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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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M. Jeffrey Maisels, Vinod K. Bhutani, Debra Bogen, Thomas B. Newman, Ann R. Stark and Jon F. Watchko

Pediatrics 2009;124;1193; originally published online September 28, 2009;
DOI: 10.1542/peds.2009-0329

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

AUTHORS: M. Jeffrey Maisels, MB, BCh, DSc,^a Vinod K. Bhutani, MD,^b Debra Bogen, MD,^c Thomas B. Newman, MD, MPH,^d Ann R. Stark, MD,^e and Jon F. Watchko, MD^f

^aDepartment of Pediatrics, Oakland University William Beaumont School of Medicine and Division of Neonatology, Beaumont Children's Hospital, Royal Oak, Michigan; ^bDepartment of Neonatal and Developmental Medicine, Lucile Salter Packard Children's Hospital, Stanford University, Palo Alto, California; ^cDivision of General Academic Pediatrics, Department of Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; ^dDepartment of Epidemiology and Biostatistics, Department of Pediatrics, University of California, San Francisco, California; ^eDepartment of Pediatrics and Section of Neonatology, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; and ^fDivision of Newborn Medicine, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

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.

www.pediatrics.org/cgi/doi/10.1542/peds.2009-0329

doi:10.1542/peds.2009-0329

Accepted for publication Jun 3, 2009

Address correspondence to M. Jeffrey Maisels, MB, BCh, DSc, Beaumont Children's Hospital, 3601 W. 13 Mile Rd, Royal Oak, MI 48073. E-mail: JMaisels@beaumont.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Dr Maisels is a consultant to and has received grant support from Draeger Medical Inc; the other authors have no financial relationships relevant to this article to disclose.

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.

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

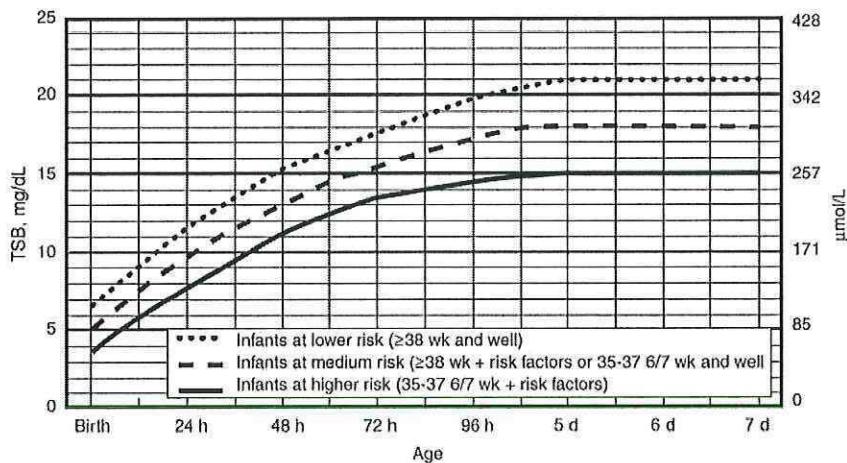


FIGURE 1

Guidelines for phototherapy in hospitalized infants \geq 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 μ mol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

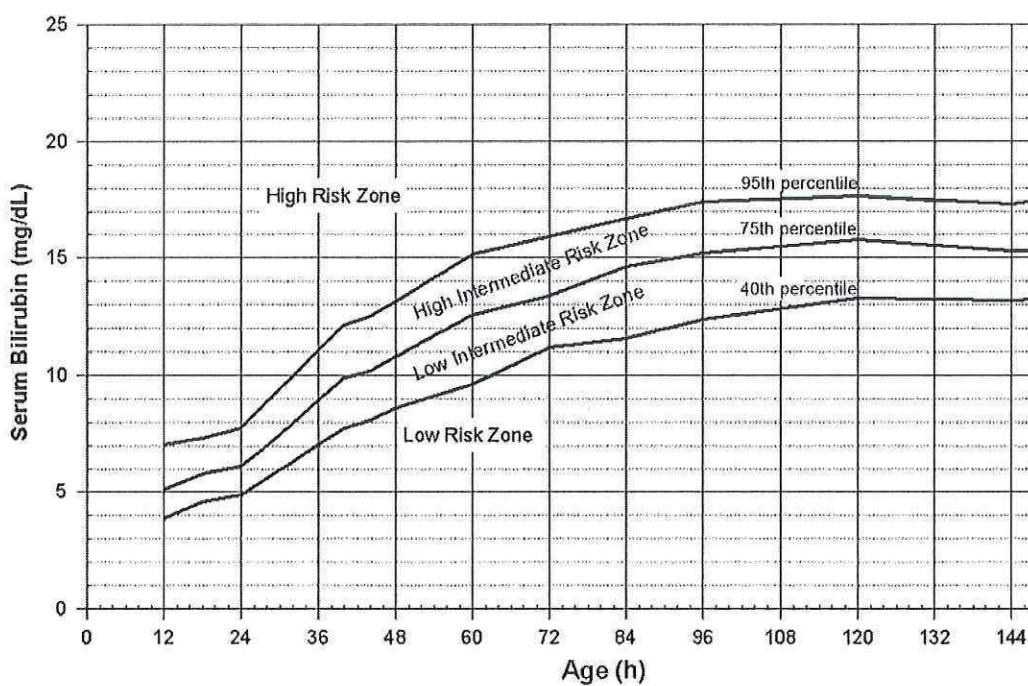


FIGURE 2

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 predischarge 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 predischarge 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 ($>8\text{--}10\%$)
Iisoimmune 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 predischarge 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).

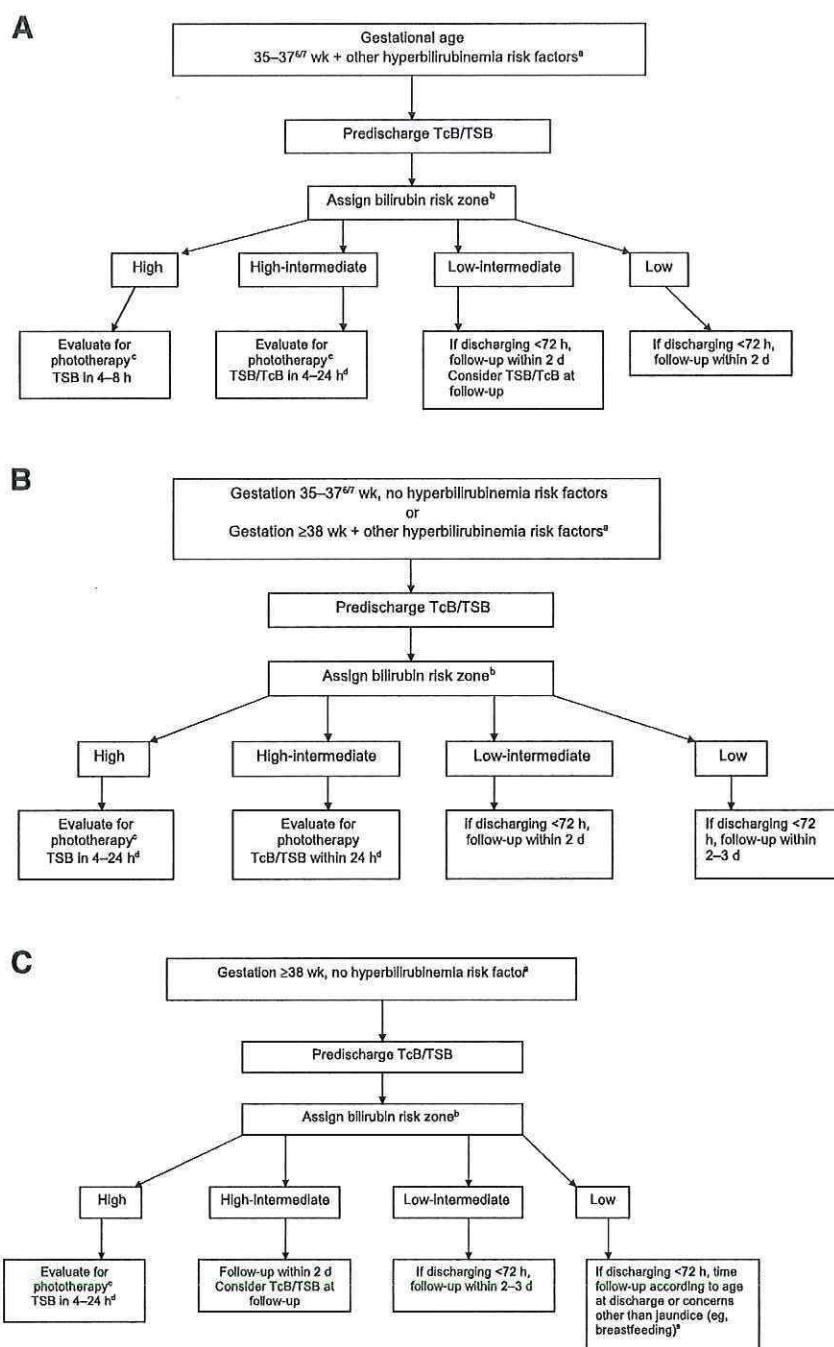


FIGURE 3

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 μmol/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 μmol/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.

ACKNOWLEDGMENTS

We are grateful for reviews and critiques of this commentary by neonatologists, bilirubinologists, pediatricians, and pediatric residents.

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ORIGINAL ARTICLE

Routine transcutaneous bilirubin measurements combined with clinical risk factors improve the prediction of subsequent hyperbilirubinemia

MJ Maisels, JM DeRidder, EA Kring and M Balasubramaniam

Department of Pediatrics and the Research Institute, William Beaumont Hospital, Royal Oak, MI, USA

Objective: To evaluate predischarge transcutaneous bilirubin (TcB) measurements combined with risk factors as predictors of the risk of a subsequent total serum bilirubin (TSB) ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$).

Study Design: Routine TcB measurements are obtained daily for all infants in our well baby nursery. We performed a nested case-control study comparing all 75 infants who had been readmitted with TSB ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$) between 1 February 2005 and 28 February 2007 with randomly selected controls that had not been readmitted.

Result: Between 1 February 2005 and 28 February 2007, 11 456 infants were discharged from the well baby nursery. Seventy-five infants (0.65%) were readmitted at a mean age of 110 ± 29.9 h with a TSB ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$). All received phototherapy. Using logistic regression analysis, three variables were statistically significant for predicting cases: the maximum predischarge TcB percentile group ($P < 0.0001$, adjusted odds ratio (AOR), >95th percentile 148; 95% confidence interval (CI) 21 to >999, AOR 76 to 95th percentile 15; 95% CI 3.1 to 70, AOR 50 to 75th percentile 6.1; 95% CI 1.3 to 28 compared with <50th percentile), exclusive breastfeeding ($P < 0.0001$, AOR 11; 95% CI 3.7 to 34) and gestational age ($P = 0.0057$, AOR 35 to 36 6/7 week 21; 95% CI 2.3 to 185, AOR 37 to 37 6/7 week 15; 95% CI 1.9 to 115, AOR 38 to 38 6/7 week 1.8; 95% CI 0.3 to 11, AOR 39 to 39 6/7 week 1.1; 95% CI 0.2 to 7 AOR ≥ 41 week 0.88; 95% CI 0.1 to 10 compared with 40 to 40 6/7 week infants). These three variables provided the best prediction of a case ($c = 0.885$, area under the receiver operating characteristic curve) and this prediction was significantly better than the use of the clinical risk factors, gestation and exclusive breastfeeding, alone ($c = 0.770$, $P < 0.001$) or the TcB percentile grouping alone ($c = 0.766$, $P < 0.001$). Substituting the TcB rate of rise ($c = 0.903$, $P = 0.316$) or the last measured TcB ($c = 0.873$, $P = 0.292$) for the maximum TcB measurement did not significantly improve the predictors of a case.

Conclusion: Combining predischarge TcB levels with two clinical risk factors—gestational age and exclusive breastfeeding—significantly improves the prediction of subsequent hyperbilirubinemia.

Journal of Perinatology (2009) **29**, 612–617; doi:10.1038/jp.2009.43; published online 7 May 2009

Keywords: transcutaneous bilirubin; hyperbilirubinemia; newborn infant

Introduction

In its clinical practice guideline on the management of hyperbilirubinemia in the newborn¹ the American Academy of Pediatrics (AAP) recommends that, before discharge, all infants be assessed, for the risk of subsequent severe hyperbilirubinemia. The AAP guideline notes that ‘the best documented method for assessing the risk of subsequent hyperbilirubinemia is to measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level and plot the results on a nomogram.’ First described by Bhutani *et al.*² in 1999, the measurement of a predischarge TSB level has been shown, in different populations, to be a valuable method for helping to assess the risk of an infant subsequently developing, or not developing, hyperbilirubinemia.^{3–6} Two recent studies^{7,8} have shown that combining a predischarge TSB or TcB measurement with clinical risk factors improved the prediction of subsequent hyperbilirubinemia. We evaluated different models for the prediction of hyperbilirubinemia to identify a simple and clinically relevant method of assessing the risk of subsequent hyperbilirubinemia in this population.

Methods

Since February 2005, nurses have routinely performed TcB measurements during the midnight shift (between 2300 and 0700 hours) on all infants in our well baby nursery. All measurements are obtained from the mid sternum as described earlier⁹ using the Konica Minolta Dräger Air-Shields Transcutaneous Jaundice Meter,

Correspondence: Dr MJ Maisels, Department of Pediatrics, William Beaumont Hospital, 3601 W. Thirteen Mile Road, Royal Oak, MI 48073, USA.

E-mail: jmaisels@beaumont.edu

Received 30 September 2008; revised 1 March 2009; accepted 9 March 2009; published online 7 May 2009

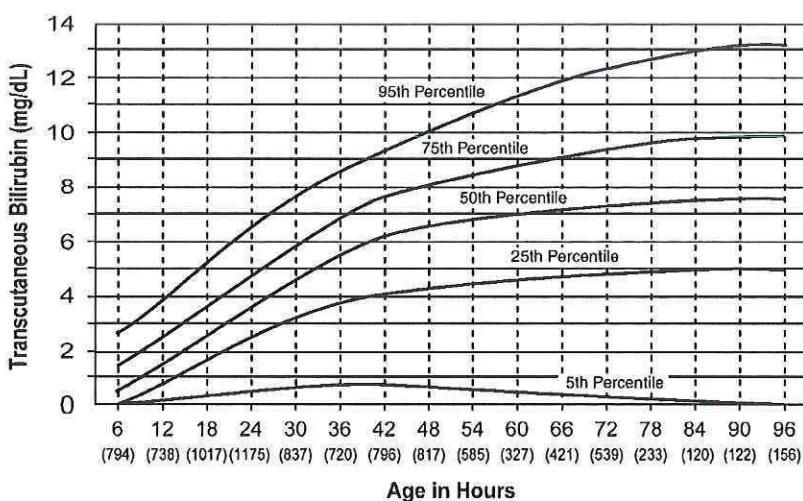


Figure 1 Nomogram showing smoothed curves for the 5th, 25th, 50th, 75th and 95th percentiles for transcutaneous bilirubin (TcB) measurements among healthy newborns (gestational age ≥ 35 weeks). A total of 9397 TcB measurements were obtained from 3984 newborns. The number of infants studied at each interval is shown in parentheses. (Adapted from Maisels and Kring,⁹ with permission.)

model JM-103 (Dräger Medical Inc., Telford, PA, USA). These measurements are entered into the hospital's computerized laboratory database and can be plotted on a nomogram in the infant's chart. Before March 2006 we used the Bhutani nomogram² and the nurses ordered a TSB whenever the TcB exceeded the 75th percentile for the infant's age in hours. From 1 March 2006, we used our own nomogram (Figure 1)⁹ and a TSB was ordered whenever the TcB exceeded the 95th percentile. Pediatricians could also order TSB levels at their discretion. Most infants had at least two TcB measurements before discharge.

Using the hospital's laboratory database, we performed a nested case-control study¹⁰ and identified all infants ($n = 75$) who, following discharge, had been readmitted with hyperbilirubinemia (a TSB ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$)) (cases). Infants who received phototherapy before discharge were omitted. From the remaining population of infants who were not readmitted for hyperbilirubinemia, we randomly selected 75 controls. We reviewed the charts and obtained demographic data on all infants and evaluated each variable and combination of variables to predict cases. For our risk calculations, all predischarge TcB measurements were plotted, retrospectively, on the Beaumont nomogram (Figure 1)⁹ developed from our population. As a predictor variable, the maximum predischarge TcB measurements were divided into four groups according to the percentiles (<50, 50 to 75, 76 to 95, >95). The TcB values used to predict hyperbilirubinemia in this study were derived from a different data set from those used to construct our nomogram. For our outcome variable we used a TSB of ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$) (cases), which is approximately the 95th percentile on the Bhutani nomogram for infants aged ≥ 96 h.² All these infants received phototherapy but none required an exchange transfusion. The

study was approved by the hospital's Human Investigation Committee.

Statistical analysis

We summarized continuous variables using mean \pm s.d., whereas categorical variables were summarized using frequencies and percentages. We compared cases with controls using the two-tailed Fisher's Exact test for nominal variables, the Exact Cochran-Armitage Trend test for ordinal variables, and the two-tailed Student's *t*-test for continuous variables. Stepwise multiple logistic regression analysis was used to determine the smallest subset of predictors that best explained the differences between cases and controls. For the model building process, we included all of the variables listed in Table 1. Significance levels for entry and exit from the models were set at 0.05. As the various fitted models were correlated, the areas under the receiver operating characteristic (ROC) curve, as denoted by the *c*-statistics, were compared statistically using the methodology described for binary responses by DeLong *et al.*¹¹ *P*-values of <0.05 were considered statistically significant. Statistical analysis was performed using The SAS System for Windows, SAS Institute Inc., Cary, NC, USA (version 9.1.3, Service Pak 2).

Results

Between 1 February 2005 and 28 February 2007, 11 456 infants were discharged from the well baby nursery and 75 (0.65%) were readmitted at a mean age of 110 ± 29.9 h with a TSB ≥ 17 mg per 100 ml, range 17.0 to 23.8 mg per 100 ml (291 to $407 \mu\text{mol l}^{-1}$).

Table 1 Demographic and clinical data

	Cases (75), n (%)	Controls (75), n (%)	P-value	Unadjusted OR (95% CI)
<i>Maternal age ≥ 25 years</i>	65 (87)	68 (91)	<0.001 ^a	
<i>Gestation (week)</i>				
35–35 6/7	2 (2.6)	0		5.7 (1.2, 22)
36–36 6/7	17 (22.6)	6 (8)		
37–37 6/7	18 (24)	7 (9)		4.1 (0.99, 17)
38–38 6/7	15 (20)	21 (28)		1.1 (0.31, 4.2)
39–39 6/7	14 (19)	27 (36)		0.71 (0.19, 2.6)
40–40 6/7 (reference group)	5 (6.6)	8 (11)		
≥41	4 (5.3)	6 (8)		1.1 (0.2, 5.8)
<i>Race</i>			0.08 ^b	
African-American	1 (1.3)	5 (6.7)		0.22 (0.03, 1.9)
Asian	9 (12)	5 (6.7)		1.96 (0.62, 6.2)
Indian/Hispanic/middle Eastern	1 (1.3)	3 (4)		0.36 (0.04, 3.6)
Unknown	6 (8)	1 (1.3)		6.53 (0.76, 55.93)
White (reference group)	58 (77)	61 (81)		
<i>Mode of delivery</i>			0.0224 ^b	
C-section	12 (16)	26 (34.7)		0.314 (0.14, 0.704)
Vaginal (reference group)	63 (84)	49 (65.3)		
<i>Sex</i>			0.511 ^b	0.76 (0.4, 1.5)
Male	44 (59)	39 (52)		
Female	31 (41)	36 (48)		
<i>Feeding</i>			0.0004 ^b	
Breast only	41 (55)	19 (25)		6.91 (2.2, 21.64)
Breast and formula	29 (38.7)	40 (53)		2.16 (0.71, 6.6)
Formula only (reference group)	5 (6.7)	16 (21)		
<i>TcB percentile group</i>			<0.0001 ^a	
>95	27 (36)	4 (5)		60.75 (12.4, 297.65)
76–95	24 (32)	19 (25)		10.42 (2.73, 39.86)
50–75	21 (38)	25 (33)		7.56 (2.01, 28.48)
<50 (reference group)	3 (4)	27 (36)		
Bruising/cephalohematoma	20 (26.7)	6 (8)	0.004 ^b	4.2 (1.6, 11)
Jaundice in first 24 h	5 (6.6)	5 (6.6)	1.00 ^b	1 (0.3, 3.6)
Length of stay after birth (hours)			0.377 ^a	
<24	0	0		NA
24–47.9	30 (40)	24 (32)		1.5 (0.63, 3.7)
48–71.9	31 (41)	34 (45)		1.1 (0.5, 2.6)
>72 (reference group)	14 (19)	17 (23)		

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

^aExact P-value based on Cochran–Armitage Trend test.^bFisher's Exact test.

Demographic and clinical data are provided in Table 1 and the results are shown in Tables 2 and 3 and Figure 2. Using logistic regression analysis, three variables were statistically significant for predicting cases: the predischarge TcB percentile group

($P<0.0001$), feeding method (exclusive breast, breast and formula vs formula only (reference group), $P=0.0001$), and gestational age group ($P=0.0057$). The odds ratios are provided in the tables. When assessing only the clinical predictors collectively (that is,

Table 2 Predischarge TcB percentiles and subsequent hyperbilirubinemia

TcB percentiles	Total population	Post discharge total serum bilirubin				Relative risk vs <50th percentile (95% CI) ^a	
		≥17 mg per 100 ml (75)		≥20 mg per 100 ml (21)		≥17 mg per 100 ml	≥20 mg per 100 ml
		n	%	n	%		
<50	5727	3	0.05	0	—		
50–75	2864	21	0.73	8	0.27	14.0 (4.2, 46.9)	16 (2.0, 128)
76–95	2291	24	1.04	7	0.31	20.0 (6, 66.3)	17.5 (2.2, 142)
>95	574	27	4.70	6	1.05	89.8 (27.3, 295)	59.9 (7.2, 496)
Total	11456	75	0.65	21	0.18		

Abbreviations: CI, conflict of interest; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

^aRelative risk calculated assuming a value of 1 for post-discharge TSB of ≥20 mg per 100 ml with predischarge TcB below 50th percentile. The denominators were calculated for each category using our TcB percentiles (Figure 1). To calculate the denominators it was assumed for each category that the non-readmitted infants did not develop a TSB ≥17 mg per 100 ml.

Table 3 Variables associated with TSB ≥17 mg per 100 ml (291 μmol l⁻¹) by stepwise multiple logistic regression

	P-value	Adjusted OR (95% CI)
<i>Gestational age (week)</i>		
35–36 6/7	0.0065	20.79 (2.34, 184.74)
37–37 6/7	0.0099	14.86 (1.91, 115.38)
38–38 6/7	0.5295	1.78 (0.29, 10.83)
39–39 6/7	0.9327	1.09 (0.16, 7.22)
40–40 6/7 (reference group)		
≥41	0.8809	0.83 (0.07, 9.71)
<i>Feeding</i>		
Breast only	0.0021	10.75 (2.37, 48.82)
Breast and formula	0.9481	0.95 (0.23, 3.94)
Formula only (reference group)		
<i>TcB percentile group</i>		
>95	<0.0001	149.89 (20.41, >999.999)
[76–95]	0.0008	14.8 (3.08, 71.19)
[50–75]	0.02	6.143 (1.33, 28.37)
<50 (reference group)		

Abbreviations: TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

excluding predischarge TcB percentile group), only the gestational age group and the feeding method were used ($P = 0.1982$, 0.0012 and 0.0001 , respectively).

Figure 2 shows the ROC curves for different combinations of predictor variables. Combining the TcB percentile, gestational age and exclusive breastfeeding provided the best prediction of a case ($c = 0.885$) and this was significantly better than the use of these clinical risk factors alone ($c = 0.770$, $P < 0.001$) or the TcB percentile grouping alone ($c = 0.766$, $P < 0.001$). The c -statistics for the different models are shown in Figure 2.

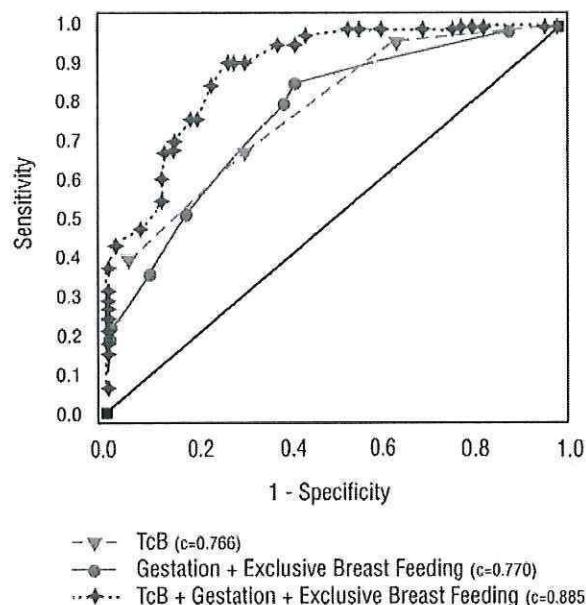


Figure 2 Receiver operating characteristic curves for three different models for prediction of a serum bilirubin level of ≥17 mg per 100 ml (291 μmol l⁻¹). The c -statistics for the other models (not shown) are transcutaneous bilirubin (TcB) + gestation 0.842, TcB + exclusive breastfeeding 0.770. The c -statistic for TcB + gestation + exclusive breastfeeding is significantly different from the other models ($P < 0.001$) but is not significantly different from TcB + gestation ($P = 0.053$).

Sixty-two (83%) of the cases and 65 (87%) of the controls had two TcB measurements obtained before discharge. The calculated hourly rate of rise between the two measurements was 0.22 ± 0.07 mg per 100 ml (3.8 ± 1.2 μmol l⁻¹) in the cases and 0.13 ± 0.07 mg per 100 ml (2.2 ± 1.2 μmol l⁻¹) in the controls ($P < 0.0001$). We also evaluated whether the rate of rise of the TcB values or the last TcB value measured before discharge might be better predictors of a case than the maximum TcB. As not every infant had two TcB levels measured, it was not possible to include

the entire sample in the calculation of the rate of rise. We therefore assumed a cord TcB level of 1.7 mg per 100 ml based on published values of mean bilirubin levels in the cord blood.^{12–14} When this was done, gestational age groups, feeding method, the calculated rate of rise and birth weight all entered the model and provided a *c*-statistic for the ROC curve of 0.903 (not significantly different from our original model $P = 0.316$). When the last measured TcB was substituted for the peak TcB, the same variables entered the model (gestational age, feeding and percentile groups) with a *c*-statistic for the ROC curve of 0.873, not significantly different from either of the earlier calculated ROC curves ($P = 0.292$).

Discussion

Several studies have shown good correlations between TcB and TSB measurements using instruments currently available in the United States^{15–18} and predischarge TcB measurements are recommended by the AAP as one method for assessing the risk of subsequently developing, or not developing hyperbilirubinemia.¹ Keren *et al.*,⁸ in a prospective cohort study, found that combining the predischarge TcB measurement with the gestational age (compared with the TcB measurement alone) improved the accuracy of the prediction of a subsequent TSB rising to within 1 mg per 100 ml of the hour-specific phototherapy treatment threshold recommended by the AAP.¹ Nevertheless, in that study, a combination of clinical risk factors was as predictive as combining the TcB with gestation and percentage of weight loss⁸. The demographic data for our cases are typical of a hyperbilirubinemic population, with a preponderance of infants at ≤ 38 weeks gestation and who were breastfed.

Our study has some strengths and limitations. Its strength is that it includes an entire population of newborn infants and their predischarge TcB measurements, obtained over a 32-month period. The limitations include the possibility of bias introduced by variations in management and follow-up. There was no standardized approach to the management of this cohort. Some 85% of our infants are followed by 236 private pediatricians and the balance by residents and pediatricians in the hospital follow-up clinic. It is likely that the predischarge TcB measurements influenced the subsequent surveillance and management of some infants. As the identification of post-discharge hyperbilirubinemia depended on the clinical judgment of the physician providing follow-up, some infants who had a TSB ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$) might not have had a TSB measurement and could have been missed. If the predischarge TcB level was low, some infants might not have been followed closely and subsequent hyperbilirubinemia could have been missed. Although this is possible, it is unlikely, because compliance among our attending pediatricians for follow-up according to the AAP Guidelines is very high and is monitored continuously as part of our quality improvement program. During the period of this study our quality improvement monitor showed that 94% of infants discharged

before 72 h were scheduled to be seen within 2 days of discharge and 98% within 3 days (unpublished data) so that it is unlikely, but not impossible, that an infant with a TSB ≥ 17 mg per 100 ml would not have had a measurement of TSB.

We chose the peak predischarge TcB as one of our main predictors because that is what has been used in earlier studies.^{8,15} Nevertheless, it could be argued that the TcB measurement obtained just before discharge or, the rate of rise of the TcB might be more predictive than the maximum TcB. We evaluated both of these possibilities and found that they did not improve the prediction of significant hyperbilirubinemia. To be user friendly, the prediction model should be as parsimonious as possible. In addition, with current the length of stays, the vast majority of the last measured TcBs is likely to represent the maximum TcB (Figure 1). Even if this is not the case, the differences will be small and, as we found, unlikely to affect the results. Using the rate of rise requires an additional calculation and brought another variable (birth weight) into the model. In contrast, if two or more TcB measurements are obtained, a visual estimate showing that the rate of rise is crossing percentiles (Figure 1) suggests an increase in bilirubin production and the importance of closer monitoring.

The number of infants readmitted (0.65% of infants discharged) is consistent with other recent studies¹⁹ as well as our data published earlier.²⁰ In our earlier study of 29 934 infants born between 1994 and 1998, only 0.4% were readmitted for phototherapy.²⁰ Finally, some of our pediatricians use home phototherapy. Although this would not have prevented us from identifying infants with TSB levels ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$) from the laboratory database, home phototherapy is usually instituted at lower TSB levels (than in hospitalized infants), and is likely to prevent the TSB in some infants from reaching 17 mg per 100 ml. Thus, the total number of infants readmitted with TSB levels ≥ 17 mg per 100 ml ($291 \mu\text{mol l}^{-1}$) is a minimum estimate.

There are benefits and potential hazards associated with the routine measurement of TSB or TcB, before discharge, in all newborns. As we and others have shown, a predischarge TcB or TSB can help predict the possibility of subsequent hyperbilirubinemia^{2–6,21} and, when combined with clinical risk factors, the accuracy of prediction is significantly improved.^{7,8} The other important benefit is that the TSB or TcB, when compared with the hour-specific nomogram, provides a quantifiable and real-time measure of the degree of hyperbilirubinemia in the infant and, in addition to its predictive value, alerts the caregiver to consider the implications, together with the clinical risk factors, of this bilirubin level: Should the TSB be repeated; is discharge appropriate; when should the follow-up take place; is the infant a candidate for phototherapy? These are some of the questions that need to be posed for every infant, before discharge, whether or not a TcB or TSB is done. In addition, there is some evidence that universal predischarge screening can reduce the number of infants

who subsequently develop a TSB of >20 mg per 100 ml.^{22,23} Whether or not this will have any effect on the incidence of bilirubin encephalopathy remains to be seen.

The risks of such a program, however, should not be ignored. It is possible that predischarge screening will lead to additional and unnecessary testing and inappropriate use of phototherapy, and there is some evidence that this has occurred.²³ More testing and treatment could have a negative effect on breastfeeding. Finally, a low predischarge TSB or TcB can produce a false sense of security leading to inadequate follow-up or failure to obtain a TSB in a jaundiced infant at follow-up. Infants who have a low predischarge TSB or TcB can, nevertheless, develop hyperbilirubinemia and require phototherapy. In our study, five infants had a predischarge TcB below the 50th percentile but nevertheless developed a TSB >17 mg per 100 ml although none exceeded 20 mg per 100 ml.

Similar to the findings of Keren *et al.*,⁸ and Newman *et al.*,⁷ we found that simply combining the predischarge TcB measurement with the infants' gestational age provided a good prediction of the risk of the subsequent development of hyperbilirubinemia. When exclusive breastfeeding was also included, the prediction was slightly, although not significantly, better.

As more than 80% of infants had at least two TcB measurements in the hospital, the calculated rate of rise (or visual inspection of the values plotted on a nomogram) can help to identify infants in whom the TcB is rising more rapidly than expected. The rate of increase of TcB in the cases (0.22 mg per 100 ml per h) is identical to the rate in the first 24 h in our population at the 95th percentile⁹ (Figure 1) and is similar to the high-risk track in the Bhutani nomogram.² Thus, infants whose TcB is increasing at >0.2 mg per 100 ml per h deserve close observation.

We conclude that routine predischarge TcB measurements, obtained by the nursing staff in a busy nursery, when combined with the infant's gestation and the method of feeding, provide a simple and relevant measure of the risk for the subsequent development of hyperbilirubinemia.

Conflict of interest

Dr Maisels reports receiving consulting fees from Dräger Medical and grant support from Dräger Medical and InfaCare. He has also served as an expert witness in cases of kernicterus.

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