

Hyperbilirubinemia in the Newborn Infant ≥ 35 Weeks' Gestation: An Update With Clarifications

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ABBREVIATIONS

AAP—American Academy of Pediatrics

G6PD—glucose-6-phosphate dehydrogenase

TSB—total serum bilirubin

TcB—transcutaneous bilirubin

Opinions expressed in this commentary are those of the author and not necessarily those of the American Academy of Pediatrics or its Committees.

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In July 2004, the Subcommittee on Hyperbilirubinemia of the American Academy of Pediatrics (AAP) published its clinical practice guideline on the management of hyperbilirubinemia in the newborn infant ≥ 35 weeks of gestation,¹ and a similar guideline was published in 2007 by the Canadian Paediatric Society.² Experience with implementation of the AAP guideline suggests that some areas require clarification. The 2004 AAP guideline also expressed hope that its implementation would “reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy. . . .” We do not know how many practitioners are following the guideline, nor do we know the current incidence of bilirubin encephalopathy in the United States. We do know, however, that kernicterus is still occurring in the United States, Canada, and Western Europe.^{3–7} In 2002, the National Quality Forum suggested that kernicterus should be classified as a “serious reportable event,”⁸ sometimes termed a “never event,”⁹ implying that with appropriate monitoring, surveillance, and intervention, this devastating condition can, or should, be eliminated. Although this is certainly a desirable objective, it is highly unlikely that it can be achieved given our current state of knowledge and practice.¹⁰ In certain circumstances (notably, glucose-6-phosphate dehydrogenase [G6PD] deficiency, sepsis, genetic predisposition, or other unknown stressors), acute, severe hyperbilirubinemia can occur and can produce brain damage despite appropriate monitoring and intervention.

In addition to clarifying certain items in the 2004 AAP guideline, we recommend universal predischarge bilirubin screening using total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) measurements, which help to assess the risk of subsequent severe hyperbilirubinemia. We also recommend a more structured approach to management and follow-up according to the predischarge TSB/TcB, gestational age, and other risk factors for hyperbilirubinemia. These recommendations represent a consensus of expert opinion based on the available evidence, and they are supported by several independent reviewers. Nevertheless, their efficacy in preventing kernicterus and their cost-effectiveness are unknown.

METHODS

We reviewed the report on screening for neonatal hyperbilirubinemia published by the Agency for Healthcare Research and Quality and prepared by the Tufts-New England Medical Center Evidence-Based Practice Center,¹¹ the current report by the US Preventive Services Task Force,¹² and other relevant literature.^{1,3–10,13–26}

TABLE 1 Important Risk Factors for Severe Hyperbilirubinemia

Predischarge TSB or TcB measurement in the high-risk or high-intermediate-risk zone
Lower gestational age
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
Jaundice observed in the first 24 h
Isoimmune or other hemolytic disease (eg, G6PD deficiency)
Previous sibling with jaundice
Cephalohematoma or significant bruising
East Asian race

RISK FACTORS

The 2004 AAP guideline includes 2 categories of risk factors, but the distinction between these 2 categories has not been clear to all users of the guideline.

Laboratory and Clinical Factors That Help to Assess the Risk of Subsequent Severe Hyperbilirubinemia

These “risk factors for hyperbilirubinemia” are listed in Table 1. Understanding the predisposition to subsequent hyperbilirubinemia provides

guidance for timely follow-up as well as the need for additional clinical and laboratory evaluation.

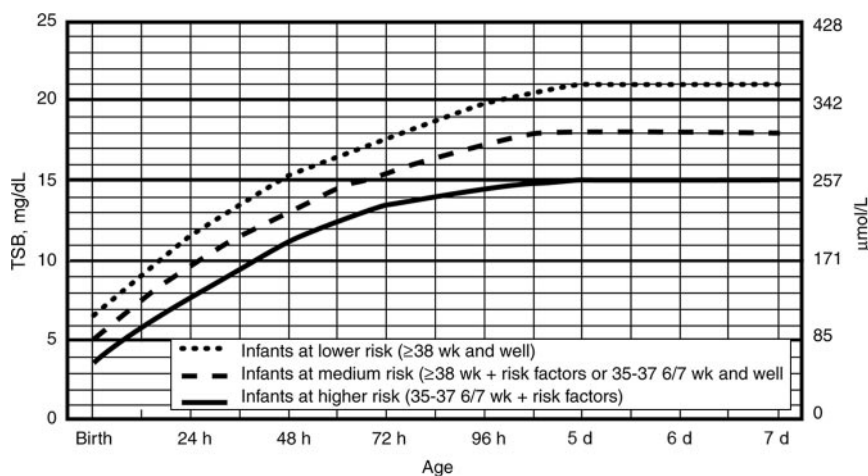
Laboratory and Clinical Factors That Might Increase the Risk of Brain Damage in an Infant Who Has Hyperbilirubinemia

These risk factors for bilirubin neurotoxicity are listed in the figures of the 2004 AAP guideline that provide recommendations for the use of phototherapy and exchange transfusion. These “neurotoxicity risk factors” encompass those that might increase the risk

TABLE 2 Hyperbilirubinemia Neurotoxicity Risk Factors

Isoimmune hemolytic disease
G6PD deficiency
Asphyxia
Sepsis
Acidosis
Albumin <3.0 mg/dL

of brain damage in an infant who has severe hyperbilirubinemia¹ (see Fig 1 and Table 2). The neurotoxicity risk factors are used in making the decision to initiate phototherapy or perform an exchange transfusion. These interventions are recommended at a lower bilirubin level when any of the neurotoxicity risk factors is present. Some conditions are found in both risk-factor categories. For example, lower gestational age and isoimmune hemolytic disease increase the likelihood of subsequent severe hyperbilirubinemia as well as the risk of brain damage by bilirubin.

**FIGURE 1**

Guidelines for phototherapy in hospitalized infants ≥ 35 weeks' gestation. Note that these guidelines are based on limited evidence and that the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the TSB level exceeds the line indicated for each category.

- Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin.
- Risk factors are isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or an albumin level of <3.0 g/dL (if measured).
- For well infants at 35 to 37 weeks' gestation, one 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 weeks' gestation and at higher TSB levels for those closer to 37 weeks' gestation.
- It is an option to provide conventional phototherapy in the hospital or at home at TSB levels of 2 to 3 mg/dL (35–50 $\mu\text{mol/L}$) below those shown, but home phototherapy should not be used in any infant with risk factors.

PREDISCHARGE RISK ASSESSMENT FOR SUBSEQUENT SEVERE HYPERBILIRUBINEMIA

The 2004 AAP guideline recommends a predischarge bilirubin measurement and/or assessment of clinical risk factors to evaluate the risk of subsequent severe hyperbilirubinemia.¹ New evidence suggests that combining a predischarge measurement of TSB or TcB with clinical risk factors might improve the prediction of the risk of subsequent hyperbilirubinemia.^{13,14,23} In addition, when interpreted by using the hour-specific nomogram (Fig 2), measurement of TSB or TcB also provides a quantitative assessment of the degree of hyperbilirubinemia. This provides guidance regarding the need (or lack of need) for additional testing to identify a cause of the hyperbilirubinemia and for additional TSB measurements.¹

The TSB can be measured from the same sample that is drawn for the

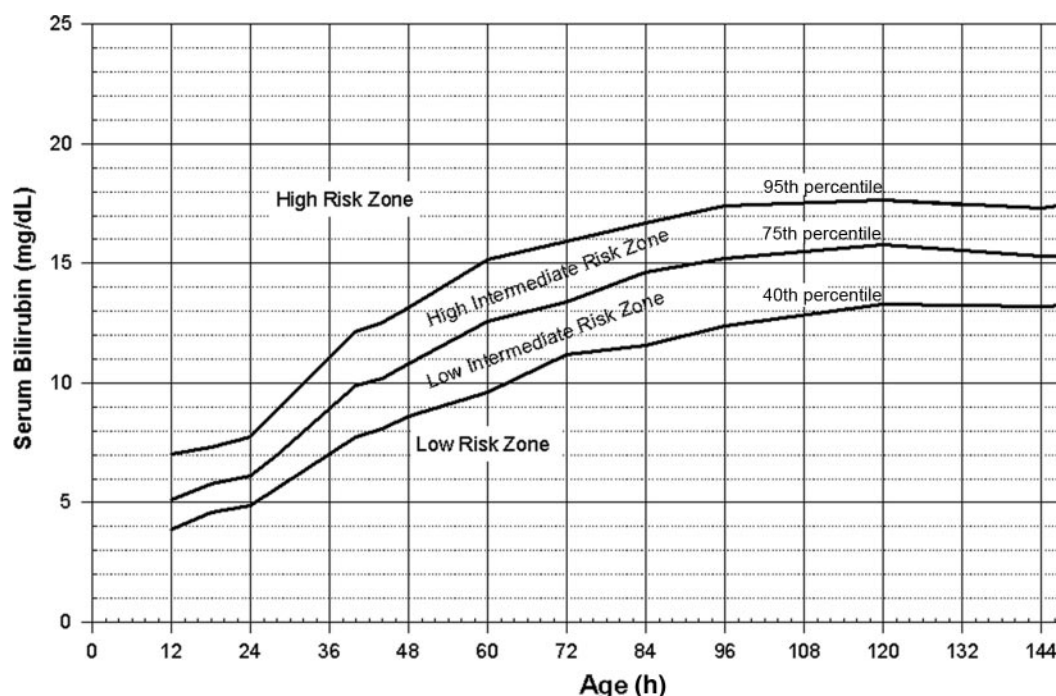


FIGURE 2

Nomogram for designation of risk in 2840 well newborns at ≥ 36 weeks' gestational age with birth weight of ≥ 2000 g or ≥ 35 weeks' gestational age and birth weight of ≥ 2500 g based on the hour-specific serum bilirubin values. (Reproduced with permission from Bhutani VK, Johnson L, Sivieri EM. *Pediatrics*. 1999;103[1]:6–14.)

metabolic screen. The risk zone (Fig 2) and the other clinical risk factors (Table 3) are then combined to assess the risk of subsequent hyperbilirubinemia and to formulate a plan for management and follow-up (Fig 3). When combined with the risk zone, the factors that are most predictive of hyperbilirubinemia risk are lower gestational age and exclusive breastfeeding.^{13,14,23} The lower the gestational age, the greater the risk of developing hyperbilirubinemia.^{13,14,23} For those infants from whom ≥ 2 successive TSB or TcB measurements are obtained, it is helpful to plot the data on the nomogram¹⁵ to assess the rate of rise. Hemolysis is likely if the TSB/TcB is crossing percentiles on the nomogram and suggests the need for further testing and follow-up (see Table 1 in the 2004 AAP guideline). Therefore, we recommend that a pre-discharge measurement of TSB or TcB be performed and the risk zone for hyperbilirubinemia determined¹⁵ on the

basis of the infant's age in hours and the TSB or TcB measurement.

It should be noted that, even with a low pre-discharge TSB or TcB level, the risk of subsequent hyperbilirubinemia is not zero,^{13,17} so appropriate follow-up should always be provided (Fig 3).

RESPONSE TO PREDISCHARGE TSB MEASUREMENTS

Figure 3 provides our recommendations for management and follow-up, according to pre-discharge screening. Note that this algorithm represents a consensus of the authors and is based on interpretation of limited evidence (see below).

FOLLOW-UP AFTER DISCHARGE

Most infants discharged at < 72 hours should be seen within 2 days of discharge.

Earlier follow-up might be necessary for infants who have risk factors for severe hyperbilirubinemia,^{1,13,14,23} whereas those in the lower risk zones with few or no risk factors can be seen later (Fig 3). Figure 3 also provides additional suggestions for evaluation and management at the first follow-up visit.

TcB MEASUREMENTS

TcB measurements are being used with increasing frequency in hospi-

TABLE 3 Other Risk Factors for Severe Hyperbilirubinemia to be Considered with the Gestational Age and the Pre-discharge TSB or TcB level (see Figure 3)

Exclusive breastfeeding, particularly if nursing is not going well and/or weight loss is excessive ($> 8 - 10\%$)
Isoimmune or other hemolytic disease (eg, G6PD deficiency, hereditary spherocytosis)
Previous sibling with jaundice
Cephalohematoma or significant bruising
East Asian race

The gestational age and the pre-discharge TSB or TcB level are the most important factors that help to predict the risk of hyperbilirubinemia. The risk increases with each decreasing week of gestation from 42–35 weeks (see Figure 3)

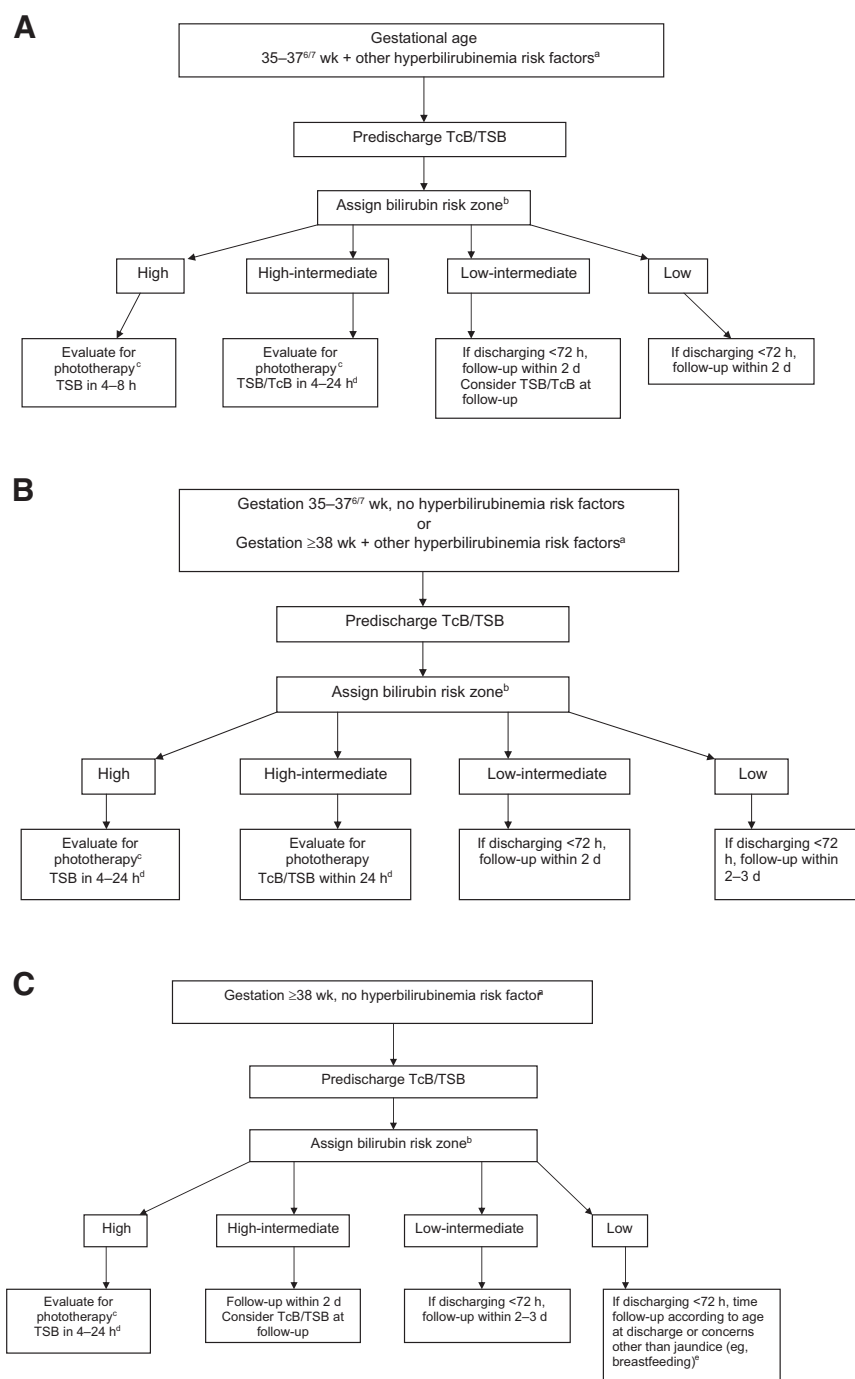


FIGURE 3

Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia.

- Provide lactation evaluation and support for all breastfeeding mothers.
- Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile (Fig 2). Higher and earlier initial TSB levels require an earlier repeat TSB measurement.
- Perform standard clinical evaluation at all follow-up visits.
- For evaluation of jaundice see 2004 AAP guideline.¹
- ^a Table 3. ^b Fig 2. ^c Fig 1. ^d In hospital or as outpatient. ^e Follow-up recommendations can be modified according to level of risk for hyperbilirubinemia; depending on the circumstances in infants at low risk, later follow-up can be considered.

tal nurseries and in some outpatient settings. They have the advantage of providing instantaneous information and probably reduce the likelihood of missing a clinically significant TSB, making them particularly useful in outpatient practice. TcB measurements can significantly reduce the number of TSB measurements that are required, but as with any point-of-care test, regular monitoring for appropriate quality assurance by comparison with TSB measurements is necessary. Significant variation can occur among instruments, and the use of a new instrument should be compared with hospital laboratory measurements to ensure that the instrument is working properly; such checks should be performed periodically. TcB is a measurement of the yellow color of the blanched skin and subcutaneous tissue, not the serum, and should be used as a screening tool to help determine whether the TSB should be measured. Although TcB measurements provide a good estimate of the TSB level, they are not a substitute for TSB values, and a TSB level should always be obtained when therapeutic intervention is being considered.

Most studies in term and late-preterm infants have indicated that the TcB tends to underestimate the TSB, particularly at higher TSB levels.¹⁸ Thus, investigators have adopted various techniques to avoid missing a high TSB level (ie, a false-negative TcB measurement). These techniques include measuring the TSB if

- the TcB value is at 70% of the TSB level recommended for the use of phototherapy¹⁹;
- the TcB value is above the 75th percentile on the Bhutani nomogram (Fig 1)¹⁵ or the 95th percentile on a TcB nomogram¹⁶ (in 1 study, if the TcB was <75th percentile on the Bhutani nomogram, 0 of 349 infants

had a TSB level above the 95th percentile [a negative predictive value of 100%]²⁰; or

- at follow-up after discharge, the TcB value is >13 mg/dL (222 $\mu\text{mol/L}$)²¹ (in this outpatient study, no infant who had a TcB value of ≤ 13 mg/dL had a TSB level of >17 mg/dL [291 $\mu\text{mol/L}$]).²¹

COSTS

The introduction of universal predischarge bilirubin screening, follow-up visits, and TSB/TcB measurements might increase costs. Ideally, a cost/benefit analysis should include the cost to prevent 1 case of kernicterus. The cost per case, however, highly depends on the incidence of kernicterus as well as its potential reduction resulting from the intervention. By using a strategy similar to that suggested in this guideline, and assuming an incidence of kernicterus of 1 in 100 000 live births and a relative risk reduction of 70%, the cost to prevent 1 case of kernicterus has been estimated as approximately \$5.7 million.²² Because we do not know the current incidence of kernicterus in the United States or the actual relative risk reduction (if these guidelines were implemented universally), we cannot calculate the true cost/benefit ratio. Taking into account the lifetime cost of an infant with kernicterus, it is possible that there could be savings.²²

DISCUSSION

While endeavoring to clarify some areas addressed in the 2004 AAP guideline, we have also introduced new recommendations, both for the predis-

charge assessment of the risk of subsequent hyperbilirubinemia and for follow-up testing. We recognize that the quality of evidence for recommending universal predischarge screening and for the suggested management and follow-up (Fig 3) is limited and, in the absence of higher levels of evidence, our recommendations must, therefore, be based on expert opinion. As indicated in the reviews by the US Preventive Services Task Force¹² and Trikalinos et al¹¹ in this issue of *Pediatrics*, there are currently no good data to indicate that the implementation of these recommendations will reduce the risk of kernicterus, although published data suggest that predischarge screening can reduce the incidence of a TSB level of ≥ 25 mg/dL,^{24,25} perhaps by increasing the use of phototherapy.²⁴ Nevertheless, because kernicterus is a devastating condition that leads to serious and permanent neurologic damage, and because published reports and our own review of cases in the medicolegal setting suggest that many of these cases could have been prevented, a reasonable argument can be made for implementing the suggested recommendations in the absence of better evidence. Because kernicterus is a rare condition, it is unlikely that we will be able to obtain adequate evidence in the short-term to support our recommendations. In their elegant polemic, Auerbach et al²⁶ discussed “the tension between needing to improve care and knowing how to do it.” They noted that, in the absence of appropriate evidence, “bold efforts at improvement can consume tremendous resources yet confer only a small benefit.”²⁶ We

also recognize that although predischarge testing is relatively inexpensive and convenient, measuring the TSB after discharge is more difficult. TcB measurement is quite easy but is not currently available in most primary care settings. In addition, more evidence is needed to support the cost and efficacy of these recommendations. There is certainly a risk that these recommendations could lead to additional testing and an increase in both appropriate and inappropriate use of phototherapy.^{1,24} Nevertheless, it is our opinion that universal screening, when combined with the clinical risk factors (of which gestational age and exclusive breastfeeding are most important) and targeted follow-up, is a systems approach that is easy to implement and understand, and it provides a method of identifying infants who are at high or low risk for the development of severe hyperbilirubinemia. In addition to risk assessment, the measurement of TSB or TcB when interpreted by using the hour-specific nomogram provides the caregiver with an immediate and quantitative mechanism for assessing the degree of hyperbilirubinemia and the need for additional surveillance and testing. As such, it could play an important role in preventing acute bilirubin encephalopathy, although this has yet to be demonstrated.

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