSB thresholds for ET [4]. We opted for the AAP criteria because of its widespread adoption or adaptation [18], even in developing countries [19]. Where information on gestational age was not available, weight on admission ≤2.7kg was used as proxy for gestational age <38weeks, as reported in a comparable study [12].

We first determined differences between those who met AAP criteria and those who actually received ET. We then explored possible reasons why infants with extreme hyperbilirubinemia (TSB ≥25mg/dL), who met the AAP criteria for ET were not so treated. Thereafter, crude association between the categorized BIND-M scores and the two performance measures was examined with univariate binary logistic regression. This was followed by separate multivariable logistic regression analyses to assess the potential confounding effects of biologically plausible clinical and non-clinical factors on the performance of BIND-M [4,12,20,21]. The clinical factors were birth asphyxia, possible sepsis (based on an elevated C-reactive protein level), G6PD deficiency (based on a lack of fluorescence after 10 minutes using methods described by Beutler et al [22], for fluorescent blood spot evaluation), ABO and Rhesus incompatibility. Direct antiglobulin testing (DAT) was also performed on the blood samples to determine the presence of hemolysis. Non-clinical factors included gender, gestational age, age on admission, weight on admission, place of delivery (hospital vs non-hospital), and feeding mode (exclusive breast feeding, formula milk, or mixed). Model performance was assessed by the c-statistic (as shown by the area under the receiver operating characteristic curve). Strength of association was estimated by odds ratios (OR) and the corresponding 95% confidence intervals (CI) as an approximation of the relative risk. All tests of significance were two-tailed at alpha level of

p<0.05. IBM SPSS Statistics for Windows software, Version 23.0 (IBM Corporation, Armonk, NY) was used for all statistical analyses.

Results

A total of 438 neonates were enrolled for this study, of which 141 (32.2%) infants received ET. The demographic characteristics of the infants, and comparison between those who received or did not receive ET are summarized in Table 1. Some 32.0% of the infants were female, 14.6% had gestational age of <38weeks, 29.9% weighed 2.7kg or less on admission and most (65.5%) presented between age 3–7 days with a median age at admission of 4 (interquartile range: 3 – 6) days. Some 27.4% were delivered outside hospital, predominantly in residential homes and maternity homes run by traditional birth attendants (TBA). The majority (77.6%) were exclusively breast-fed.

The clinical characteristics of the infants are summarized in Table 2. Some 8.9% of the infants had a history of birth asphyxia or sepsis, 43.6% were G6PD deficient, 19.9% had ABO incompatibility and 1.6% had Rhesus incompatibility. None of the 173 (39.5%) infants who received the Coombs test had a positive outcome. The infants had a mean maximum TSB of 19.8 ± 8.6 (range: 4.5 – 67.0) mg/dL. Seventy (16.0%) infants had a max TSB of at least 30mg/dL, with one infant recording 67mg/dL on admission at age 6 days. This male infant was born at 36 weeks' gestation, was G6PD deficient, weighed 2.3kg on admission, had severe ABE (BIND score of 8) and received repeat ET. The TSB dropped to 19.8mg/dL on the second day of admission after the first ET, and further to 8.2mg/dL before discharge. All infants in this study received phototherapy on admission.

Over one-third (37.5%) of the infants had moderate-to-severe ABE. Of those who received ET, 121 (85.8%) met AAP criteria for ET, while 34 (21.9%) out of the 155 infants who met AAP criteria did not receive ET. An overview of the infants in this latter group with extreme hyperbilirubinemia (TSB ≥25mg/dL) is presented in Supplementary Table S1. The predominant reasons for not receiving the required ET were due to difficulties with cannulation. Two infants died prior to receiving ET. The parents of three infants requested for voluntary discharge prior to ET, one of whom was a Jehovah Witness. ET was avoided for two infants due to rapid drop in TSB following intensive phototherapy. Reasons why ET was not done for one infant could not be retrospectively established from available records. Only 20 (7.1%) of the 283 infants who did not meet the AAP criteria received ET, out of which 9 (45.0%) had moderate-to-severe ABE (BIND-M >6) and mean maximum TSB of 18.9 ± 2.9mg/dL (data not shown). All but three infants were within 20.0 ± 2.0mg/dL of the hospital TSB threshold for ET.

Age on admission, birth asphyxia, ABO incompatibility, maximum TSB, ABE determined by BIND score, and AAP criteria for ET were significantly associated with infants who received ET in this population (Tables 1 and 2). The relationship between BIND-M scores and ET is presented in Table 3. The unadjusted model showed increasing risk of requiring ET in the hospital or based on AAP criteria with increasing BIND-M scores. However, only infants with scores >2 (moderate-to-severe ABE) were significantly more likely to require ET compared to those with no ABE. This pattern was not significantly modified even when

adjusted for the confounding effects of either clinical or non-clinical covariates. Infants with severe ABE had at least three-fold risk of requiring ET compared to infants with moderate ABE. The concordance statistics showed that the unadjusted models had a modestly satisfactory and comparable discriminative ability for detecting the need for ET with the adjusted models. This was corroborated by the receiver operating characteristic curve analysis of the raw BIND-M scores under the AAP criteria (AUC: 0.706, 95% CI: 0.652 – 0.762) or among infants likely to receive ET in the hospital (AUC: 0.696, 95% CI: 0.639 – 0.752) (data not shown).

Discussion

Prioritizing infants who present late with severe hyperbilirubinemia in emergency units is a frequent challenge for clinicians prior to TSB determination in resource-limited settings. This study set out to evaluate the potential usefulness of a standardized neurologic dysfunction protocol (BIND-M) in identifying infants who require ET in such settings. The scoring protocol was found to be predictive of ET with or without adjustment for potentially confounding factors. Thus, it would appear that the difficulty frequently encountered in establishing known clinical risk factors for neurotoxicity accurately and routinely on admission is unlikely to adversely affect the decision to use the scoring protocol for initiating ET. However, the c-statistic clearly suggests that the predictability of the protocol is not perfect. For this reason, and considering the complex and multifactorial underpinnings of bilirubin neurotoxicity across racial populations, the scoring protocol should, as much as practicable, be complemented with more objective measures of free (unbound) unconjugated bilirubin [23].

Our study suggests also that infants with mild ABE (BIND-M score of 1 or 2) may not have statistically significant need for ET. This accords with the recommendation in most practice guidelines, especially AAP, for immediate ET in any jaundiced infant with signs of intermediate or advanced stages of ABE [4–6]. However, as argued elsewhere [24], there may be situations in which clinical judgement favors priority consideration for infants with mild and reversible ABE over those with frequently irreversible intermediate-to-advanced ABE. One study from India, for example, reported significant adverse outcomes (cerebral palsy, developmental delays and auditory deficit) in infants with moderate or severe ABE, despite intervention with ET [25]. In essence, BIND-M, like any scoring algorithm, is best applied as a decision-making aid rather than a substitute for clinical judgement. It should facilitate systematic neurological examination of jaundiced infants for the presence or absence of ABE. In the absence of such a protocol it may be difficult, for example, to distinguish between the various classes of ABE. Some of the subtle danger signs of ABE may also be missed easily in a busy emergency setting with infants presenting with diverse critical illnesses. Moreover, the BIND-M is simple and more practical than a similar protocol consisting of 84 items reported in one study from Zimbabwe [26].

It is important to emphasize that ET should be avoided wherever possible for several reasons. Firstly, the procedure is not entirely risk-free, even in the best of hands. It is associated with complications such as sepsis, electrolyte imbalance, air embolism, portal vein thrombosis, cardiac overload, thrombophlebitis, thrombocytopenia, necrotizing

enterocolitis, as well as the transmission of blood-borne diseases, even in settings with facilities for advanced clinical care [27]. Secondly, there are several biological and facility-based challenges in providing timely and effective ET in resource-poor settings [28]. For example, in our study, some infants who required ET could not receive the treatment because of parental refusal, usually on religious grounds, difficulties with umbilical cannulation, or even unexpected death. Investment in intensive phototherapy (irradiance of at least $30\mu W/cm^2/nm$ from either a single or multiple units) should therefore, be considered a priority as demonstrated by cases in our study, and elsewhere [7,29], in which ET was avoided altogether as a result of intensive phototherapy. One study from Jordan, for example, found that phototherapy was sufficient for about half of the infants who exceeded the AAP threshold for ET [19].

The significant association observed with age on admission, birth asphyxia, ABO incompatibility, maximum TSB, ABE, and AAP criteria for ET among infants who actually received ET are consistent with evidence in prior studies [11,12,20,21]. Addressing the modifiable risk factors of neurotoxicity such as late presentation, and late detection of hemolysis should be considered [12,19–21]. Late presentation usually from the 5^{th} day of life also accounted for inability to undertake ET where required because of difficulties with cannulation. In fact, about 43% of the infants in this study presented as from the fifth day of life, and as late as 13^{th} day. Although delivery outside hospital was not found to be a predictor of ET in our study, it was forced into the regression models based on evidence in comparable studies on the potential confounding effects of this factor on the risk of ABE [19–21].

It was not unsual to find infants who received ET, that was not so indicated by the AAP guidelines [19,30]. In the study from Jordan, about 14.3% of the 70 infants (approximrely one in every six infants) who received ET did not meet AAP criteria, compared to 7.1% in our study. This was attributed to the physicians' greater concern for bilirubin-induced neurotoxicity and more liberal disposition to ET [19]. In our study, provision of ET for infants who did not meet AAP criteria was predominantly due to the lack of awareness or familiarity with the AAP guidelines, cautious adherence to local guidelines and concern for the risk of kernicterus even at lower TSB levels, given the high prevalence of G6PD deficiency in this population. However, it is noteworthy that based on current practice in our hospital, about 86% of infants who will receive ET are likely to meet the AAP criteria. Although, evidence in the literature suggests that this percentage may be lower when the care-givers are not pediatricians [30], it is unlikely that the clinical procedure of ET will be entrusted to non-clinicians in any setting.

A notable strength of this study is the use of a previously validated scoring system in the study population. To the best of our knowledge, this is the first study to explore the usefulness of a neurological dysfunction protocol to identify infants who may require ET. However, some limitations are worth noting. Firstly, this is a retrospective study from a single children's hospital which limits the generalizability of the findings. Secondly, we did not adjust for all the suggested risk factors for neurotoxicity by AAP, although there is no evidence that those omitted such as birth trauma and hypoalbuminemia (<3g/dL) would have materially affected the findings. Thirdly, because our hospital is a referral center, very

limited data was available on pertinent birth histories as well as post-discharge outcomes. Nonetheless, our study demonstrates the potential usefulness of a neurologic evaluation scoring protocol in facilitating decision-making for ET, especially in settings where rapid TSB determination cannot be readily assured.

Conclusions

BIND-M protocol is a potentially useful decision tool for identifying infants who require ET promptly, prior to TSB determination. It should also facilitate the identification of infants with intermediate-to-advanced ABE who require immediate ET irrespective of TSB levels as recommended by AAP and other guidelines. Preparatory to ET, intensive phototherapy should be routinely provided. Maternal counselling to discourage late presentation and discharge against medical advice should be considered to ensure that ET is feasible and provided when required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ABE	acute bilirubin encephalopathy
AAP	American Academy of Pediatrics
BIND-M	Modified bilirubin-induced neurologic dysfunction
ET	exchange transfusion
G6PD	Glucose 6-phospho-dehydrogenase
TSB	Total serum/plasma bilirubin

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Table 1.

The demographic characteristics of infants enrolled into the study

Factors	Total (%)	No ET (%)	Received ET (%)	p-value
Gender				p=0.650
Female	140 (32.0)	97 (32.7)	43 (30.5)	
Male	298 (68.0)	200 (67.3)	98 (69.5)	
Gestational age				p=0.444
<38 weeks	64 (14.6)	41 (13.8)	23 (16.3)	
≥38 weeks	357 (81.5)	246 (82.8)	111 (78.7)	
Missing data	17 (3.9)	10 (3.4)	7 (5.0)	
Mean (± SD)	38.6 ± 1.4			
Weight on admission				p=0.291
≤2.7 kg	131 (29.9)	84 (28.3)	47 (33.3)	
>2.7 kg	306 (69.9)	212 (71.4)	94 (66.7)	
Missing data	1 (0.2)	1 (0.3)	0 (0.0)	
Mean (± SD)	3.0 ± 0.5			
Age on admission				p=0.003
0 – 2 days	100 (22.8)	77 (25.9)	33 (16.3)	
3 – 7 days	287 (65.5)	179 (60.3	108 (76.6)	
>7 days	51 (11.6)	41 (13.8)	10 (7.1)	
Median (Interquartile range)	4 (3 – 6)			
Place of birth				p=0.091
Hospital	318 (72.6)	223 (75.1)	95 (67.4)	
Outside hospital	120 (27.4)	74 (24.9)	46 (32.6)	
Feeding mode				p=0.058
Breast milk only	340 (77.6)	221 (74.4)	119 (84.4)	
Formula only	58 (13.2)	46 (15.5)	12 (8.5)	
Mixed	40 (9.1)	30 (10.1)	10 (7.1)	

ET: exchange transfusion

Table 2.

Clinical characteristics of infants enrolled into the study

Factors	Total (%)	No ET (%)	Received ET (%)	p-value
Birth asphyxia				p<0.001
No	399 (91.1)	260 (87.5)	139 (98.6)	
Yes	39 (8.9)	37 (12.5)	2 (1.4)	
Sepsis				p=0.381
No	380 (86.8)	260 (87.5)	120 (85.1)	
Yes	39 (8.9)	24 (8.1)	15 (10.6)	
Missing data	19 (4.3)	13 (4.4)	6 (4.3)	
G6PD deficient				p=0.920
No	247 (56.4)	167 (56.2)	80 (56.7)	
Yes	191 (43.6)	130 (43.8)	61 (43.3)	
ABO incompatibility				p=0.001
No	351 (80.1)	251 (84.5)	100 (70.9)	
Yes	87 (19.9)	46 (15.5)	41 (29.1)	
Rhesus incompatibility				p=0.154
No	431 (98.4)	294 (99.0)	137 (97.2)	
Yes	7 (1.6)	3 (1.0)	4 (2.8)	
Maximum TSB				p<0.001
<12mg/dL	67 (15.3)	67 (22.6)	0 (0.0)	
12 – 19.9mg/dL	208 (47.5)	189 (63.6)	19 (13.5)	
20 – 29.9mg/dL	93 (21.2)	30 (10.1)	63 (44.7)	
30mg/dL and over	70 (16.0)	11 (3.7)	59 (41.8)	
Mean (± SD)	19.8 ± 8.6			
ABE (BIND-M Score)				p<0.001
None (0)	187 (42.7)	148 (49.8)	39 (27.7)	
Mild (1–2)	87 (19.9)	70 (23.6)	17 (12.1)	
Moderate (3–6)	76 (17.4)	48 (16.2)	28 (19.8)	
Severe (7–12)	88 (20.1)	31 (10.4)	57 (40.4)	
Met AAP Exchange Transfusion Criteria				p<0.001
No	283 (64.6)	263 (88.6)	20 (14.2)	
Yes	155 (35.4)	34 (11.4)	121 (85.8)	

ET: exchange transfusion; TSB: total serum bilirubin; AAP: American Academy of Pediatrics; ABE: Acute bilirubin encephalopathy; BIND-M: Modified Bilirubin-induced Neurologic Dysfunction

Table 3.

Logistic regression models to determine the association between BIND-M scores and exchange transfusion

BIND-M Score	ABE	Model A		Model B		Model C	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Met AAP criteria for ET							
0	None	Reference		Reference		Reference	
1–2	Mild	1.10 (0.60 – 2.00)	0.759	1.18 (0.63 – 2.20)	0.600	1.10 (0.57 – 2.13)	0.780
3–6	Moderate	2.01 (1.13 – 3.59)	0.018	2.14 (1.16 – 3.94)	0.015	2.16 (1.14 – 4.10)	0.018
7 – 12	Severe	9.21 (5.15 – 16.47)	0.000	9.29 (4.99 – 17.30)	0.000	10.42 (5.26 – 20.65)	0.000
	c-statistic	0.700 (0.646 – 0.754)		0.732 (0.678 – 0.786)		0.762 (0.711 – 0.814)	
Received ET							
0	None	Reference		Reference		Reference	
1–2	Mild	0.92 (0.49 – 1.74)	0.802	0.97 (0.50 – 1.88)	0.932	0.91 (0.45 – 1.82)	0.784
3–6	Moderate	2.21 (1.23 – 3.97)	0.008	2.41 (1.31 – 4.44)	0.005	2.38 (1.25 – 4.54)	0.008
7 – 12	Severe	6.98 (3.98 – 12.24)	0.000	6.61 (3.64 – 12.01)	0.000	8.02 (4.08 – 15.73)	0.000
	c-statistic	0.693 (0.638 – 0.749)		0.726 (0.671 – 0.780)		0.791 (0.743 – 0.839)	

ABE: Acute bilirubin encephalopathy; CI: Confidence interval; ET: exchange transfusion; Model A: Unadjusted BIND-M scores;

Model B: BIND-M scores adjusted for non-clinical risk factors (gender, gestational age, age on admission, weight on admission, place of delivery and feeding mode);

Model C: BIND-M scores adjusted for non-clinical and clinical factors (birth asphyxia, sepsis, G6PD deficiency, ABO incompatibility, Rhesus incompatibility)