Revisiting the Criteria for Exchange Transfusion for Severe Neonatal Hyperbilirubinemia in Resource-Limited Settings

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Key Words

Bilirubin encephalopathy · Kernicterus · Neurotoxicity · Hemolysis · Developing countries

Abstract

Background: Exchange transfusion (ET) for severe neonatal hyperbilirubinemia (SNH) is frequently undertaken in low- and middle-income countries (LMIC), in sharp contrast to the prevailing practice in high-income countries. However, the criteria for initiating this procedure in settings with limited resources for treating infants with SNH have not been systematically explored. **Objective:** To identify key considerations for initiating ET in resource-poor countries to curtail its unnecessary use for the prevention of kernicterus. **Methods:** A review of the existing guidelines and literature on the management of neonatal hyperbilirubinemia worldwide was conducted to identify criteria and underlying factors for initiating ET. **Results:** There is a dearth of evidence from randomized clinical trials to support clear criteria for indicated ET worldwide. Because risk assessment for kernicterus based solely on the levels of total serum bilirubin (TSB) has often proved inadequate, a combination of plasma/serum bilirubin estimation and clinical evaluation for acute bilirubin encephalopathy (ABE) has been recommended for predicting the risk of kernicterus. However, there is a lack of consistency regarding the TSB levels for which ET should be initiated in

relation to the clinical signs/symptoms of ABE and hemolytic disorders. **Conclusions:** A decision-making framework that combines TSB thresholds and evidence of neurotoxicity is needed for evaluating the risk of kernicterus and prioritising infants for ET in LMICs to curtail unnecessary interventions.

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Introduction

Since its introduction in the late 1940s [1], exchange transfusion (ET) has been universally established as an efficacious and reliable treatment for severe neonatal hyperbilirubinemia (SNH) and the prevention of bilirubin-induced neonatal mortality and long-term morbidity [2–4]. This clinical procedure, which is not entirely risk free, lowers the total plasma/serum bilirubin (TSB) concentration by removing circulating bilirubin, antibody-coated red blood cells in hemolytic disease (e.g. in rhesus and ABO sensitization), or vulnerable red blood cells due to glucose-6-phospho-dehydrogenase (G-6-PD) deficiency and other red cell enzyme deficiencies [5]. Adverse events associated with ET, even in settings with advanced clinical care, include sepsis, electrolyte imbalance, air embolism, portal vein thrombosis, cardiac overload, thrombophlebitis, thrombocytopenia, and necrotizing enterocolitis, as well as the transmission of blood-borne diseases

[4–6]. ET is therefore, generally regarded as the last line of defense after phototherapy has failed to lower TSB to safe levels in babies with SNH or has been ineffective in preventing rapidly rising bilirubin levels in infants with hemolytic SNH [2, 7].

The requirement for ET in developed countries has declined largely due to improved surveillance of infants with clinically significant jaundice, routine use of rhesus immunoglobulin prophylaxis to prevent primary isoimmunization of Rh-negative women, and optimization of blue-light phototherapy [8, 9]. In contrast, excessive rates of ET, with its associated risks, persist in low- and middle-income countries (LMIC) [4, 10, 11]. A hospital-based study from the Middle East found that 99 (61.1%) of 162 infants admitted for SNH over a 4-month period received ET [11]. Another study from Latin America reported that 78 (21.5%) of 362 infants who received phototherapy over a 5-year period still required ET [4].

Striking a balance between undertreatment and overtreatment in LMIC is complicated by several factors including the prevalence of hemolytic triggers unique to many LMIC, the late presentation of severe cases, and the lack of adequate clinical and laboratory facilities [11–13]. This paper reviews the existing criteria for initiating ET in late-preterm and term infants with SNH and how these can be optimized to provide timely (while avoiding unnecessary) ET in resource-poor countries. It excludes discussions regarding the technique, resources, and provider expertise for the procedure as these are well described in the literature [5, 14].

Methods

The key terms used in this review are consistent with American Academy of Pediatrics (AAP) guidelines for the management of neonatal hyperbilirubinemia [7]. For example, SNH refers to neonatal jaundice with serum bilirubin at/near ET levels based on postnatal age and etiology, and/or any elevated bilirubin levels associated with signs of acute bilirubin encephalopathy (ABE). The term ABE refers to the acute manifestations of bilirubin toxicity seen in the first weeks after birth. Signs and symptoms of ABE are typically classified as mild (poor feeding, lethargy, and tone abnormalities), moderate/intermediate (high-pitched cry, irritability, and increasing hypertonia), or severe/advanced (deep stupor, fever, apnea, inability to feed, retrocollis, opisthotonus, and obtundation). The term kernicterus refers to the chronic and permanent clinical sequelae of bilirubin toxicity, frequently characterized by choreoathetoid cerebral palsy, upward gaze paralysis, and auditory neuropathy spectrum disorders with or without hearing loss.

We conducted an electronic search of National Guideline Clearinghouse (www.guideline.gov) and www.g-i-n.net/), PubMed, Scopus, Ovid EMBASE, and the Cumulative Index to Nursing and

Allied Health Literature (CINAHL), as well as the references in relevant guidelines and review papers on ET for hyperbilirubinemia between January 1990 and June 2015. The search terms were: 'neonatal hyperbilirubinemia', 'neonatal jaundice', 'exchange transfusion', 'bilirubin encephalopathy', and/or 'kernicterus'. Guidelines without any specific criteria for ET or an English version were excluded from the final review. As this paper was designed as a narrative review, no systematic evaluation of the retrieved articles and reports was undertaken.

Results

Current Criteria for ET in Developed Countries

An overview of the recommended criteria for ET in published guidelines is presented in table 1 [2, 7, 15–30]. The AAP guidelines, first published in 1994 and updated in 2004 [7], have been adopted, with or without modifications, in many countries. Nomograms recommend intervention levels for phototherapy and ET based on the TSB level and postnatal age to reflect the perceived increased risk using gestational age and certain clinical factors. ET is warranted whenever intensive phototherapy does not significantly lower TSB levels at the exchange threshold for that age or whenever a baby shows signs of intermediate-to-advanced stages of ABE even if the TSB is falling. The AAP guideline considers $\text{TSB} \geq 25 \text{ mg/dl}$ ($428 \mu\text{mol/l}$) at any time to be a medical emergency requiring immediate intensive phototherapy preparatory to ET. Countries like Canada [15], The Netherlands [18], Australia [21], South Africa [24], and India [25–27] have adopted these criteria with little or no modifications (table 1). A few countries like Switzerland [19] and Norway [16] have incorporated baby weight in addition to or in lieu of gestational age into their guidelines. In Israel, separate ET thresholds are provided for infants with hemolytic and nonhemolytic conditions [23].

Criteria for ET in Resource-Poor Countries

Clinical guidelines for neonatal jaundice do not exist in the vast majority of LMIC. In the few countries (e.g. India and Kenya) where consensus guidelines have been established, the criteria for ET have been adapted from AAP and National Institute for Clinical Excellence (NICE; UK) guidelines (table 1). The clinical reference material, widely promoted by the World Health Organization for the care of sick infants in LMIC, recommends ET at $\text{TSB} \geq 15 \text{ mg/dl}$ ($260 \mu\text{mol/l}$) on the first day of life and $\text{TSB} \geq 25 \text{ mg/dl}$ ($425 \mu\text{mol/l}$) on the second day of life [30]. The threshold is lowered by at least 5 mg/dl for high-risk infants with evidence of hemolysis or sepsis. A major limita-

Table 1. Overview of the criteria for ET in published guidelines for the management of neonatal hyperbilirubinemia

Country/ region	Reference	Criteria for ET in near- and full-term infants
USA	American Academy of Pediatrics [7]	<p>Calibrated based on gestational age, postnatal age, and risk profile</p> <p>In the first 24 h: TSB 12–19 mg/dl</p> <p>Between 1–3 days: TSB 15–25 mg/dl</p> <p>At least 4 days: TSB $\geq$25 mg/dl (428 μmol/l) and does not decrease sufficiently with phototherapy alone</p> <p>Immediate ET for any infant who is jaundiced and manifests the signs of the intermediate to advanced stages of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, and a high-pitched cry) even if the TSB is falling</p>
UK	National Institute for Health and Clinical Excellence [2]	<p>Different charts have been prepared for infants with a gestational age of 24–38 weeks or more</p> <p>ET for babies whose serum bilirubin level indicates a need for it (as assessed by the threshold table and treatment threshold graphs) and/or babies with clinical features and signs of ABE</p>
Canada	Canadian Paediatric Society [15]	<p>ET should only be performed in centers with the appropriate expertise under the supervision of an experienced neonatologist</p> <p>Treatment chart is adapted from AAP criteria and the TSB level is calibrated only in micromoles per liter</p> <p>Infants with a TSB concentration above the thresholds shown in the chart should have immediate intensive phototherapy and should be referred for further investigation and preparation for ET; infants with clinical signs of acute bilirubin encephalopathy should have an immediate ET</p>
Norway	Bratlid et al. [16]	<p>Birth weight is used as a measure of prematurity instead of gestational age as in the AAP guideline; the guidelines therefore include treatment recommendations for low, very low, and extremely low birth weight infants</p> <p>ET is recommended for infants with nonhemolytic hyperbilirubinemia at a TSB level of 50–100 μmol/l above the maximum concentration for phototherapy, giving an indication for ET of 450 μmol/l in term infants with nonhemolytic hyperbilirubinemia</p>
Denmark	Ebbesen et al. [17]	<p>ET for all infants when the TSB level is 100 μmol/l above the phototherapy limit (300 μmol/l $\pm$ 50 μmol/l)</p> <p>ET when the TSB level rises by more than 10 μmol/l/h during intensive phototherapy or if the TSB level does not fall considerably during double/triple phototherapy</p>
The Netherlands	Dijk et al. [18]	<p>Treatment chart adapted from AAP criteria</p> <p>ET is planned when the TSB value is above the ET border or if despite intensive phototherapy the concentration of TSB does not fall and the ET limit is approaching</p> <p>Immediate ET if there are signs of acute bilirubin-encephalopathy or if the TSB level is above the ET border by more than 85 μmol/l</p>
Switzerland	Swiss Society of Neonatology [19]	<p>Treatment chart based on risk profile</p> <p>Term infant >2,500 g, healthy: 400–430 μmol/l</p> <p>Term infant >2,500g, ill or with hemolysis: 350–370 μmol/l</p> <p>Premature infant of 35 and 36 weeks of gestation or term infant <2,500 g: 270–320 μmol/l</p>
Italy	Romagnoli et al. [20]	<p>Separate treatment charts for hemolytic and nonhemolytic jaundice</p> <p>TSB threshold for ET in newborns with nonhemolytic jaundice are generally 5–6 mg/dl higher than the TSB threshold for phototherapy</p> <p>The TSB threshold for ET in newborns with Rh or ABO hemolytic jaundice is lower than that of newborns with nonhemolytic jaundice</p> <p>ET if the TSB level is $\geq$5 mg/dl (85 μmol/l) above the ET threshold</p> <p>ET if the TSB level exceeds the ET threshold after 4 h of intensive phototherapy</p> <p>The TSB level continues to rise by more than 1 mg/dl/h during intensive phototherapy</p> <p>Infants with clinical signs and symptoms of ABE are present</p>

Table 1 (continued)

Country/ region	Reference	Criteria for ET in near- and full-term infants
Australia	Queensland Maternity and Neonatal Clinical Guidelines Program [21]	Treatment chart adapted from AAP criteria ET if the TSB level is above the ET threshold and is not expected to be below the threshold after 6 h of continuous multiple phototherapy Immediate ET in infants with signs of bilirubin encephalopathy
New Zealand	Auckland District Health Board [22]	Treatment chart for infants without hemolytic jaundice ET in infants with a TSB level $>510 \mu\text{mol/l}$ from the second day of life Consider ET in infants with a TSB level $>50 \mu\text{mol/l}$ above the threshold for phototherapy
Israel	Kaplan et al. [23]	Adapted from an AAP nomogram and presented in a tabular format Separate tables for hemolytic and nonhemolytic jaundice, e.g. ET in term infants with hemolytic jaundice initiated at TSB levels of 18–20 mg/dl from 24 h after birth ET in term infants with nonhemolytic jaundice initiated at TSB 20–25 mg/dl from 24 h after birth In less acute situations, ET is recommended after a trial of 3–4 h of intensive phototherapy
South Africa	Horn et al. [24]	AAP nomogram for ET adopted without any modifications
India	National Neonatal Forum of India [25]	AAP criteria for ET is recommended Immediate EBT is recommended if the infant shows signs of ABE or if the TSB level is $\geq 5 \text{ mg/dl}$ above the recommended values
	Mishra et al. [26]	AAP criteria for ET is recommended Additional criteria for hemolytic jaundice is recommended Initiate ET if the TSB level: is $\geq 10 \text{ mg/dl}$ up to 24 h of life is $\geq 15 \text{ mg/dl}$ at 25–48 h of life is $\geq 20 \text{ mg/dl}$ at 48 h of life or later rises at a rate $\geq 0.5 \text{ mg/dl/h}$
	Postgraduate Institute of Medical Education and Research [27]	Consider ET if the TSB level rises at a rate $>1 \text{ mg/dl/h}$ despite PT or rises at a rate $>0.5 \text{ mg/dl/h}$ despite PT if the hemoglobin level is between 10–12 g/dl Any TSB level $>12 \text{ mg/dl}$ in first 12 h and any TSB level $>20 \text{ mg/dl}$ in the neonatal period in the setting of hemolysis In the DVET zone as per AAP charts for near-term and term babies
Kenya	Ministry of Health of the Republic of Kenya [28]	Adapted from NICE criteria and presented in a tabular format Initiate ET unless the TSB falls below the following thresholds while treatment is being prepared: $>100 \mu\text{mol/l}$ within 24 h of life $>300 \mu\text{mol/l}$ at 24–36 h of life $>450 \mu\text{mol/l}$ after 42 h of life
Malaysia	Ministry of Health of Malaysia [29]	Adapted from AAP and College of Family Physicians of Canada criteria ET is recommended if TSB levels, though declining with intensive phototherapy, persists above the ET thresholds ($>400 \mu\text{mol/l}$ after 24 h) ET is recommended in infants whose levels continue to rise to ET levels despite being on phototherapy ET is initiated in healthy term infants when the TSB level is $>340 \mu\text{mol/l}$ from 24 h of life
All developing countries	World Health Organization [30]	ET is recommended at the following thresholds: day 1: TSB $\geq 260 \mu\text{mol/l}$ (15 mg/dl) for infants ≥ 35 weeks day 2/3: TSB $\geq 425 \mu\text{mol/l}$ (25 mg/dl) for infants ≥ 35 weeks

tion of this protocol is the daily rather than 6- to 12-hourly monitoring of jaundiced infants especially when ET may be required for rapidly rising TSB in the first 48 h of life.

Reported practices also vary between and within countries [5, 11, 31, 32]. For example, in one hospital in Iraq, indications for ET included all infants admitted with TSB >20 mg/dl (342 μ mol/l) and/or clinical signs of bilirubin-induced neurologic dysfunction (BIND), except when the infant clearly responded to intensive phototherapy prior to availability of blood for ET [11]. In another hospital in Egypt, ET was indicated when phototherapy failed to reduce the TSB level to <25 mg/dl (428 μ mol/l) in healthy term infants or to lower thresholds in the presence of neurotoxicity risk factors, including prematurity, severe hemolysis, significant lethargy, and temperature instability [31]. In Nigeria, ET is routinely indicated at TSB $\geq$ 20 mg/dl (340 μ mol/l) in apparently healthy term infants and sometimes at TSB <20 mg/dl (340 μ mol/l) in very ill term infants with or without features of kernicterus, and at TSB levels between 10 and 12 mg/dl/kg (170–204 μ mol/l) in preterm infants [32]. In India, some hospitals simply use the medium- and high-risk thresholds for intervention in AAP nomograms for all infants [5].

Discussion

The overarching finding from this review is that the decision to initiate ET to prevent or minimize the risk of kernicterus crucially depends on 3 main considerations: (1) accurate TSB measurement, (2) accurate evaluation of clinical risk factors, and (3) accurate clinical assessment of the neurological state. The available evidence of the effectiveness of ET itself is largely based on a consensus among experts rather than classic evidence from randomized controlled trials [2, 3]. This is possibly because it is ethically not permissible to prospectively assign infants with SNH randomly to either phototherapy or the more risky ET regardless of their risk status. The only randomized controlled trial so far reporting the effectiveness of ET in preventing bilirubin-induced mortality (albeit compared to simple transfusion for the relief of anemia) was conducted in 1952, before the advent of phototherapy [33, 34].

Real-time and/or point-of-care TSB remains the gold standard for estimating and monitoring the severity of jaundice. However, neonatal units in many LMIC lack side laboratory to support real-time TSB measurement. Rather, blood samples have to be conveyed to a central laboratory where the results may take 2–4 h before be-

coming available for decision-making. The noninvasive transcutaneous bilirubin measurement is therefore more widely used. Though it is valuable as a screening tool, it is inaccurate for measuring high TSB levels likely to produce ABE and may not be affordable in many resource-limited settings [35, 36]. Transcutaneous bilirubin values above 12 mg/dl (205 μ mol/l) also need to be confirmed via TSB measurement before initiating ET [36]. A low-cost, minimally invasive point-of-care instrument for measuring the total plasma bilirubin concentration is currently being piloted and holds promise for LMIC [37].

Although the precise mechanisms of bilirubin-induced cytotoxicity have not been fully understood, clinical assessment of the risk of neurotoxicity is most commonly guided by prespecified TSB thresholds based on gestational and postnatal age. The limitation of sole reliance on TSB as a predictor of neurotoxicity or as the primary intervention/outcome measure has been highlighted in several reports [3, 38]. In particular, TSB has been shown to have a high sensitivity but a low specificity for identifying infants at risk of ABE. Since only unbound free bilirubin can cross the blood-brain barrier, the level of plasma-free bilirubin is considered to be a more reliable index of the risk of neurotoxicity and acute auditory impairment than TSB [39]. However, presently, it cannot be measured routinely in most clinical settings. Use of the bilirubin/albumin ratio as a surrogate for plasma-free bilirubin had been suggested because it contains 2 of the 3 components for deriving free bilirubin (i.e. TSB, albumin, and the binding constant K) [38–40]. Despite this, clinical studies, especially in preterm infants, have demonstrated that bilirubin/albumin does not improve the prediction of ABE or residual encephalopathy over TSB alone [40]. The same findings have also been demonstrated in near-term and full-term infants in LMIC [41].

Clinical risk factors promoting neurotoxicity at lower TSB levels include prematurity, hemolytic disease, G6PD deficiency, asphyxia, sepsis, acidosis, and hypoalbuminemia (<3 g/dl) [7, 42]. It is difficult to accurately determine most of these factors routinely in LMIC. Gestational age, most frequently used for risk factor determination, may be difficult to ascertain where women do not attend regular antenatal care and deliver at home. Birth weight or weight at admission ($\geq$ 2.0 kg) is a commonly used threshold for late-preterm and term infants. Sepsis is often based on clinical assessment rather than on laboratory confirmation, and it is more frequently overdiagnosed. While routine testing for blood group incompatibilities is widespread, passive immunization for rhesus disease is either not available or prohibitively expensive

in most LMIC. Although cost-effective tools for routine G6PD screening are presently available, universal screening is lacking even in LMIC with a significant G6PD deficiency [43]. Simple and inexpensive technologies for detecting morphological abnormalities of erythrocytes leading to hemolytic jaundice have also been reported and can be utilized in resource-poor settings [44]. These issues need to be addressed systematically to enhance the decision-making process for ET.

In LMIC, a high proportion of babies with SNH are born outside hospital settings, while the onset of jaundice more frequently occurs at home. It is common for mothers and caregivers to first attempt home treatment, failing which medical intervention is sought, usually when the child is irritable, is unable to feed, or becomes lethargic [45]. Many infants therefore present late with early signs of ABE or symptoms of intermediate/advanced ABE. The BIND scoring system is a useful clinical tool for identifying infants with ABE [46, 47]. A modified version of the protocol (BIND-M) has been validated for use in resource-poor countries [47]. It incorporates an additional component for abnormal eye movements to improve its clinical effectiveness in the identification of the various degrees of ABE, especially by primary care physicians. For in-born babies, predischARGE TSB screening along with assessment of clinical risk factors to identify infants at risk of SNH should be routinely considered [7, 42].

These 3 criteria may present in a variety of combinations and exert a considerable influence on judgement when assessing the risk of kernicterus. Decision-making will be compounded by the fact that there is presently no consistency in TSB thresholds for ET among infants with or without evidence of neurotoxicity, stratified by neurological status, for assessing the risk of kernicterus. For example, some reports suggest that TSB levels between 25 mg/dl (428 $\mu\text{mol/l}$) and 30 mg/dl (513 $\mu\text{mol/l}$) in infants without neurotoxicity risk factors are rarely associated with intermediate/advanced ABE [3, 31, 41, 48]. Other authors have argued that ET should be considered only when the TSB level is 15 mg/dl (257 $\mu\text{mol/l}$) or more above the AAP threshold, which translates to TSB >35 mg/dl (600 $\mu\text{mol/l}$) [49, 50]. In contrast, a threshold of TSB >20 mg/dl (342 $\mu\text{mol/l}$) is advocated for ET in infants with neurotoxicity risk factors, especially in countries with a high prevalence of G6PD deficiency [32, 51]. A practical approach that reflects these criteria and possibilities in a way that can facilitate decision-making by clinicians is therefore essential and worth exploring. Where ET facilities are limited, it may be necessary, in particular, to prioritize infants based on such individual risk assess-

ments. The decision to initiate ET must also take into consideration the timing of ET vis-à-vis the complex interaction between the magnitude and duration of exposure of the neuronal cells to unbound bilirubin [52].

The procedural steps and delays often encountered between the time the decision to initiate is made and the ET is conducted are outside the scope of this review. However, the roughly 6- to 24-hour delay in conducting the ET often offers an opportunity to establish whether the TSB level can be lowered with phototherapy. Intensive phototherapy (with irradiance maintained at levels $\geq 30 \mu\text{W/cm}^2/\text{nm}$) is critical to reducing the need for ET in all infants with SNH, with or without ABE and neurotoxicity risk factors, and to halting the potential damage that may occur while waiting for the exchange [7, 53]. However, in many LMIC the availability of effective phototherapy is frequently constrained by erratic power supply, inadequate skin exposure due to overcrowding (with multiple infants placed under a single device), suboptimal irradiance levels, and poor device maintenance. Practical steps for addressing these and related issues have been discussed in greater detail elsewhere [35]. The use of filtered sunlight phototherapy as a possible alternative in tropical regions is also currently being piloted in Nigeria [54].

Conclusions

ET is an effective treatment for preventing or limiting BIND in infants with SNH; however, it is not entirely risk free and needs to be initiated after careful evaluation of the risk of kernicterus. A tool that incorporates TSB thresholds, the presence or absence of neurotoxicity risk factors with clinical signs of ABE in the jaundiced infant should facilitate more accurate decision making. In settings where the requirement for ET is high but available resources are limited, this tool can also be used to prioritize infants based on the risk assessment for kernicterus. Provision of effective phototherapy along with interventions addressing the socio-cultural, biological, genetic, and systems-based factors that lead to excessive rates of ET in LMIC should also be addressed.

Acknowledgements

The authors received valuable comments from Michael Kaplan, Thomas Newman, Tinuade Ogunlesi, and Richard Wennberg on an earlier draft of this paper.

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