Seminars in Fetal & Neonatal Medicine 15 (2010) 136–140

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Enduring controversies in the management of hyperbilirubinemia in preterm neonates

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Keywords:
Bilirubin:albumin ratio
Exchange transfusion
Extremely low birthweight
Phototherapy
Prematurity
Neurodevelopmental outcome

SUMMARY

Although it is generally believed that preterm infants are at greater risk for the development of bilirubin-associated brain damage than term infants, quantification of the magnitude of this risk has proven elusive, as has a consensus among experts on the level of total serum bilirubin at which therapy should be initiated. Two large randomized studies have been performed that shed some light on the risk hyperbilirubinemia poses for preterm neonates and both studies are reviewed. Additional study is needed to further clarify the risk posed by hyperbilirubinemia in premature neonates and to frame guidelines for phototherapy and exchange transfusion that are more evidence-based.

1. Introduction

Despite the near universal finding of hyperbilirubinemia in preterm neonates, kernicterus has virtually disappeared in post-mortem series of premature infants,[1–3] and classic findings of chronic bilirubin encephalopathy including choreoathetosis and auditory neuropathy/dyssynchrony (an abnormal auditory brainstem response with normal otoacoustic emissions) have not emerged as prevalent clinical sequelae in neurodevelopmental follow-up of premature infants.[4] It is unclear if this is the result of overall improvements in care and/or the aggressive use of phototherapy.[5,6] Certainly, the widespread use of phototherapy in the neonatal intensive care unit has controlled bilirubin levels in almost all preterm infants, with the possible exception of the occasional infant with severe erythroblastosis fetalis, acute hemolysis, and/or marked bruising. As a result the number of exchange transfusions performed for hyperbilirubinemia has markedly declined.[5–7]

Yet kernicterus has occurred and continues to be reported in preterm infants, some at low total serum bilirubin (TSB) levels[8–11] and in the absence of acute neurologic signs.[8–12] Investigators also speculate that moderate hyperbilirubinemia may be associated with milder forms of central nervous system dysfunction and sequelae in this at-risk cohort.[13–15] Recent reports of kernicterus in preterm neonates,[10,11,12,16] including two infants at 31 and 34 weeks of gestation, neither of whom were acutely ill and whose TSB levels were 13.1 mg/dL (224 μmol/L) and 14.7 mg/dL (251 μmol/L) respectively, raise renewed concerns about low bilirubin kernicterus in the premature infant.[10] Moreover, recent studies of hyperbilirubinemic extremely low birth weight (<1000 g) (ELBW) premature neonates, heretofore an infrequently studied cohort regarding bilirubin-induced neurologic dysfunction, show an association between peak serum bilirubin and (i) death or neurodevelopmental impairment (odds ratio: 1.068; 95% confidence interval: 1.03–1.11); (ii) psychomotor development index <70 (1.057; 1.00–1.12); and (iii) hearing impairment (1.138; 1.00–1.30).[17] ELBW neonates may also evidence athetotic cerebral palsy and abnormal brainstem auditory evoked potentials, with features similar to term infants with kernicterus[11] and magnetic resonance imaging characteristic of chronic bilirubin encephalopathy.[11,16,18]

There is an enduring debate regarding how to calibrate the risk neonatal hyperbilirubinemia poses for neuronal injury in the premature neonate, how to disentangle bilirubin-induced neurologic dysfunction from other contributors to preterm CNS injury and when to intervene with phototherapy or exchange transfusion. Central to this discussion remains the inability to relate specific TSB levels in premature neonates to developmental outcome or pathological kernicterus.[19–24] As a result, the framing of guidelines for the use of phototherapy and exchange transfusion in preterm infants has been a capricious exercise at best and one for which no claim of an 'evidence base' can be made.[5] These guidelines are provided by different experts none of whom would likely make any claim for the greater validity of one approach versus another[5]; an example is shown in Table 1.[25] A recent report from the UK showing

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doi:10.1016/j.siny.2009.12.003

Table 1
Guidelines for the use of phototherapy and exchange transfusion in low birth weight infants based on birth weight.[a,b]

Birth weight (g)	Total bilirubin level [mg/dL (μmol/L)[c]]	
	Phototherapy[d]	Exchange transfusion[e]
≤1500	5–8 (85–140)	13–16 (220–275)
1500–1999	8–12 (140–200)	16–18 (275–300)
2000–2499	11–14 (190–240)	18–20 (300–340)

[a] From Maisels.[25]
[b] These guidelines reflect ranges used in neonatal intensive care units. They cannot take into account all possible situations. Lower bilirubin levels should be used for infants who are sick (e.g. presence of sepsis, acidosis, hypoalbuminemia) or who have hemolytic disease.
[c] Consider initiating therapy at these levels. Range allows discretion based on clinical conditions or other circumstances. Note that bilirubin levels refer to total serum bilirubin concentrations. Direct reacting or conjugated bilirubin levels should not be subtracted from the total.
[d] Used at these levels and in therapeutic doses, phototherapy should, with few exceptions, eliminate the need for exchange transfusions.
[e] Levels for exchange transfusion assume that bilirubin continues to rise or remains at these levels despite intensive phototherapy.

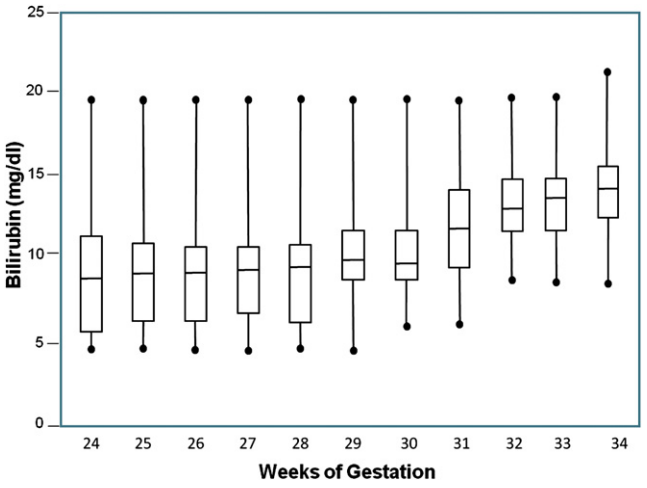

Fig. 1. Box-and-whisker plot of phototherapy treatment threshold bilirubin levels (mg/dL) as a function of gestational age at birth by each week of gestation between 24 and 34 weeks. The five boundary points on each plot include: the minimum, the maximum, the median, the first quartile, and the third quartile. Adapted from Table 1 in Rennie et al.[26] Reproduced from Arch Dis Child Fetal Neonatal Ed, Rennie JM, Sehgal A, De A, Kendall GS, Cole TJ, 94:F323–F327, 2009 with permission from BMJ Publishing Group LTD.

a wide range of treatment thresholds for phototherapy and exchange transfusion in premature neonates further underscores this uncertainty (Fig. 1).[26]

Few large randomized studies have been performed that shed light on the risk hyperbilirubinemia poses for preterm neonates. The National Institute of Child Health and Human Development (NICHD) multicenter collaborative phototherapy study (1974–1976) was undertaken primarily to determine if phototherapy was as effective as exchange transfusion for preventing brain damage from neonatal hyperbilirubinemia.[27] Infants were randomly assigned to a control group that received no phototherapy or to a group that received phototherapy. Phototherapy commenced 24 ± 12 h after birth in infants <2000 g; at TSB ≥10 mg/dL in the first 96 h of life in infants 2000–2499 g, and at TSB ≥13 mg/dL in those ≥2500 g.[28] The criteria for exchange transfusion are shown in Table 2 and were mandated at low levels of serum bilirubin [10 mg/dL (171 μmol/L) in high risk newborns with birth weights <1250 g].[27] The study clearly showed that phototherapy is effective in preventing hyperbilirubinemia and in markedly reducing the need for exchange transfusion.[28] Kernicterus was found in four out of 76 autopsied infants whose birth weights ranged from 760 to 1270 g.[29] Their peak TSB levels ranged from 6.5 to 14.2 mg/dL (111 to 243 μmol/L). The clinical course of the four affected infants was complicated by asphyxia and/or hyaline membrane disease, and all had some degree of IVH. Two had periventricular leukomalacia (PVL).[29] In this regard, some studies have suggested an association between hyperbilirubinemia and cystic PVL in low birth weight infants,[30–32] but others have not found this.[21] Despite the associations described (all from multiple significance testing with the resultant possibility of spurious conclusions), it is unlikely that hyperbilirubinemia is causally related to cystic PVL. PVL is primarily an ischemic lesion, most likely caused by hypoperfusion of the periventricular white matter. Bilirubin normally is not deposited in the periventricular region and is primarily toxic to neurons and not the glial elements that predominate in the periventricular white matter.

Surviving infants in the NICHD cooperative phototherapy trial (1974–1976) were followed and evaluated at 6 years of age with the Wechsler Verbal and Performance IQ test. No differences were found between the control and phototherapy groups in the incidence of definite and suspected cerebral palsy, clumsy or abnormal movements, hypotonia, or an IQ <70. There were no differences between the two groups in growth, speech, hearing loss, or evidence of hyperactivity.[33] Scheidt et al.[34] published a 6-year follow-up of the 224 control children with birth weights <2000 g. None of these infants received phototherapy, but bilirubin levels were maintained below specified levels by the use of exchange transfusion. No association was found between serum bilirubin levels and the incidence of cerebral palsy, nor was there any association between maximum bilirubin level and IQ. IQ was not associated with mean bilirubin level, time and duration of exposure to bilirubin, nor with measures of bilirubin–albumin binding.[34] These data suggest that therapeutic measures to keep TSB levels below these treatment thresholds afford protection against bilirubin-induced neurologic dysfunction; it must be remembered, however, that this 1974–1976 cohort was largely comprised of infants >1250 g and only a limited number of ELBW were included.

By contrast, the recent NICHD Neonatal Network study was exclusively focused on ELBW neonates and compared aggressive vs conservative phototherapy on a series of outcomes, shedding some new insight on hyperbilirubinemia risk and treatment options in the tiniest preterm neonates but also raising important new questions.[35] Table 3 outlines the aggressive and conservative phototherapy treatment guidelines and exchange transfusion thresholds used in this study. Their results suggest that aggressive phototherapy may be preferred for infants of 751–1000 g birth weight because of significant neurodevelopmental benefit including a reduction in athetosis and severe hearing loss.[35] Not surprisingly the mean TSB levels were lower in the aggressive group (4.7 ± 1.1 mg/dL) than in the conservative group (6.2 ± 1.5 mg/dL) and although these differences were statistically significant ($P < 0.001$) one would not have predicted that this numeric difference would be associated with a difference in

Table 2
Serum bilirubin level (mg/dL) as criterion for exchange transfusion in 1974–1976 NICHD phototherapy trial.[a]

	Birth weight (g)				
	<1250	1250–1499	1500–1999	2000–2499	≥2500
Standard risk	13	15	17	18	20
High risk	10	13	15	17	18

NICHD, National Institute of Child Health and Development.
[a] From Bryla.[27] Reproduced with permission from Pediatrics Volume 75 (suppl), pages 387–441, Copyright © 1985 by the AAP.

Table 3
Guidelines for initiating phototherapy and exchange transfusions (NICHD Neonatal Research Network Trial).[a]

Birth weight	Aggressive management		Conservative management	
	Phototherapy begins	Exchange transfusion	Phototherapy begins	Exchange transfusion
501–750 g	ASAP after enrollment	≥13.0 mg/dL	≥8.0 mg/dL	≥13.0 mg/dL
751–1000 g	ASAP after enrollment	≥15.0 mg/dL	≥10.0 mg/dL	≥15.0 mg/dL

NICHD, National Institute of Child Health and Development; ASAP, as soon as possible.
Enrollment is expected within the period 12–36 h after birth, preferably between 12 and 24 h.
[a] From Morris et al.[35]

Table 4
Guidelines for exchange transfusion in low birth weight infants based on total bilirubin (mg/dL) and bilirubin:albumin ratio (mg/g).[a,b]

	Birth weight (g)			
	<1250	1250–1499	1500–1999	2000–2499
Standard risk	13	15	17	18
Or bilirubin:albumin ratio	5.2	6.0	6.8	7.2
High risk[c]	10	13	15	17
Or bilirubin:albumin ratio	4.0	5.2	6.0	6.8

[a] From Ahlfors.[44] Reproduced with permission from Pediatrics Volume 75 (suppl), pages 387–441, Copyright © 1985 by the AAP
[b] Exchange transfusion at whichever comes first.
[c] Risk factors: Apgar <3 at 5 min; $PaO_2 \leq 40$ mmHg at >2 h, pH ≤7.15 at ≥1 h; birth weight <1000 g, hemolysis; clinical or central nervous system deterioration; total protein ≤4 g/dL or albumin ≤2.5 g/dL.

outcome. Of interest, mean TSB levels in the surviving impaired and unimpaired infants were identical (5.4 mg/dL) although the mean peak TSB was marginally higher in the impaired cohort (8.6 ± vs 8.3 ± 2.3 mg/dL, $P = 0.02$).

Their findings are also notable for a 5% increase in mortality in infants with birth weights of 501–750 g treated in the aggressive phototherapy arm.[35] Although this difference did not achieve statistical significance, post-hoc Bayesian analysis estimated an 89% probability that aggressive phototherapy increased the rate of death in this subgroup; offsetting any potential neurologic benefit of aggressive treatment in these smallest of infants.[35] Although it is unclear why phototherapy might increase mortality in this birth weight cohort, speculation focuses on greater light penetration deep into subcutaneous tissues via thin gelatinous skin and possible oxidative injury to cell membranes.[36] Few neonates required exchange transfusion, confirming again the broad efficacy of phototherapy in preterm neonates.

What should neonatologists do with this information? In many units, phototherapy is initiated in ELBW neonates when their TSB reaches 5 mg/dL (86 μmol/L). As the TSB at the start of phototherapy in the aggressive group was 4.8 mg/dL (82 μmol/L), instituting phototherapy at a TSB of 5 mg/dL (86 μmol/L) will likely have a similar effect on TSB levels, as does prophylactic phototherapy initiated in every infant soon after birth. When one combines these data with the previous observations from the NICHD Neonatal Research Network[17] it appears that modest elevations of TSB in these tiny babies are potentially harmful and, when used in a manner similar to that employed in this study, phototherapy could help to reduce long-term neurodevelopmental impairment.

The 'target irradiance level' in this study was 15–40 $\mu W/cm^2/nm$ but we are not told what irradiance was actually achieved. Are levels of 30–40 $\mu W/cm^2/nm$ necessary or even desirable in these tiny babies? Even when used in the manner of the 'aggressive' group, this is still, primarily, prophylactic phototherapy employed with the goal of preventing further elevation of the TSB. It is quite possible, perhaps likely, that significantly lower irradiance levels might be equally effective and, in view of the observed increase in mortality, it seems prudent, at least in infants <750 g, to initiate phototherapy at lower irradiance levels. The irradiance can then be increased, if necessary, or more surface area of the infant exposed to phototherapy if the TSB continues to rise.

Additional study is needed to further clarify the risk posed by hyperbilirubinemia in premature neonates and to frame guidelines for phototherapy and exchange transfusion that are more evidence-based.[5] Of continued discussion in this regard is the potential utility of unbound or 'free' bilirubin (B_f) measurement in predicting the risk of bilirubin-induced brain injury.[37,38]

Whereas most bilirubin in the circulation is bound to albumin, a relatively small fraction remains unbound. The concentration of B_f is believed to dictate the biologic effects of bilirubin in jaundiced newborns, including its neurotoxicity. Elevations of B_f have been associated with kernicterus in sick, pre-term newborns.[39,40] In addition, elevated B_f concentrations are more closely associated than are TSB levels with transient abnormalities in the audiometric brainstem response in both term[41] and pre-term[42] infants. Although in one study a B_f level of >1.0 μg/dL discriminated toxic from asymptomatic LBW preterm neonates with high sensitivity and specificity,[40] there remains debate on what constitutes the neurotoxic B_f threshold,[43] i.e. the threshold at which B_f produces changes in cellular function culminating in permanent cell injury and cell death. In addition, clinical laboratory measurement of B_f is not generally available.

The ratio of bilirubin (mg/dL) to albumin (g/dL) does correlate with measured B_f in newborns[44] and has been used as an approximate surrogate for the measurement of B_f.[44] It must be recognized, however, that albumin binding capacity varies significantly between newborns,[44,45] is impaired in sick infants[46–48] and increases with increasing gestational age[46,49] and postnatal age.[48,49] A recent study of VLBW infants from one NICHD Neonatal Network institution confirmed that bilirubin-binding capacity was lower and B_f higher in unstable versus stable neonates but did not report on longer term neurodevelopmental outcomes.[50] Follow-up of 224 infants born in 1974–1976 phototherapy trial with birth weights <2000 g evaluated at age 6 years showed no association between measures of bilirubin–albumin binding and IQ scores.[34] It will be of keen interest to see how measures of B_f correlate with short and long term outcomes in the NICHD Neonatal Network ELBW cohort and how the bilirubin:albumin ratio correlates with neurodevelopmental outcome in the prospective Bilirubin Albumin Ratio Trial (BARTrial) in The Netherlands.[51]

Crucially important in the measurement of B_f is the bilirubin-albumin binding constant k, a term whose numeric value may actually vary considerably depending on conditions including, among other factors: sample dilution, albumin concentration, and the presence of competing compounds.[37,38,43] Moreover, the risk of bilirubin encephalopathy is likely not simply a function of the B_f concentration alone or TSB level but a combination of both, i.e. the total amount of bilirubin available (the miscible pool of bilirubin) as well as the tendency of bilirubin to enter the tissue (the B_f concentration).[44] An additional factor is the susceptibility of the cells of the central nervous system to damage by bilirubin.[52,53] The bilirubin:albumin ratio can therefore be used together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion (Table 4).[44] Meritorious lines of clinical and translational research include clarifying and defining clinically germane B_f concentrations, bilirubin:albumin ratios, exposure conditions, and exposure durations; as well as improving, standardizing, and validating B_f measurements.

Practice points

- Hyperbilirubinemia in preterm infants is more prevalent and its course more protracted than in term neonates.
- Guidelines for the use of phototherapy and exchange transfusion in preterm infants are empirical for which little claim of an 'evidence base' can be made.
- Phototherapy if used appropriately is capable of controlling bilirubin levels in almost all premature infants with the exception of the occasional infant with severe hemolytic disease or marked bruising.
- In infants <750 g, it seems prudent to initiate phototherapy at lower irradiance levels; irradiance can be increased, if necessary, or more surface area of the infant exposed to phototherapy if the TSB continues to rise.

Research directions

- Additional clinical study is needed to further clarify the risk posed by hyperbilirubinemia in premature neonates and frame guidelines for phototherapy and exchange transfusion that are more evidence-based.
- Clarifying and defining clinically germane B_f concentrations, bilirubin to albumin ratios, exposure conditions, and exposure durations; as well as improving, standardizing, and validating Bf measurements are meritorious lines of clinical and translational research.

Conflict of interest statement

None declared.

Funding sources

None.

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