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SPECIAL FEATURE

An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation

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We provide an approach to the use of phototherapy and exchange transfusion in the management of hyperbilirubinemia in preterm infants of <35 weeks of gestation. Because there are limited data for evidence-based recommendations, these recommendations are, of necessity, consensus-based. The recommended treatment levels are based on operational thresholds for bilirubin levels and represent those levels beyond which it is assumed that treatment will likely do more good than harm. Long-term follow-up of a large population will be needed to evaluate whether or not these recommendations should be modified.

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Introduction

The American Academy of Pediatrics (AAP) has published a guideline for the management of hyperbilirubinemia in the newborn infant ⩾35 weeks gestation,[1] and similar consensus-based guidelines have been published recently in Canada, Israel, Norway, South Africa, the Netherlands, and the United Kingdom (UK).[2–7] The AAP guideline[1] has been widely adopted in the United States and elsewhere but there is no similar guideline in the United States for the treatment of infants <35 weeks gestation. In lieu of such direction, neonatal intensive care units (NICUs) have established their own criteria for the use of phototherapy and exchange transfusion in these infants, most often based on birth weight or gestational age.

It is generally believed that infants <35 weeks gestation are at greater risk for the development of bilirubin-associated brain damage than term infants, although a paucity of data has made quantification of the magnitude of this risk difficult,[8] and the reported range of bilirubin thresholds used to initiate treatment at different birth weights and gestations is remarkably wide.[5,9,10] The recent, consensus-based national guidelines published in the UK, South Africa and Norway, include recommendations for the management of preterm infants.[5,11] Recognizing the need, the AAP Committee on Fetus and Newborn in 2007 asked a group of experts to develop a guideline for the management of jaundiced infants <35 weeks of gestation and a recent survey of neonatologist members of the Section on Perinatal Pediatrics of the AAP,[12] confirmed this need. But the current AAP policy requires that guidelines be evidence-based and, as the evidence for such a guideline is limited, it was not possible to comply with this requirement. Thus the recommendations that follow are, of necessity, consensus-based.

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Hyperbilirubinemia and the preterm infant

Chronic bilirubin encephalopathy, including kernicterus at postmortem, is currently a rare event in premature neonates but has not disappeared completely and, whether modest elevations in total serum bilirubin (TSB) contribute to subtle forms of central nervous system dysfunction in premature infants, remains controversial.[13–15] In past decades, autopsy proven kernicterus was reported in sick, very low birth weight infants who were exposed to low TSB levels (the so-called 'low bilirubin kernicterus')[16,17] and recent case series document that this remains a clinical risk.[18–21] In a recent study from the Netherlands,[18] 5 sick, preterm infants (25 to 29 weeks gestation) with peak TSB levels ranging from 8.7 to 11.9 mg dl^{-1} (148 to 204 μmol l^{-1}) developed the classical MRI findings of kernicterus. Serum albumin levels in these infants were strikingly low, ranging from 1.4 to 2.1 g dl^{-1}. Two extremely low birth weight (ELBW) neonates with complicated neonatal courses and comorbid CNS injury, had peak TSB levels of 7.5 mg dl^{-1} (128 μmol l^{-1}) and 9.9 mg dl^{-1} (168 μmol l^{-1}) and developed clinical sequelae and MRI findings consistent with chronic bilirubin encephalopathy.[19] Choreoathetosis, and the classical MRI

findings of kernicterus at follow-up, were documented in two preterm infants of 31 and 34 weeks gestation.[20] Neither of these infants was acutely ill in the newborn period and their peak TSB levels were 13.1 mg dl^{-1} (224 μmol l^{-1}) and 14.7 mg dl^{-1} (251 μmol l^{-1}) respectively.

Recent studies of large populations of ELBW infants suggest an association between neurodevelopmental impairment (NDI) and modest elevations in TSB.[21,22] In a retrospective analysis of ELBW infants born between 1994 and 1997, peak TSB levels, generally in the 5 to 12 mg dl^{-1} (85 to 204 μmol l^{-1}) range were directly correlated with the risk of (i) death or NDI (odds ratio (OR): 1.068; 95% confidence interval (CI): 1.03 to 1.11), (ii) hearing impairment (OR: 1.138; CI 1.00 to 1.30) and (iii) a psychomotor development index <70 (OR: 1.057; CI 1.00 to 1.12)[22] although the effect size of each association was very small and barely significant. Nevertheless, other studies suggest that moderate hyperbilirubinemia in these infants poses no risk of neurotoxicity.[23,24] These conflicting data prompted the Neonatal Research Network to perform a prospective randomized controlled trial in ELBW infants of aggressive phototherapy (used prophylactically and started at 23 ± 9 h after birth) vs conservative phototherapy (started when the TSB level was ⩾8 mg/dl (137 μmol l^{-1}) for infants 500 to 750 g, or 10 mg dl^{-1} (171 μmol $^{-1}$) for infants 751 to 1000 g).[25] There was no difference in the primary outcome of death or NDI at 18 to 20 months of corrected age but, among survivors, when compared with conservative phototherapy, aggressive phototherapy produced a significant decrease in NDI, hearing loss, profound impairment and athetosis.[25] The mean TSB level in infants with hearing loss was 6.5 ± 1.7 mg dl^{-1} vs 5.4 ± 1.5 mg dl^{-1} (111 ± 29.1 vs 94 ± 25.7 μmol l^{-1}) in those with no hearing loss ($P<0.001$). Peak TSB levels in infants with NDI were 8.6 ± 2.3 vs 8.3 ± 2.3 (147 ± 39.3 vs 142 ± 39.3 μmol l^{-1}, $P = 0.02$) in unimpaired survivors. Whether these small differences in TSB levels, the use of aggressive phototherapy, or other factors were responsible for the outcomes is difficult to say.

An unexpected finding in this study was an increase in mortality in infants with birth weights 501 to 750 g who received aggressive phototherapy (discussed in more detail below), and this must be balanced against the apparent benefit of this therapy.

Unbound or free bilirubin

Bilirubin–albumin binding is a function of the concentrations of bilirubin and albumin, and the binding affinity for bilirubin (strength of bilirubin binding to albumin). The fraction of unbound (UB) bilirubin (nonalbumin-bound or free bilirubin) increases significantly as the bilirubin approaches the binding capacity of albumin or when the apparent albumin affinity decreases.[26] The binding affinity may be decreased in the presence of sepsis, acidosis, hypoxia, free fatty acids and various albumin-binding drugs.[26] Because the peak TSB level, by itself, is a rather poor predictor of the likelihood of NDI or kernicterus, it has been suggested that measurement of UB or free bilirubin might be a better index of neurodevelopmental risk.[27,28]

Most bilirubin in the circulation is albumin bound, but a relatively small fraction remains UB. The concentration of UB is believed to dictate the biological effects of bilirubin in jaundiced newborns, including its neurotoxicity, and elevations of UB have been associated with kernicterus or NDI in sick, preterm infants.[29–31] Routine, clinical laboratory measurement of UB is not commercially available in the United States, so that even if there was agreement regarding UB levels that require intervention, such recommendations, currently, could not be implemented. Some experts have recommended using the ratio of bilirubin (mg dl^{-1}) to albumin (g dl^{-1}) as an approximate surrogate for the measurement of UB.[1,32]

It is also important to understand that the risk of bilirubin encephalopathy may not be a function of the UB concentration alone or the TSB level, but a combination of both, that is, the total amount of bilirubin available (the miscible pool of bilirubin), as well as the tendency for UB to enter the tissue.[32] The susceptibility of the cells of the central nervous system is also an important factor in determining the likelihood of damage by bilirubin.[33,34] Currently, no recommendations can be made with regard to the use of UB in the management of infants <35 weeks gestation. As noted in the table legend, it is probably appropriate to treat those with low albumin levels at lower TSB levels.

Phototherapy

The remarkable decrease in the incidence of kernicterus at autopsy in infants who have died in the NICU in the last 2 to 3 decades is likely the result of overall improvements in the care of preterm neonates and the liberal use of phototherapy. Certainly, effective phototherapy has dramatically decreased the need for exchange transfusion in preterm infants, so that this procedure has become increasingly rare in the NICU.[23,25,35,36] In the Neonatal Research Network Study,[25] only 5 of 1974 (0.25%) ELBW infants received an exchange transfusion.

Although, as noted above, survivors in the Neonatal Research Network study who received aggressive phototherapy were less likely to have NDI, there was a 5% increase in mortality in infants with birth weights 501 to 750 g who received aggressive phototherapy[25] (relative risk 1.05 (CI 0.90 to 1.22)). The difference was not statistically significant but a *post hoc*, Bayesian analysis, estimated an 89% probability that aggressive phototherapy increased the rate of deaths in this subgroup. In an earlier NICHD study,[17,37] infants with birth weights ⩽1000 g, who received phototherapy, had a 19% increase in mortality compared with control infants (no phototherapy) ($P = 0.14$). The reasons for these findings are not clear, but these tiny, immature infants have gelatinous, thin skin, through which light will penetrate readily reaching more deeply

into the subcutaneous tissue. There is some evidence that phototherapy can produce oxidative injury to cell membranes and DNA,[38–41] and such injury could have a negative effect on these immature infants. In the Neonatal Research Network study, the average irradiance level was reported as 22 to 23 $\mu W\,cm^{-2}\,nm^{-1}$ and the 'target irradiance level' was 15 to 40 $\mu W\,cm^{-2}\,nm^{-1}$.[25]

Effective use of phototherapy

Phototherapy in most infants ⩽35 weeks of gestation is generally used in a prophylactic mode—the goal being to prevent further elevation of the TSB. The most effective irradiance is delivered by a light source (such as special blue fluorescent lamps or LED systems) that will deliver irradiance predominately in the 430 to 490 nm band.[42,43] Detailed information on phototherapy use can be found in a recent technical report.[43] If, in spite of phototherapy, the TSB continues to rise, either the irradiance can be increased by bringing the phototherapy lamp closer to the baby (except when halogen or tungsten lights are used) or by increasing the body surface area of the infant exposed to phototherapy (by placing a light source beneath the infant and reflecting material around the incubator or radiant warmer bed). Because there is significant variation in the irradiance measurements provided by commercial radiometers,[39,43] it is difficult to recommend a specific irradiance level. Nevertheless, when possible, clinicians should use the radiometer recommended by the manufacturer of the phototherapy system and provide sufficient irradiance to prevent an increase in the TSB.

Because of the reported increase in mortality in infants with birth weights 501 to 750 g,[25] it seems prudent, at least in infants with birth weights <750 g, to initiate phototherapy at lower irradiance levels and only to increase these levels, or to increase the surface area of the infant exposed to phototherapy, if the TSB continues to rise (see Table 1).

Exchange transfusion

Most reports suggest that sick, preterm infants, are more likely than term infants to experience a wide range of serious complications as well as mortality from exchange transfusion.[44–46] The complications include cardio-respiratory arrest, arrhythmias, thrombosis, thrombocytopenia, hypothermia, necrotizing enterocolitis and infection, among others.[45,46] Of the total of 25 sick infants who received exchange transfusions at the Children's Hospital and University of Washington Medical Center in Seattle between 1980 to 1995, 3 (12%) had serious complications and 2 (8%) died, whereas in 81 healthy infants there were no deaths and there was one case of necrotizing enterocolitis.[45] Between 1992 and 2002, at two perinatal centers in Cleveland, OH, 15 infants ⩽32 weeks gestation, received exchange transfusions and there was one death (7%).[46] This infant was a 731-g, 25-week gestation infant with hydrops fetalis, respiratory distress syndrome and pulmonary hemorrhage before the exchange. On the other hand, less serious complications such as thrombocytopenia (38 to 67%) and hypocalcemia (13 to 38%) in very low birth weight infants are quite common.[35,46] In a recent study, there were no significant

Table 1 Suggested use of phototherapy and exchange transfusion in preterm infants <35 weeks gestational age

	Phototherapy	*Exchange transfusion*
Gestational age (week)	*Initiate phototherapy total serum bilirubin (mg dl^{-1})*	*Total serum bilirubin (mg dl^{-1})*
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

This table reflects the authors' recommendations for operational or therapeutic TSB thresholds—bilirubin levels at, or above which, treatment is likely to do more good than harm.[58] These TSB levels are not based on good evidence and are lower than those suggested in the recent UK[11] and Norwegian[5] guidelines.

The wider ranges and overlapping of values in the exchange transfusion column reflect the degree of uncertainty in making these recommendations.

Use the lower range of the listed TSB levels for infants at greater risk for bilirubin toxicity, for example, (1) lower gestational age, (2) serum albumin levels <2.5 g dl^{-1}, (3) rapidly rising TSB levels, suggesting hemolytic disease and (4) those who are clinically unstable.[31] When a decision is being made about the initiation of phototherapy or exchange transfusion, infants are considered to be clinically unstable if they have one or more of the following conditions: (a) blood pH <7.15; (b) blood culture positive sepsis in the prior 24 h; (c) apnea and bradycardia requiring cardio-respiratory resuscitation (bagging and or intubation) during the previous 24 h; (d) hypotension requiring pressor treatment during the previous 24 h; and (e) mechanical ventilation at the time of blood sampling.[31]

Recommendations for exchange transfusion apply to infants who are receiving intensive phototherapy to the maximal surface area but whose TSB levels continue to increase to the levels listed.

For all infants, an exchange transfusion is recommended if the infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, high-pitched cry) although it is recognized that these signs rarely occur in VLBW infants.

Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin from the total.

For infants ⩽26 weeks gestation, it is an option to use phototherapy prophylactically starting soon after birth.

Use postmenstrual age for phototherapy for example, when a 29 0/7 week infant is 7 days old, use the TSB level for 30 0/7 weeks.

Discontinue phototherapy when TSB is 1–2 mg dl^{-1} below the initiation level for the infant's postmenstrual age.

Discontinue TSB measurements when TSB is declining and phototherapy is no longer required.

Measure the serum albumin level in all infants.

Measure irradiance at regular intervals with an appropriate spectroradiometer.

The increased mortality observed in infants ⩽1000 g who are receiving phototherapy[17,25,37] suggests that it is prudent to use less intensive levels of irradiance in these infants. In such infants, phototherapy is almost always prophylactic—it is used to prevent a further increase in the TSB and intensive phototherapy with high irradiance levels usually is not needed. In infants ⩽1000 g, it is reasonable to start phototherapy at lower irradiance levels. If the TSB continues to rise, additional phototherapy should be provided by increasing the surface area exposed (phototherapy above and below the infant, reflecting material around the incubator). If the TSB, nevertheless, continues to rise, the irradiance should be increased by switching to a higher intensity setting on the device or by bringing the overhead light closer to the infant. Fluorescent and LED light sources can be brought closer to the infant, but this cannot be done with halogen or tungsten lamps because of the danger of a burn.

differences in the frequency of exchange transfusion-related complications in neonates <1500 g birth weight compared with those >1500 g.[35] The sample sizes for infants <1500 g birth weight in all of these studies were small.

Effective phototherapy and the prevention of Rh hemolytic disease with Rh (D) immunoglobulin[47] have produced a dramatic decrease in the number of exchange transfusions performed in the NICU and, in particular, in infants with birth weights <1500 g.[23,25,36] Before the introduction of phototherapy, as many as one in three infants with birth weights <1500 g received an exchange transfusion during their stay in the NICU[48] compared with between 0 to 0.25% of these infants admitted to NICU's in the last three decades.[23,25,36]

Elevated direct-reacting or conjugated bilirubin levels

There are no good data to guide the clinician in dealing with the occasional infant who has a significant elevation of direct-reacting or conjugated bilirubin. Kernicterus has been described in term infants with TSB levels >20 mg dl^{-1} (314 μmol l^{-1}) but in whom, because of significant elevations in direct bilirubin levels, the indirect bilirubin levels were well below 20 mg dl^{-1}.[49,50] There is some evidence that elevated direct bilirubin levels can decrease the infant's albumin-binding capacity[51] and it has been suggested, but not confirmed, that infants with the bronze baby syndrome might be at an increased risk of developing bilirubin encephalopathy.[51,52] As a general rule, when considering the use of phototherapy or exchange transfusion, the direct-reacting (or conjugated) bilirubin level should not be subtracted from the total. Infants with conjugated bilirubin levels >50% of the TSB require individual expert evaluation.

Hemolytic disease

Infants with hemolytic disease are generally considered to be at a greater risk for the development of bilirubin encephalopathy than are nonhemolyzing infants with similar bilirubin levels.[1] Thus, exchange transfusion is recommended at lower levels for infants who have hemolytic disease (see Table 1). Although the use of intravenous gamma-globulin has been shown, in several randomized controlled trials, to reduce the need for exchange transfusions in both Rh and ABO hemolytic disease,[53–55] a recent study of intravenous gamma-globulin administration to infants with severe Rh hemolytic disease did not confirm these findings.[56] It is possible that the severity of hemolysis has a role in determining the response to intravenous gamma-globulin.[57]

New recommendations

The table provides an approach to the use of phototherapy and exchange transfusion based on gestation. As there are limited data for evidence-based recommendations, this table is, of necessity, consensus-based. The recommended treatment levels are based on operational thresholds or therapeutic normal levels (a level beyond which specific therapy will likely do more good than harm).[58] Other guidelines have suggested lower intervention levels in the first 72–96 h,[5,11] but we have opted to keep the table as simple as possible.

Based on a recent survey,[12] the levels are close to those currently in use in many NICUs in the United States. They do represent a fairly aggressive approach to the use of phototherapy, perhaps influenced by the results in the recent NICHD Neonatal Network Study.[25] Compared with both the NICE[11] and Norwegian[5] guidelines, we recommend phototherapy at lower bilirubin levels although our thresholds are similar to the Dutch recommendations.[2] A long-term follow-up of a large population of such infants might identify which of these suggested approaches is preferred.

Conflict of interest

The authors declare no conflict of interest.

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