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Urgent Clinical Need for Accurate and Precise Bilirubin Measurements in the United States to Prevent Kernicterus

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Kernicterus, a preventable brain injury resulting from severe neonatal jaundice, has reemerged in the US *(1–3)*. Newborn jaundice, a usually benign condition that typically resolves with supervision and appropriate nutritional intake, can progress to severe hyperbilirubinemia in ~8–10% of healthy newborn infants. Severe hyperbilirubinemia may need treatment with phototherapy. Some newborns discharged as healthy have developed severe hyperbilirubinemia after discharge and succumbed to serious and often irreversible posticteric sequelae.

Kernicterus, as described in neonates, refers to the icteric (yellow) staining of the basal ganglia, specifically the globus pallidus *(4)*. The voluntary Pilot Kernicterus Registry now recognizes a syndrome of bilirubin-induced neurologic dysfunction (BIND), which includes kernicterus in its most severe acute and chronic forms. Using the Registry eligibility criteria, Johnson et al. *(1)* have documented the reemergence of kernicterus in a population of term and near-term "healthy" infants after its near eradication following prevention of Rh sensitization and widespread availability of phototherapy.

The common insult in all cases of BIND results from a total serum bilirubin (TSB) concentration that exceeds the infant's neuroprotective defenses and leads to neuronal injury, primarily in the basal ganglia, central and peripheral auditory pathways, hippocampus, diencephalon, subthalamic nuclei, midbrain, cerebellum and pontine and brain-stem nuclei for oculomotor function and for respiratory, neurohumoral, and electrolyte control. The manifestations of acute bilirubin encephalopathy and chronic kernicteric sequelae may be minimal to severe and occur as various combinations (or possibly, isolated findings) of extrapyramidal disorders, neuromotor abnormalities, sensorineural hearing loss, and visual disability. Although not yet demonstrated, some experts believe that milder and subtler neurologic manifestations of BIND exist.

The current reemergence of kernicterus in babies discharged as healthy from US hospitals represents a crisis of credibility and calls into question our ability to measure TSB with accuracy and precision. There is a need to address the societal demand for patient safety and to respond to calls for a public health policy to better manage a preventable injury. After reviewing lapses in care and their root causes, we provide here empiric evidence on which to model a practical, family-centered, system-based approach to monitor and manage hyperbilirubinemia to prevent acute kernicterus and the clinical spectrum of BIND.

After a workshop on Strategies for a System-wide Approach in the Management of Hyperbilirubinemia to Prevent Kernicterus [held at Pennsylvania Hospital with the joint sponsorship of Parents of Infants and Children with Kernicterus (PICK) in February 2001], several organizations reviewed their roles, and suggestions for action were considered. Alerts and updates for prevention of severe hyperbilirubinemia and kernicterus were subsequently disseminated by The Joint Commission for Accreditation of Hospital Organizations *(2)*, the CDC *(3)*, and the American Academy of Pediatrics *(5)*. The National Quality Forum (at the Agency for Healthcare Research for Quality) has since declared kernicterus and/or TSB concentrations >300 mg/L (30 mg/dL, or 513 μmol/L) as a "never-event". It is the only pediatric condition on this list *(6)*.

Hyperbilirubinemia in Healthy Newborns

All healthy newborns are at potential risk of kernicterus if their newborn jaundice is unmonitored and/or managed inappropriately. When a TSB concentration is measured to assess the severity of jaundice, the first question from

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the family to the pediatrician is invariably, "what is a normal value?" A "normal" TSB concentration should be assessed in relation to the newborn's postnatal age in hours, and the severity of the jaundice should be expressed by percentiles *(7, 8)*. An hour-specific bilirubin percentile nomogram has been developed using bilirubin data from term and near-term infants without evidence of hemolytic disease or other illness (Fig. 1). TSB concentrations may be tracked on such a nomogram, similar to the tracking of amniotic fluid absorbance on Liley curves *(9)*. TSB concentrations plotted on this nomogram before a newborn's discharge are predictive of the degree of risk for subsequent hyperbilirubinemia. In term or near-term infants, the nomogram is helpful in identifying infants with early hyperbilirubinemia (those in the high-risk zone or with a rapid increase) who require further evaluation for the cause of the hyperbilirubinemia. When an infant has known hemolysis, the nomogram may potentially be used as a useful clinical guide for tracking and clinical management. The thresholds for intervention (170 and 200 mg/L beyond 72 h) in the American Academy of Pediatrics guidelines *(10)* correspond to the 95th and 99th percentiles in the bilirubin nomogram.

Relationship between Hyperbilirubinemia and Kernicterus

The only published prospective study that has shown an association between TSB concentrations and occurrence of acute bilirubin-related encephalopathy is that reported by Mollison and Cutbush *(11)* in a follow-up report of untreated infants with hyperbilirubinemia and hypoalbuminemia attributable to Rh hemolytic disease. However, it is now well recognized that kernicterus can occur in a well baby with severe hyperbilirubinemia not attributable to hemolysis *(1, 5)*. On the basis of these and the historical data, TSB concentrations >300 mg/L carry a decidedly higher risk of kernicterus, although some infants may escape overt injury. More recent data from the Pilot Kernicterus Registry *(1)* indicated that although the median TSB concentration at readmission was 350 mg/L (35 mg/dL, or 600 μmol/L), 7 of the 61 infants with classic signs of acute kernicterus had peak TSB concentrations <300 mg/L (range, 215–295 mg/L), or 513 μmol/L, at readmission at age 2.5–7 days. All of these TSB concentrations, including those of the seven babies with TSB <300 mg/L, were well into the high-risk zone and above the 99.9th percentile for postnatal age in hours in the nomogram. From a clinical perspective, we hypothesized that these infants had hyperbilirubinemia, regardless of recognition of jaundice. On review, we found that a majority of these kernicteric infants (based on actual predischarge TSB values or an estimated progression of TSB values) had a predischarge TSB concentration above the 75th percentile for age in hours. Using the bilirubin nomogram, we have categorized well babies who have a predischarge TSB above the 75th percentile for age in hours as having a clinically significant bilirubin load attributable to increased hemolysis and/or unrecognized impaired bilirubin clearance *(12–14)*. Additional increases in the bilirubin load associated with a rapid increase in TSB (>2 mg · L^{-1} · h^{-1}) further increase the risk of extreme hyperbilirubinemia and kernicterus. We believe that predischarge identification of a moderately at-risk population (transcutaneous bilirubin or TSB above the 75th percentile) helps in targeting attention to that smaller group of well babies in whom strategies for kernicterus prevention can be implemented efficiently, effectively, and safely *(7, 8, 14, 15)*.

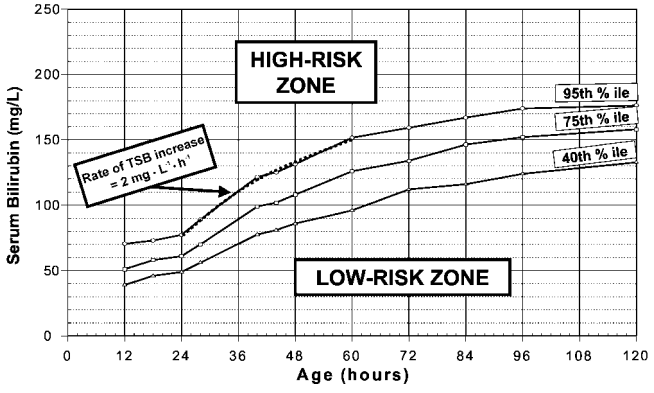

Fig. 1. Hour-specific bilirubin nomogram.

Adapted from Bhutani et al. *(7)*. The *dashed line* indicates a TSB increase of 2 mg · L^{-1} · h^{-1}.

Incidence of Severe and Extreme Hyperbilirubinemia

One of the safest practices still prevalent at most clinical laboratories is the "panic" call to the attending physician for TSB concentrations >200 mg/L (342 μmol/L) while the laboratory verifies the result *(16)*. Technicians who make these calls are to be applauded for their efforts to ensure timely and efficient management of extreme hyperbilirubinemia. Adjectives to gauge the severity of hyperbilirubinemia have been anecdotal. We have used "severe" for TSB concentrations above the 95th percentile for age in hours, "extreme" for TSB values ≥250 mg/L (428 μmol/L; above the 99.9th percentile), and "dangerous" for values ≥300 mg/L (513 μmol/L; above the 99.99th percentile). These TSB thresholds in seemingly healthy near-term and term infants provide potentially useful surrogate indices of concern (Table 1).

The incidence of babies who may develop extreme TSB concentrations (>250 mg/L, or 428 μmol/L) and brain damage if prompt treatment is not instituted to rapidly decrease the systemic bilirubin load (deemed a "close call") has been calculated by us from two observational studies and ranges from 0.14% to 0.16%. In Table 1, we compare the pooled incidence of severe and extreme hyperbilirubinemia based on studies that used predischarge screening for jaundice or predischarge TSB screening. From these data, we have estimated that 1 in 700 well newborns can develop extreme hyperbilirubinemia; these infants can be at major risk for kernicterus if there are no failsafe, system-based protocols. The potential incidence

Table 1. Comparison of combined data obtained in infants with predischarge screening based primarily on visual assessment of jaundice *(18)* and infants followed based on predischarge bilirubin screening *(7, 8, 14, 15)*.[a]

Postdischarge TSB, mg/L	Estimated incidence	Mean % based on retrospective data reviewed in a population without predischarge bilirubin screening (n = 54 547)	Prospective data obtained from several studies using predischarge bilirubin screening	
			Sample size, n	Mean (95% CI),[b] %
>170	1:10	9.50	5835	8.33 (6.40–10.3)
>200	1:70	1.39	11 683	0.94 (0.06–1.82)
>250	1:700	0.16	33 913	0.0 (−0.01 to 0.01)
>300	1:7000	0.03	33 913	0.0 (0–0)

[a] Prospective validation studies are needed to assess the ability and cost-effectiveness of mandatory universal bilirubin screening to prevent adverse effects of severe neonatal hyperbilirubinemia.

[b] CI, confidence interval.

of a never-event or TSB concentration >300 mg/L (513 μmol/L; above the 99.99th percentile) is 1 in 10 000 in a population that is well managed by a mature Health Maintenance Organization *(17, 18)*.

We believe that universal screening for hyperbilirubinemia has the potential to ensure patient safety by reducing the incidence of close calls for never-events and adverse events attributable to newborn jaundice so as to achieve a "zero tolerance of kernicterus". Over the past decade (1992–2003) at Pennsylvania Hospital, an urban, semiprivate, community-oriented hospital that provides universal bilirubin screening and system-based neonatal bilirubin management as a standard of care, no never-events occurred, and the rate of close calls was only 1 in 15 000 well infants *(19)*.

BIND in Sick and Preterm Newborns

TSB concentrations are known to be poor predictors of bilirubin toxicity in the sick or preterm infant. Binding of bilirubin to albumin, which is thought to decrease the entry of bilirubin into the brain, is decreased by conditions such as near-term (35 to <38 weeks) or preterm (<34 weeks) gestation, hypoalbuminemia, disruption of the blood–brain barrier (with asphyxia and birth trauma), and hemolysis (intra- or extravascular). Infection and hypoglycemia predispose a newborn to BIND at lower TSB concentrations. It has been hypothesized that a more appropriate predictor of neurotoxicity would be a measure of unbound, or "free" bilirubin, as recommended by several investigators in a recent review by Poland *(20)*. However, no such tests have been validated or widely used.

Pending availability of evidence-based data, neonatologists have defined (Table 2) lower TSB thresholds for intervention in infants in neonatal intensive care units than for healthy newborns *(21, 22)*. Because increased non-protein-bound bilirubin concentrations (>80 μg/L) have been associated with increased risk of BIND *(21)*, the bilirubin:albumin ratio can be used because it provides an indication of bilirubin binding to albumin.

Table 2. Summary of existing recommendations for the management of hyperbilirubinemia in sick term and preterm infants [adapted from Refs. *(21, 22)*].

Infant weight, g	TSB concentration cutoffs, mg/L: Initiation of intensive phototherapy[a]	TSB concentration cutoffs, mg/L: Double blood volume exchange transfusion (190 mL/kg)
Preterm infants		
<1000	30–60	A preventive approach is essential such that the need for exchange transfusion is minimized. In presence of suspicious neurologic signs, prepare to perform an exchange transfusion or when TSB concentrations are >50 mg/L above the values listed as cutoffs
1001–1500	60–80	
1501–2000	80–100	
2001–2500	100–120	
>2500	120–140	
Term infants		
>2500	120–150	180–200

[a] In view of diminished bilirubin-binding ability of albumin at age <72 h (even in healthy preterm infants), the lower thresholds for initiation of intensive phototherapy are suggested for infants <72 h of age.

In conclusion, the reemergence of kernicterus in healthy term infants is a public health issue, and the clinical concerns for BIND in the sick and preterm neonatal population challenge us. We recommend that newborn jaundice management be safe, family centered, practical, and system based. Immediate implementation of system-based preventive solutions is crucially dependent on accurate, precise, and universally available measures of hyperbilirubinemia. Care of the vulnerable and sick infant could be optimized by better techniques to assess neurotoxic potential of bilirubin, such as measures of bilirubin-binding reserve of albumin. In case we forget, kernicterus is preventable, and severe hyperbilirubinemia is both preventable and treatable.

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