

Editorial Commentary

Title: Acute Bilirubin Encephalopathy: Does Intervention Influence Outcome?

Author: Vinod K. Bhutani, MD, FAAP

Professor of Pediatrics

Department of Pediatrics

Division of Neonatal and Developmental Medicine

Stanford University School of Medicine

and Lucile Packard Children's Hospital

Stanford, CA

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Contact Address

Vinod K. Bhutani, MD, FAAP

Stanford University School of Medicine

Department of Pediatrics

Division of Neonatal and Developmental Medicine

300 Pasteur Drive, Grant Building: S-226.

Stanford University, Stanford, CA 94305

Telephone: 650-723-5711

E-mail: bhutani@stanford.edu

Acute Bilirubin Encephalopathy (ABE): Does Intervention Influence Outcome?

Vinod K. Bhutani, MD, FAAP

Case History 1

A Hispanic late preterm male infant born at 36 weeks' gestation was discharged at a postnatal age of 29.5 hours as a "healthy" newborn. He had the following risk factors for subsequent severe hyperbilirubinemia: (a) Pitocin induction of labor; (b) facial bruising; (c) large size for gestational age with a birth weight of 3310 g (at 95th percentile); (d) skin color and pigmentation that added to the difficulty of recognizing jaundice; (e) breast feeding with suboptimal intake. In addition, when he was 23 hours of age, the physician performed the discharge examination. At discharge, no appointment was made for early follow-up (within 2 days of discharge) for breast-feeding, neonatal well-being, jaundice, and weight loss but he was scheduled for a 2-week visit. During the first week after birth, by age 132 hours, he became symptomatic with onset of lethargy and poor feeding at home. When he was brought to an Emergency Room at age 142 hours, the nurse documented that he was listless and irritable. He also was febrile with a temperature of 103.2°F. The nurse's examination indicated that the infant was extremely jaundiced to his feet. A total serum bilirubin (TSB) level was obtained at age 143 hours and reported to be 33.7 mg/dL. Clinical neurologic signs progressed to hypertonicity and opisthotonos by age 146 hours. He was transferred to the NICU at age 146 hours, and he was noted to be in an opisthotonic posture by the receiving NICU nurse. Two hours after phototherapy was initiated, the TSB was 26.6 mg/dL at age 148 hours. Progressive changes in neurologic signs were recorded between ages 149 to 152 hours. At age 153 hours, the TSB level was 25.5 mg/dL after about 5.5 hours of phototherapy and just prior to initiation of an exchange transfusion. The infant underwent two exchange transfusions. He subsequently sustained irreversible and posticteric sequelae of chronic athetoid cerebral palsy and hearing impairment consistent with a clinical diagnosis of kernicterus. The diagnosis was confirmed by magnetic resonance imaging (MRI) during the neonatal period and during infancy.

During the 11-hour interval from admission to the emergency room until the initiation of exchange transfusion, the infant was exhibiting progressive clinical findings consistent with known signs of acute of bilirubin encephalopathy (Table 1).

***The Dilemma:** A clinician managing a severely hyperbilirubinemic infant with ABE has to decide whether a potentially life-threatening exchange transfusion to prevent or minimize the chronic posticteric sequelae of bilirubin-induced neurologic dysfunction (BIND) should be undertaken because the signs and symptoms would suggest that bilirubin has already crossed the blood-brain barrier.*

***The Rationale for Current Strategy:** Clinical options for safe and optimal but emergency management of ABE raise the following clinical questions and underscore the basis for a “crash cart” approach.*

Clinical Questions

- A. Is there scientifically reliable evidence that phototherapy or exchange transfusion can prevent or ameliorate bilirubin-induced neurologic dysfunction (including kernicterus)?
- B. Is there sufficient evidence to conclude that early use of phototherapy with or without exchange therapy in an infant with severe hyperbilirubinemia can prevent or ameliorate kernicterus?
- C. Is the outcome of an infant with acute bilirubin encephalopathy different if phototherapy and/or exchange transfusion is provided sooner?
- D. Are there alternative causes of a clinical condition that is similar in manifestation to ABE and that would avoid the need for specific bilirubin reduction therapies?

Background: The classic signs of ABE in the severely hyperbilirubinemic term infant (Figure 1), as described by Van Praagh,¹ Jones,² Volpe,³ and Perlstein,⁴ include increasing hypertonia, especially of extensor muscles, with retrocollis and opisthotonos, in association with varying degrees of drowsiness, poor feeding, hypotonia, and alternating tone. These signs can be described in terms of the infant's mental status, muscle tone, and cry. To facilitate the accurate documentation of progression of ABE, Table 1 provides a schema for grading the severity of ABE. This has been used as a clinical tool in a retrospective study and may help clinicians understand the progression of BIND.⁵ Increasing scores are indicative of worsening BIND and may be of prognostic value.

The earliest signs of ABE are subtle and nonspecific and may be missed. They need to be elicited by direct questioning of parents and close clinical observation. During the early phases of BIND, prompt and effective interventions can prevent chronic kernicteric sequelae.⁵ BIND abnormalities with progression to scores between 4 and 6 often are reversible. These signs include early hypertonia and retrocollis, which increase in severity and are usually accompanied by a shrill cry and unexplained irritability alternating with increasing lethargy. Advanced signs are marked by cessation of feeding, bicycling movements, inconsolable irritability and crying, possible seizures, fever, and coma. These are late findings and ominous predictors of the likelihood of severe kernicteric sequelae, even with intensive treatment. The extent of brain

damage is likely to be reduced by rapid reduction of the bilirubin load (by a combination of intensive phototherapy and exchange transfusion). The rate of progression of clinical signs depends on rate of bilirubin rise, duration of hyperbilirubinemia, adequacy of albumin-binding reserves, level of unbound bilirubin, host susceptibility, and presence of co-morbidities. Death from acute kernicterus is due to respiratory failure and progressive coma or intractable seizures.

Preventive management for ABE is the most effective of clinical strategies.⁶⁻⁸ Implementation needs to be a system-based approach that allows for individualized care to accommodate the clinician's concerns, informed participation of the family, and monitoring of the progression of hyperbilirubinemia of at-risk newborns. The practice parameters developed by the American Academy of Pediatrics (AAP) provide useful guidelines for the management of term healthy newborns provided these are followed diligently (see Case History 2, Table 1). These include a “crash-cart” approach to prevent or minimize sequelae of acute bilirubin encephalopathy.⁸ The timing of bilirubin reduction strategies and differential diagnosis of ABE has an impact on outcome. Because randomized controlled trials are not ethically feasible, the available evidence is outlined in this commentary for each of the clinical questions listed above with the case history.

Review of Evidence for the Rationale for a Crash-Cart Approach

Clinical Question A. *Is there scientifically reliable evidence that phototherapy or exchange transfusion can prevent or ameliorate ABE (acute kernicterus)?* There is sufficient and reliable evidence that a “crash-cart” approach prevents or minimizes sequelae of acute bilirubin encephalopathy. Moreover, in infants with acute bilirubin encephalopathy, exchange transfusion (with and without phototherapy) can prevent or minimize the chronic sequelae.

In their reiteration of 1994 guidelines,⁶ the more recent 2004 AAP guidelines⁷ state that “most jaundice is benign but, because of the potential toxicity of bilirubin, newborn infants must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus. The focus of this guideline is to reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy by providing a framework

for the prevention and management of hyperbilirubinemia in newborn infants ≥ 35 weeks of gestation.” For every infant, the guidelines recommend several preventive strategies as well as a treatment guideline for “phototherapy or exchange transfusion to prevent the development of severe hyperbilirubinemia and, possibly, bilirubin encephalopathy (kernicterus).” On the basis of a comprehensive review of the evidence including a comprehensive literature review (of nearly 5000 original research articles in the English language) by the New England Medical Center Evidence-based Practice Center and commissioned by the Agency of Healthcare Research and Quality (AHRQ),⁹ there is sufficient reliable and convincing historical, investigative, and clinical literature to state that “in the early phase of acute bilirubin encephalopathy, severely jaundiced infants become lethargic and hypotonic and suck poorly. The intermediate phase is characterized by moderate stupor, irritability, and hypertonia. The infant may develop a fever and high-pitched cry and this may alternate with drowsiness and hypotonia. The hypertonia is manifested by backward arching of the neck (retrocollis) and trunk (opisthotonus).” The guidelines go on to describe evidence that “an emergent exchange transfusion at this stage might, in some cases, reverse the central nervous system changes.” Furthermore, a review of the literature indicates that in the absence of definitive attempts to emergently reduce the bilirubin load, acute bilirubin encephalopathy progresses to an advanced phase, “in which central nervous system damage is probably irreversible, is characterized by pronounced retrocollis-opisthotonus, shrill cry, no feeding, apnea, fever, deep stupor to coma, sometimes seizures, and death.”

Clinical Question B. *Is there sufficient evidence to conclude that early use of phototherapy and/or exchange therapy in an infant with severe hyperbilirubinemia can prevent or ameliorate kernicterus?* There is sufficient and immutable laboratory and clinical literature that the timely use of phototherapy and/or exchange transfusion used in infants with severe hyperbilirubinemia can prevent kernicterus.

Overall, current laboratory and clinical data indicate that “bilirubin damages brain tissue cells via necrosis and apoptosis, either alone or in combination, in a neuroanatomic distribution dependent on the amount, duration, and developmental timing of exposure of sensitive brain tissue to free bilirubin.” As described by Shapiro,¹⁰ “the extent of neuronal injury depends on (1) the amount and duration of exposure to free bilirubin (high level, short duration exposure not necessarily the

same as lower level, long duration exposure), (2) the susceptibility of the developing nervous system, (3) the relative amount of necrosis vs. apoptosis produced, and (4) whether surviving neurons will be functionally normal or more susceptible to other stressors either at the time of hyperbilirubinemia or afterwards.”

The risk of neuronal injury by bilirubin is primarily determined by the concentration of unbound or “free” unconjugated bilirubin and hydrogen ion in blood. Unconjugated free bilirubin can be measured indirectly or estimated by calculating the molar ratio of total serum bilirubin to albumin. Bilirubin enters brain tissue as free bilirubin when the blood-binding capacity is exceeded or from bilirubin-binding sites on albumin. The blood-brain barrier has long been considered to play a role in protection of the brain from bilirubin toxicity. In contrast to other reservoirs for bilirubin binding, the brain is unique in having a barrier that slows the equilibrium between plasma and brain. If the blood-brain barrier is disrupted, bilirubin-albumin moves rapidly into the extracellular space of brain, and at sufficiently high free bilirubin levels, bilirubin will produce immediate global neurotoxicity. The blood-brain barrier acts as a pump through ATP-dependent export by transporter molecules to remove free bilirubin from the brain. The blood-brain barrier is quite permeable to free bilirubin, with single-pass uptakes estimated as high as 28% in rats. Bilirubin uptake may be increased by alterations in blood-brain barrier permeability to free bilirubin or albumin (such as respiratory distress), prolonged transit time (e.g., increased venous pressure), an increase in blood flow (e.g., hypercarbia), or an increase in the dissociation rate (e.g., as infants become sicker).

Because the transit time is short, about 1 second, and the bilirubin-albumin dissociation rate is slow, there is little time to replenish the unbound bilirubin transported across the brain capillary. At a given free bilirubin level, brain uptake of bilirubin could theoretically be facilitated by a high TSB, simply because there would be a larger plasma pool to replenish the extracted free bilirubin. Robinson and Rapoport¹¹ concluded that the slow dissociation rate precludes rapid replenishment of bilirubin removed and that brain uptake is largely governed by the TSB until the primary bilirubin binding sites are saturated. More recent evidence indicates that bilirubin neurotoxicity, occasionally irreversible, will occur before primary sites are saturated. Because of the slow transport of bilirubin across the blood-brain barrier, time of exposure to high free bilirubin may be critical in determining the magnitude of brain load and

toxicity. In primates, several hours of exposure to a very high TSB and free bilirubin are usually required to create neurotoxicity, and even longer exposure is needed to produce nuclear staining. Most cases of kernicterus in term babies occur at several days of age and often after the TSB has been very high for an extended period of time.

According to Watchko,¹² net transport of bilirubin across the blood-brain barrier is also influenced by the energy-dependent multidrug-resistant transporter, or P-glycoprotein. This is one of several transporters involved in cellular efflux of xenobiotics, and it is expressed in capillary endothelial cells of the blood-brain barrier, astrocytes, and the choroid plexus. In a study by Watchko et al,¹³ brain uptake of bilirubin in knockout mice infused with high concentrations of bilirubin was twice that of controls. Inhibition of P-glycoprotein potentiates bilirubin-induced apoptosis in a human neuroblastoma line and increases bilirubin content in brains of young adult rats (measured at very high TSB). Other potential cellular defense mechanisms include mitochondrial bilirubin oxidase, other transporters, and anti-apoptosis factors. The extent to which these cellular defense mechanisms contribute to variations in sensitivity to the toxic effects of bilirubin is a subject of ongoing research. The cellular mechanisms of early reversible bilirubin toxicity at low free bilirubin exposure (i.e., behavioral changes and prolongation of inter-peak latencies in the auditory brainstem response) are unknown, but exposure of neurons to high levels of free bilirubin will produce apoptosis and/or necrosis associated with mitochondria dysfunction, possibly through bilirubin disruption of the proton gradient required for oxidative phosphorylation. Watchko's recent review of *in vitro* studies done at clinically relevant free bilirubin concentrations indicates that free bilirubin impairs mitochondrial function and viability of astrocytes to induce apoptosis in neurons.¹⁴ Higher concentrations of free bilirubin impair mitochondrial function and cellular proliferation in neurons, and inhibit uptake of glutamate in astrocytes. Another important determinant of toxicity is neuronal susceptibility. Shapiro¹⁵ examined cerebella of jaundiced Gunn rats made toxic at various developmental ages and found that neurons undergoing differentiation at the time of exposure were the most susceptible to cell death, while those that were slightly more or less mature showed only transient changes or seemed to be less sensitive. These data indicate that there is a critical or sensitive period when elevated bilirubin may be most toxic to neuronal development.

In summary, scientific evidence from several studies indicates that bilirubin kills specific neurons by causing necrosis; *in vitro* studies show that it induces apoptosis and support *in vivo* observations in older literature showing neuroanatomic changes consistent with apoptosis. Evidence also suggests that bilirubin interferes with intracellular calcium homeostasis by altering function and expression of calcium/calmodulin kinase II, by selectively decreasing calcium-binding proteins in susceptible brainstem areas and increasing intracellular calcium in cultured neurons, and by sensitizing the cell to other injuries or triggering apoptosis. Bilirubin may also kill cells by causing neuronal hyperexcitability, perhaps via excitatory amino acid neurotoxicity, or it may have other membrane or neurotransmitter effects. Finally, it may act by interfering with mitochondrial respiration and energy production. Thus, interventions that reduce bilirubin exposure to the neonatal brain have been shown to prevent bilirubin neurotoxicity.

Clinical Question C. *Is the outcome of an infant with acute bilirubin encephalopathy different if phototherapy and/or exchange transfusion is provided sooner?* The timing of bilirubin reduction strategies impacts the outcome of severe hyperbilirubinemia complicated by ABE. Early implementation of strategies to rapidly and effectively reduce the excessive bilirubin load prior to the onset of neurologic signs, in all likelihood, would prevent chronic posticteric sequelae or kernicterus. Once the clinical signs of bilirubin neurotoxicity are evident, emergent intervention to expeditiously reduce the bilirubin load is the only known recourse in clinical practice. To date, exchange transfusion remains the only known clinical option.

Even though there is no predictive evidence that a specific bilirubin level will or will not cause neurotoxic damage, the critical bilirubin level, in any healthy baby, is influenced by postnatal age, maturity within the range of term gestational age, duration of hyperbilirubinemia, and rate of TSB rise.¹⁶ The only prospective study that has shown an association between TSB levels and occurrence of ABE is that reported by Mollison and Cutbush¹⁷ in a 1954 follow-up report of babies with hyperbilirubinemia and hypoalbuminemia due to Rh hemolytic disease. These data are from over four decades ago and the sample size is small (N=60) and applicable to babies with severe hemolytic disease. Presence of co-morbidities such as near-term gestation (35 to <38 weeks' gestation), hypoalbuminemia, disruption of the blood-brain barrier (due to asphyxia or trauma), hemolysis (intravascular or extravascular), factors that interfere with albumin binding of bilirubin, infection, and hypoglycemia predispose a newborn to BIND at

lower TSB values. A number of investigators, as noted by Poland,¹⁸ have presented evidence that unbound, or “free,” bilirubin is an appropriate predictor of neurotoxicity. At present, there are no commercial assays for albumin-binding reserve or unbound bilirubin in the United States. Both U.S. and Japanese studies have suggested that levels greater than 0.86 $\mu\text{g/dL}$ of unbound bilirubin are associated with an increasing risk of kernicterus.

The questions—(a) does TSB identify healthy infants at risk for kernicterus with values greater than 20 mg/dL? and (b) is there a specific TSB in patients who develop kernicterus?—have been addressed by clinical consensus (AAP guidelines) and review of the literature. Data relating TSB to kernicterus in otherwise healthy term infants are extensive, but final conclusions are unlikely because of logistic and ethical constraints in conducting prospective outcome research with controlled intervention and inadequate documentation of TSB prior to readmission with symptoms. Newman and Maisels conducted an extensive analysis of available data in 1990, dominated by a reanalysis of outcome data from the Collaborative Perinatal Project, a multicenter cohort study of more than 54,000 pregnancies between 1959 and 1965 in which peak bilirubin values were obtained in all study infants.¹⁹ The original study reported that “infants without hemolysis are not at risk of mental or physical impairment until serum bilirubin levels rise well above 20 mg/dL” and assumed a linear relationship between TSB and outcome. In a subsequent study of outcome at 7–8 years of age, a significant association between hyperbilirubinemia and abnormal or suspicious neurologic abnormalities was found when infants with neonatal TSB levels below 10 mg/dL were compared with those with TSB levels above 20 mg/dL.²⁰ More recent studies have also reported that mild neurologic abnormalities are more frequent in babies with high bilirubin levels evaluated at ages ranging from 12 months to 15 years.^{21–23}

Retrospective studies of large data bases are limited by their study designs, sample definitions, and lack of a specific objective outcome that can be related to a uniformly measured predictive test. Three retrospective chart reviews of babies readmitted with severe hyperbilirubinemia provide additional evidence of risk. Newman et al²⁴ reviewed the outcome of all infants with a TSB greater than 30 mg/dL readmitted to a large health care maintenance organization over a 4-year period. In 11 patients, the TSB ranged from 30.7 mg/dL (525 $\mu\text{mol/L}$) to 45.5 mg/dL (778 $\mu\text{mol/L}$). None had acute symptoms of encephalopathy, and 9 were reported

to be normal when evaluated at ages ranging from 18 months to 5 years. It is unclear whether any infant with a diagnosis of kernicterus may have been excluded from the study sample. Of the infants reported, one died of SIDS and another was receiving speech therapy but was otherwise normal. Ahlfors and Herbsman²⁵ examined 8 term infants with TSBs ranging from 28.3 to 34.2 mg/dL. One infant with a TSB of 32.1 mg/dL failed an ALGO hearing screen, and a second, admitted with a TSB of 33.1 mg/dL, had acute symptoms of encephalopathy, seizures, and apnea and died, with pathologic kernicterus found at autopsy. The infant had G6PD deficiency but no evidence of hemolysis or infection. The remaining infants were asymptomatic, but follow-up was not reported. Harris et al²⁶ reported 6 readmissions with TSB greater than 25 mg/dL and acute toxicity at their hospital, but they did not state the number of admissions with TSB greater than 25 mg/dL without symptoms during the same time interval. Admission TSB ranged from 26.4 to 36.9 mg/dL (451 to 631 μ mol/L). In contrast to the report by Newman et al,²⁷ 5 of 6 infants were symptomatic on admission. The MRI was abnormal in 3 of 4 tested (including an asymptomatic infant with a TSB of 26.4 mg/dL), and 2 in 5 had abnormal brainstem auditory evoked responses. Follow-up was normal in 4 infants, one had residual hearing loss, and one had severe cerebral palsy and mental retardation, atypical of kernicterus but consistent with global bilirubin encephalopathy observed in animals with a permeable blood-brain barrier. These three studies illustrate that most infants had no acute or residual effects from severe hyperbilirubinemia and that the TSB level did not differentiate which infants would or would not develop kernicterus. Most of these infants received aggressive intervention, which may relate to the good outcome of several infants with severe early toxicity.

The relationship of TSB to acute bilirubin encephalopathy has been evaluated in several studies and recently reviewed by Shapiro and Nakamura.²⁸ Bilirubin can produce changes in behavior as well as alterations in the auditory brainstem evoked response (ABR) at TSB concentrations well below 20 mg/dL. As the TSB increases, changes in the ABR progress from small increases in latency to decreased amplitude in wave forms to complete obliteration of waves III to V. Even severe changes will usually (but not always) improve or resolve following exchange transfusion but may require months to normalize. This slower recovery may be testimony to the plasticity of developing injured brain rather than truly “reversible” bilirubin toxicity. Permanent neurosensory hearing loss may be the only clinical manifestation of kernicterus. Although severe ABR changes occur at high TSB (usually >20 mg/dL), TSB does

not identify newborns with and without severe changes. In addition to ABR changes, elevated TSB (16–33 mg/dL) can produce changes in electrocortical activity (increased delta wave frequency and decreased frequency and amplitude of theta, alpha, and beta waves) and delay EEG maturation in term newborns.

To prevent all cases of kernicterus by intervention for hyperbilirubinemia, a TSB (or free bilirubin) level must be chosen that will include all babies at risk. Two recent studies examined the readmission or peak TSB in babies with acute-phase bilirubin toxicity, residual neurologic injury, and/or autopsy-proven kernicterus in term and near-term infants. A literature search conducted by AHRQ²⁹ at the behest of AAP reviewed 123 cases of kernicterus reported in 28 articles published between 1955 and 2001. Twenty-one in 123 cases had idiopathic hyperbilirubinemia with chronic neurologic sequelae or autopsy-proven kernicterus (4 cases). The mean TSB was 37 mg/dL with a range of 23 to 49.7 mg/dL (Table 1). More than 90% of cases of kernicterus with idiopathic jaundice had TSB levels greater than 25 mg/dL. In 25% of cases, the TSB was below 30 mg/dL, and 50% had peak TSB levels up to 34.9%. An additional 5 infants with a mean TSB of 32.3 mg/dL (range, 27–36 mg/dL) had acute-phase encephalopathy but no permanent injury. The review included 5 infants with chronic kernicterus associated with sepsis (TSB ranged from 14.5 to 49.8 mg/dL) and 39 patients with ABO or Rh isoimmune hemolytic disease (mean TSB about 32 mg/dL with a range of 17.7 to 51 mg/dL). The mean TSBs and lowest TSBs in these infants were about 5 mg/dL lower than in kernicteric infants with idiopathic hyperbilirubinemia.

The Pilot Kernicterus Registry³⁰ contains a separate cohort of 125 cases of acute and/or chronic bilirubin encephalopathy occurring in term infants without Rh isoimmune hemolytic disease. Of the 125 cases, 117 have recorded admission or peak TSB and documented outcomes. Peak or admission TSB values ranged from 20.7 mg/dL to 59.9 mg/dL. Nine of these infants had acute bilirubin toxicity, including seizures in one infant, but normal outcome; 108 infants developed residual neurologic injury or died with kernicterus. Nine of these infants (8.3%) had a TSB of 25 mg/dL or lower; 15% of those with kernicterus had a TSB below 30.1 mg/dL, and 50% had a TSB below 38.5 mg/dL. The peak TSB (37.6 mg/dL) in kernicteric babies with idiopathic hyperbilirubinemia was similar to published levels in previous decades. The distribution of TSB and kernicterus was independent of etiology. In the absence of Rh isoimmune hemolytic disease, there was no evidence that hemolysis, whether from G6PD

deficiency or other causes (bruising, undiagnosed hemolytic anemia), lowered the threshold for kernicterus compared with idiopathic hyperbilirubinemia. Both the AHRQ review and registry data indicate that some patients with sepsis may have a lower threshold for kernicterus. In summary, kernicterus is a complication of neonatal hyperbilirubinemia, and most healthy term infants with a TSB of 25–40 mg/dL escape without significant permanent damage. Most of these infants received intensive therapy (phototherapy and/or exchange transfusion), so clinical risk assessment for kernicterus with prolonged exposure and without intervention cannot be determined. On the other hand, 8% to 9% of reported kernicterus cases occur below a TSB of 25 mg/dL, with documented admission TSBs as low as 20.7 mg/dL. It is clear from available data that the sensitivity (92%) and especially the specificity of a TSB of 25 mg/dL (with signs of acute bilirubin encephalopathy) in predicting risk for kernicterus is limited but currently remains the only available test. Augmentation by either an abnormal ABR or a failed automated ABR or measurement of unbound bilirubin (if available) also provides useful clinical information. Alternatively, the 2004 AAP guidelines suggest the potential role for bilirubin-albumin ratio as limited to a surrogate for unbound bilirubin.

Clinical Question D. *What are the alternative causes of a clinical condition that is similar in manifestation to ABE?* The clinical syndrome of kernicterus is occurrence of excessive hyperbilirubinemia during the first week after birth that is complicated by clinical and progressive signs of acute bilirubin encephalopathy followed by a lack of recurrence of hyperbilirubinemia but associated with the onset of chronic neurologic sequelae in a specific pattern during infancy. When this series of historical events and progression of clinical signs and symptoms occurs, no other plausible alternative causes remain. Healthy infants with or without hyperbilirubinemia exposed to inhaled carbon monoxide have shown clinical neurologic sequelae consistent with the chronic sequelae of kernicterus.

Conclusions

Severe hyperbilirubinemia and ABE are continuing outpatient risks for infants born in the United States and discharged healthy from their birth hospital. Because the margin of safety between a specific TSB level and the onset of ABE is narrow and often unpredictable, prevention of ABE is

the only safe medical option. Awareness, recognition, and identification of the subtle neurologic signs in any infant with severe jaundice and/or hyperbilirubinemia are crucial to a successful outcome, with a “crash cart” approach in the management of ABE. Current evidence suggests that, in its early and intermediate phases, ABE is reversible with timely, rapid, and effective bilirubin reduction strategies. Nine infants who were treated with intensive phototherapy and an exchange transfusion in a timely and prompt manner of the 117 infants with severe hyperbilirubinemia and ABE (reported to the Pilot Kernicterus Registry) escaped long-term neurologic sequelae. Thus, in an infant with acute bilirubin encephalopathy, rapid, timely, and effective reduction of total bilirubin load does influence long-term outcome.

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Case History 2

Table 1. Clinical Progression of Acute Bilirubin Encephalopathy (ABE)⁴

Clinical Evaluation*	Nonspecific, Subtle	Progressive Toxicity	Advanced Toxicity
<i>Score for a clinical sign in each column</i>	<i>1</i>	<i>2</i>	<i>3</i>
<i>Ranges of Score</i>	<i>1 to 3</i>	<i>4 to 6</i>	<i>7 to 9</i>
Mental Status	Sleepy + poor feeding	Lethargy + irritability	Semi-coma and/or seizures
Muscle Tone	Slight decrease	Hyper- or hypotonia depending on arousal state, or mild nuchal/truncal arching	Markedly increased (opisthotonos), or decreased tone, or bicycling movements
Cry	High-pitched	Shrill	Inconsolable

*Individual score is assigned for each clinical sign to obtain a maximum BIND score of 9. Infants with scores of 4 to 6 usually have reversible ABE. Progression to a higher score is indicative of worsening BIND.⁸