

Hyperbilirubinemia and Bilirubin Toxicity in the Late Preterm Infant

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Hyperbilirubinemia is the most common clinical condition requiring evaluation and treatment in the newborn [1] and the most common cause for hospital readmission during the first week of postnatal life [2–5]. Although generally a benign transitional phenomenon of no overt clinical significance, in a select few, the total serum bilirubin (TSB) may rise to hazardous levels that pose a direct threat of brain damage. Acute bilirubin encephalopathy, an uncommon disorder [4], may ensue, frequently evolving into kernicterus, a devastating, chronic and disabling condition characterized by the clinical tetrad of:

- Choreoathetoid cerebral palsy
- High-frequency central neural hearing loss
- Palsy of vertical gaze
- Dental enamel hypoplasia, the result of bilirubin-induced cell toxicity [6]

Originally described in newborns with Rh hemolytic disease, kernicterus more recently has been reported in apparently healthy term and late preterm gestation breast-fed infants without documented hemolysis [4,7,8]. Late preterm gestation (34^{0/7} to 36^{6/7} weeks [9,10]) is one of the most prevalent identified risk factors for the development of severe hyperbilirubinemia (TSB at least 20 mg/dL [342 μmol/L]) [11] and kernicterus [4,12], and is the focus of this article.

Late preterm infants frequently are cared for in normal newborn nurseries, wherein caretakers may be lured into thinking they are as mature as term

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(at least 37^{0/7} weeks) neonates. Indeed, late preterm infants often can be managed in many respects like their more mature term counterparts for:

- They are typically large enough to maintain their temperature in an open crib
- They often have an established suck–swallow reflex and can take their feedings by mouth (although not necessarily breast-feed vigorously)
- They generally have a strong respiratory drive and are thus not prone to periodic breathing or apnea of prematurity (although the author’s hospital monitors all neonates born between 34^{0/7} and 34^{6/7} weeks gestation on a cardiorespiratory monitor for the first 24 hours of postnatal life to ensure they are apnea-free) [13].

In contrast, the late preterm infant remains relatively immature compared with term newborns in their capacity to handle unconjugated bilirubin, placing them at risk for marked neonatal jaundice [12]. Indeed, as in preterm infants [14], neonatal hyperbilirubinemia in late preterm newborns is more prevalent, more pronounced, and more protracted in nature than it is in their term counterparts. Underscoring the singular importance of late preterm gestational age are:

- The approximately eightfold increased risk of developing a TSB of greater than 20 mg/dL (342 μ mol/L) in infants born at 36 weeks gestational age (5.2%) as compared with those born at 41 or 42 or more weeks gestation (0.7% and 0.6% respectively) [11]
- The over-representation of late preterm infants in the US Pilot Kernicterus Registry [4,12], a database of voluntarily reported cases of kernicterus

Pathobiology

Late preterm and full-term infants become jaundiced by similar mechanisms. There is:

- An increased bilirubin load on the hepatocyte as a result of decreased erythrocyte survival, increased erythrocyte volume, and increased enterohepatic circulation of bilirubin
- Decreased hepatic uptake of bilirubin from plasma
- Defective bilirubin conjugation

The imbalance between bilirubin production and elimination in neonates is illustrated by the unitless bilirubin production–conjugation index described by Kaplan and colleagues [15]. This index is given by the numeric ratio of the blood carboxyhemoglobin corrected for ambient carbon monoxide (COHbc) and the serum total conjugated bilirubin [15]. The former is a measure of heme catabolism and therefore bilirubin production (the rate-limiting step in bilirubin production is the conversion of heme to

biliverdin by heme-oxygenase, an enzymatic reaction that produces an equimolar amount of carbon monoxide), whereas the latter is an indirect measure of hepatic bilirubin conjugation capacity [15]. Late preterm infants evidence a similar degree of red blood cell (RBC) turnover and heme degradation as indexed by comparable COHbc levels as their term counterparts. They differ from their term counterparts, however, in how effectively they handle the resultant bilirubin load, demonstrating a significantly lower conjugated bilirubin fraction and resultant increased bilirubin production–conjugation index (Table 1 [16]). Moreover, late preterm neonates demonstrate a slower postnatal maturation of hepatic bilirubin uptake and bilirubin conjugation as compared with their term counterparts. This exaggerated hepatic immaturity [16,17] contributes to the greater prevalence, severity, and duration of neonatal jaundice in late preterm infants.

Kernicterus

Compared with term neonates, infants born prematurely are considered to be at an increased risk for developing kernicterus [18,19]. It may be that late preterm neonates are also at a higher risk compared with their term counterparts. Indeed, late preterm infants are represented disproportionately in the US Pilot Kernicterus Registry [4,12]. Moreover, the registry demonstrates that late preterm neonates evidence signs of bilirubin neurotoxicity at an earlier postnatal age than term newborns, indirectly suggesting a greater vulnerability to bilirubin-induced brain injury [12]. Clinical hyperbilirubinemia management guidelines for preterm [20,21] and late preterm [22] infants therefore recommend treatment at lower total serum bilirubin thresholds than term newborns, a distinction that is an important component of the most current American Academy of Pediatrics (AAP) practice parameter on neonatal jaundice [22].

Table 1

Comparison of values for the production-conjugation index for neonates ≤ 37 weeks gestation and those > 37 weeks

Variable	≤ 37 weeks gestation	> 37 weeks gestation	<i>p</i> value
Production-conjugation index (unitless)	2.31 (2.12–3.08)	1.05 (0.53–1.81)	0.003
COHbc (% tHb)	0.88 (0.21)	0.82 (0.20)	0.46
TCB (% TSB)	0.39 (0.31–0.42)	0.74 (0.44–1.69)	0.009
STB ($\mu\text{mol/L}$)	160 (35)	141 (72)	0.48

Values are mean (SD) or median (interquartile range), as appropriate.

Abbreviations: COHbc, carboxyhemoglobin corrected for inspired carbon monoxide; TCB, total conjugated bilirubin; tHb, total hemoglobin; TSB, Total serum bilirubin.

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The mechanisms that potentially could account for an increased susceptibility to bilirubin-induced central nervous system (CNS) injury in late preterm newborns have not been defined. Theoretically, however, they include a diminished serum bilirubin binding capacity, an enhanced permeability of the blood–brain or blood–CSF barriers to unconjugated bilirubin influx, or an immaturity of neuronal protective mechanisms, among others. In this regard, the serum albumin level is low in premature neonates and increases significantly with increasing gestational age [23], but increases only minimally between 34 and 35 weeks gestation (3.02 plus or minus 0.21 g/dL) and term (3.57 plus or minus 0.37 g/dL) [23]. In addition, there is little to suggest the existence of developmental differences in serum’s actual bilirubin binding capacity between the late preterm and term neonate [24]. With respect to the anatomy and function of the blood–brain and blood–CSF barriers, there has been considerable controversy regarding their relative maturity in neonates [25]. Although gestational age may be an important variable in modulating blood–brain and blood–CSF permeability to selected substrates in experimental animals (eg, ontogenic decreases in ovine blood–brain barrier permeability [26]), clinical and morphologic data on people are less convincing, at least from the gestational age of viability onward [25,27]. Similarly, virtually nothing is known about potential developmental differences in human neuronal vulnerability to unconjugated bilirubin (UCB) *in vivo*. It has, however, been shown repeatedly that UCB-induced toxicity *in vitro* in murine-derived CNS primary cell cultures is modulated by culture age (ie, younger presumably less mature neurons and astrocytes are more susceptible to bilirubin-induced apoptosis and necrosis than their older presumably more mature counterparts) [28–31]. Whether these findings are reflective of a clinically relevant *in vivo* phenomenon is unclear, but they collectively suggest that CNS cellular maturity may be a factor in modulating UCB-induced injury. Purportedly these *in vitro* cell culture models reflect ontogenic changes in brain development (ie, differentiation) [32], as opposed to postnatal maturational effects. The importance of postnatal maturation on reducing susceptibility to bilirubin-induced CNS injury is documented in experimental animals [25,33,34] and presumably operational in human newborns also.

Breast-feeding and late preterm gestation neonates

Several clinical risk factors for marked hyperbilirubinemia and kernicterus have been identified in late preterm neonates and are shown in **Box 1**. Of these, breast milk feeding has been identified the most consistently (almost uniformly) and therefore appears to be of paramount importance. Indeed, late preterm infants who are breast-fed may be at greatest risk for severe neonatal hyperbilirubinemia and merit close postbirth hospitalization discharge follow-up and lactation support. Late preterm neonates, because of their immaturity, often demonstrate less effective sucking and swallowing

Box 1. Clinically associated risk factors for marked hyperbilirubinemia and/or kernicterus in late preterm neonates

Breast milk feeding

- J Perinatol 2004;24:650–62 [4]
- Semin Perinatol 2006;30:89–97 [12]

Large for gestational age status

- Semin Perinatol 2006;30:89–97 [12]

Male sex

- J Perinatol 2004; 24:650–62 [4]
- Semin Perinatol 2006;30:89–97 [12]

Glucose-6-phosphate dehydrogenase deficiency and breast-feeding

- J Pediatr 2006; 149:83–8 [62]

and may have difficulties achieving consistent nutritive breastfeeding [35], phenomena that may predispose to varying degrees of lactation failure. Sub-optimal feeding was the leading reason for discharge delay during birth hospitalization in late preterm neonates in one recent study [35]. This propensity may be compounded in primiparous women [36] who are known to produce significantly less milk than multiparous women during the first several days after giving birth, some with markedly low volumes [37].

Inadequate breast milk intake, in addition to contributing to varying degrees of dehydration, can enhance hyperbilirubinemia by increasing the enterohepatic circulation of bilirubin and resultant hepatic bilirubin load. The enterohepatic circulation of bilirubin already is exaggerated in the neonatal period, in part because the newborn intestinal tract is not colonized yet with bacteria that convert conjugated bilirubin to urobilinogen, and because intestinal β -glucuronidase activity is high [38,39]. Earlier studies in newborn humans and primates confirmed that the enterohepatic circulation of bilirubin accounts for up to 50% of the hepatic bilirubin load in newborns [40, 41]. Moreover, fasting hyperbilirubinemia is largely due to intestinal reabsorption of unconjugated bilirubin [42,43] suggesting an additional mechanism by which inadequate lactation or poor enteral intake may contribute to the genesis of marked hyperbilirubinemia in some neonates. A recent study confirmed that early breast-feeding-associated jaundice is associated with a state of relative caloric deprivation [44] and resultant enhanced enterohepatic circulation of bilirubin [44,45]. In the context of the exaggerated hepatic immaturity of the late preterm neonate, any further increase in hepatic bilirubin load likely will result in more marked hyperbilirubinemia. Breast-feeding-related jaundice, however, is not associated with increased bilirubin production [46,47].

It is notable that almost every reported case of kernicterus over the past two decades has been in breast-fed infants and that suboptimal lactation

was the most frequent experience in late preterm infants who developed acute bilirubin encephalopathy [12]. Pediatricians need to be alert to the potential of suboptimal breast milk feeding in late preterm neonates and not be misled by the seemingly satisfactory breastfeeding efforts of late preterm newborns during the birth hospitalization when limited colostrum volumes make it a challenge to adequately assess the effectiveness of breast milk transfer [48]. While recognizing the relationship between breast milk feeding and jaundice in late-preterm neonates, it is important to emphasize that the benefits of breast milk feeds far outweigh the related risk of hyperbilirubinemia.

Large for gestational age status and risk

In addition to the almost uniform prevalence of breast milk feedings, another salient clinical feature of kernicterus risk in late preterm neonates in the US Pilot Kernicterus Registry is a large for gestational age (LGA) categorization. Indeed, more than a third of kernicteric late preterm infants were LGA [12]. Not surprisingly, prevalent birth-related risk factors for hyperbilirubinemia in this LGA subgroup included oxytocin induction, vacuum or forceps delivery, and cutaneous bruising [12]. No other specific underlying mechanisms for hyperbilirubinemia were identified. Whether the LGA status of late preterm neonates (ie, birth weight comparable to a typical term neonate) served to mask their immaturity is not clear, nor is it known if antecedent or concomitant hypoglycemia occurred in the hyperbilirubinemic LGA cohort and possibly contributed to the risk for injury [12].

Male sex and risk

Another clinical feature of affected neonates in the US Pilot Kernicterus Registry is the predominance of males ($n = 84$) to females ($n = 38$) [12]. This approximately twofold greater prevalence of kernicteric males is also evident in the late preterm subgroup in the registry [4]. Previous observations demonstrated that males have higher bilirubin levels than females [2,49,50], and not surprisingly, they are over represented in that cohort of infants readmitted to the hospital for evaluation and management of neonatal jaundice, with an odds ratio of 2.89 (confidence interval [CI] 1.46 to 5.74) as compared with their female counterparts [2]. Taken together, these findings suggest an increased risk for marked jaundice and an increased susceptibility to bilirubin-induced injury in male neonates. Regarding the former, it is of interest that the prevalence of the Gilbert's syndrome is reportedly more than twofold higher in males (12.4%) than in females (4.8%). Additionally, within this cohort, male TSB levels are significantly higher than female TSB levels [51]. Gilbert's syndrome, an inherited disorder of impaired bilirubin conjugation capacity, would be expected to enhance the risk of neonatal hyperbilirubinemia, particularly when coexpressed with other icterogenic conditions [52,53]. Regarding the susceptibility to bilirubin-induced injury, early

studies on neonates who had hemolytic disease demonstrated a male predominance in neonatal mortality attributable to kernicterus [54–56], a finding also reported in hyperbilirubinemic premature neonates [57]. Studies in the hyperbilirubinemic Gunn rat model of kernicterus are also consistent with the notion of an increased male susceptibility to bilirubin-induced injury, demonstrating an increased prevalence of kernicterus [58] and higher cerebellar brain bilirubin contents in jaundiced male pups [59] as contrasted with their jaundiced female counterparts. The similar total serum bilirubin and serum albumin levels in hyperbilirubinemic male and female Gunn rat pups in the latter study suggest sex-specific differences in:

- Blood–brain barrier permeability to unbound bilirubin
- Neuronal plasma membrane bilirubin passage
- CNS bilirubin binding, metabolism, or clearance [59]

A potential role for sex hormones in this process remains unexplored but merits study, as surges in gonadotropin secretion during late embryonic and early postnatal life impact CNS development in rodents [60].

Glucose-6-phosphate dehydrogenase deficiency and risk

Of additional note regarding male sex and risk of neonatal hyperbilirubinemia is the cohort of newborns who are glucose-6-phosphate dehydrogenase (G-6-PD) deficient. Given that G-6-PD deficiency is an X-linked condition, affected males predominate (although as a result of X chromosome inactivation [lyonization] female heterozygotes have two red cell populations, normal and G-6-PD deficient, and can be affected when inactivation is non-random, in addition to homozygous deficient females). Of clinical note, many affected neonates in the US Pilot Kernicterus registry are G-6-PD deficient (20.8% of all cases [4]); most of those being African American males [4]. A recent report assessing risk factors for the prediction of hyperbilirubinemia in term and late preterm African American male neonates demonstrated that G-6-PD deficient males who were also late preterm and breast-feeding represented the subgroup at highest risk for hyperbilirubinemia (defined as any bilirubin values greater than 95% on the hour-of-life-specific bilirubin nomogram of Bhutani and colleagues [61]), affecting approximately 60% of such newborns (odds ratio 10.2, 1.35 to 76.93 95% CI) [62].

Treatment guidelines

The current management guidelines of the AAP Subcommittee on Hyperbilirubinemia outline hour-specific phototherapy (Fig. 1) and exchange transfusion (Fig. 2) treatment thresholds for three separate groups of neonates:

- Infants at lower risk (at least 38 weeks gestation and well)

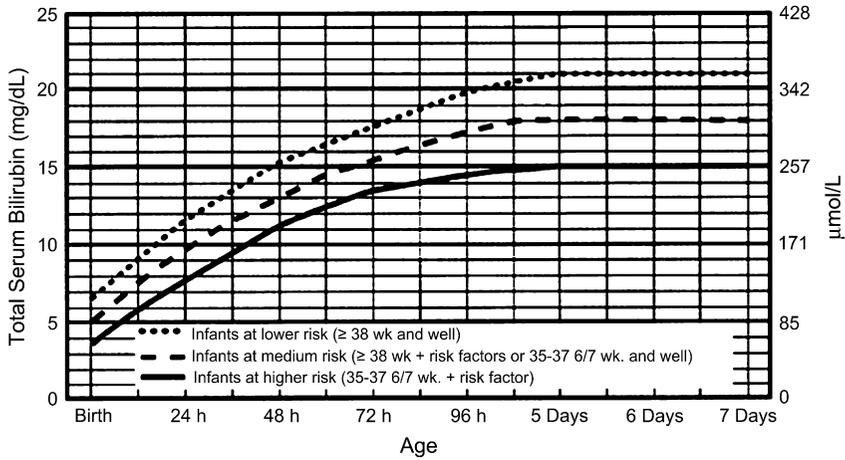


Fig. 1. Phototherapy guideline from the 2004 practice parameter of the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin. Risk factors include isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin less than 3.0g/dL (if measured). For well infants ($35^{0/7}$ – $37^{6/7}$ wks), can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to $37^{6/7}$ wks. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:304; with permission. © Copyright 2004 by the American Academy of Pediatrics.)

- Infants at medium risk (at least 38 weeks gestation with risk factors [defined as isoimmune hemolytic disease, G-6-PD deficiency, asphyxia, significant lethargy, temperature instability, acidosis, or albumin less than 3.0 g/dL (if measured)] or $35^{0/7}$ to $37^{6/7}$ weeks gestation and well)
- Infants at higher risk ($35^{0/7}$ to $37^{6/7}$ weeks gestation with risk factors) [22]

These three risk groups, lower, medium, and higher, are identified in Figs. 1 and 2 and in Table 2, which shows the bilirubin to albumin (B/A) ratios that can be used as an additional risk factor, but not in lieu of the TSB in determining the need for exchange transfusion (see Fig. 2 legend). Because the AAP guidelines are hour-, gestational age-, and risk-specific it is often helpful to use instruments such as BiliTool (access at www.bilitool.org), which are designed to assist the clinician in characterizing an individual patient's risk toward the development of hyperbilirubinemia and in accurately identifying relevant phototherapy treatment and exchange transfusion thresholds. Such tools can be accessed online or downloaded to personal hand-held computer devices. Of note, the AAP guideline treatment thresholds are lower in well late preterm neonates than in healthy term neonates and lower still if the late preterm neonate also evidences risk factors [22]. Of additional note, the management of late preterm newborns born between

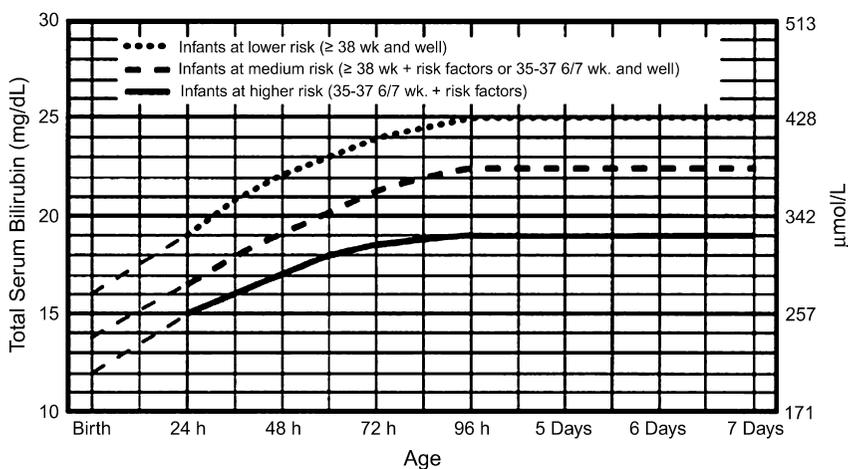


Fig. 2. Exchange transfusion guideline from the 2004 practice parameter of the American Academy of Pediatrics subcommittee on hyperbilirubinemia. The dashed lines for the first 24 hours indicate uncertainty caused by a range of clinical circumstances and a range of responses to phototherapy. Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry [functional immaturity of the late preterm neonate may mask these signs of acute bilirubin encephalopathy [12]]) or if TSB is ≥ 5 mg/dL (85 $\mu\text{mol/L}$ above these lines). Risk factors include isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, and acidosis. Measure serum albumin and calculate B/A ratio (see Table 2). Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin. If infant is well and 35^{0/7}–37^{6/7} wks (median risk), can individualize TSB levels for exchange based on actual gestational age. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:305; with permission. © Copyright 2004 by the American Academy of Pediatrics.)

34^{0/7} and 34^{6/7} weeks gestation is not addressed by the 2004 AAP clinical practice guideline [22]. Also, infants born between 37^{0/7} and 37^{6/7} weeks gestation, although strictly defined as term, are characterized in the AAP guideline as medium to higher risk and are to be managed as late preterm regarding phototherapy and exchange thresholds [22]. The latter underscores the importance of maturity in defining risk and reflects a consensus that even 37^{0/7} to 37^{6/7} weeks gestation newborns are predisposed to develop hyperbilirubinemia and bilirubin-induced CNS injury. The management of late preterm neonates born between 34^{0/7} and 34^{6/7} weeks gestation is akin to guidelines for preterm neonates, the framing of which has proven to be a capricious exercise at best and one for which no claim of evidence base can be made [20]. Nevertheless, it seems prudent in the absence of additional data to apply treatment thresholds that approximate those of the AAP higher risk group to this cohort of late preterm neonates, even when they are clinically well, commensurate with several other published management guidelines for premature newborns [21].

Table 2

The following B/A ratios can be used together with, but not in lieu of, the total serum bilirubin level as an additional factor in determining the need for exchange transfusion

Risk category	B/A ratio at which exchange transfusion should be considered	
	TSB mg/dL/Alb, g/dL	TSB $\mu\text{mol/L}$ /Alb, $\mu\text{mol/L}$
Infants $\geq 38^{0/7}$ wks	8.0	0.94
Infants $35^{0/7}$ – $37^{6/7}$ wks and well or $\geq 38^{0/7}$ wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2	0.84
Infants $35^{0/7}$ – $37^{6/7}$ wks if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114:305; with permission. © Copyright 2004 by the American Academy of Pediatrics.

Intravenous immune globulin

In addition to phototherapy and exchange transfusion, several studies have demonstrated the effectiveness of early high-dose (500–1000 mg/kg) intravenous immune globulin (IVIG) therapy in attenuating hemolysis and resultant hyperbilirubinemia associated with Coombs-positive hemolytic disease (Rh isoimmunization and ABO incompatibility) [63–65]. Indeed, IVIG significantly decreased blood carboxyhemoglobin levels by 24 hours after IVIG, a sensitive marker of neonatal hemolysis [63]. Additionally, a recent systematic review reported that the number needed to treat with IVIG to prevent one exchange transfusion was low, at 2.7, attesting to the efficacy of this intervention [65]. IVIG should be given slowly (over at least 2 hours), and it can be repeated at 12-hour intervals until the bilirubin stabilizes [64]. This effective means of attenuating hemolysis should be considered strongly in late preterm neonates who have Coombs-positive hemolytic disease to reduce their risk of hyperbilirubinemia reaching exchange levels.

Prevention

Ultimately, the best clinical strategy to avoid the development of marked hyperbilirubinemia and attendant risk of acute bilirubin encephalopathy in the late preterm neonate is preventive and includes screening for jaundice in the newborn nursery, the provision of lactation support, parental education, timely postdischarge follow-up, and appropriate treatment when clinically indicated. Screening for neonatal jaundice before birth hospitalization discharge is critical in late preterm neonates, and it is the author's current practice to obtain either a TSB or transcutaneous bilirubin measurement to

accurately assess their risk for hyperbilirubinemia using the hour-specific Bhutani nomogram [22,61]. The provision of lactation support during the birth hospitalization and during the early postdischarge period, coupled with regular neonatal weight checks, is helpful in averting lactation difficulties and in the early identification of those mother–infant pairs prone to sub-optimal lactation or lactation failure. This practice is encouraged for all breast-feeding primiparous mothers. Parental education about neonatal jaundice and counseling regarding when to call the pediatrician is also important. A shortened hospital stay (less than 48 hours after delivery), although permitted for selected healthy term neonates [66], is not recommended for late preterm neonates. The AAP recommends close post-discharge follow-up for all newborns [66], a recommendation strongly reinforced in the current 2004 practice parameter, and one that is particularly relevant to the late-preterm neonate [22]. Indeed, timely post-discharge follow-up should identify many infants at risk in time to initiate appropriate treatment. Finally, when significant hyperbilirubinemia occurs, attention to phototherapy and exchange transfusion treatment thresholds as a function of gestational age and risk is a critical component in efforts to prevent brain injury.

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