Treating acute bilirubin encephalopathy—before it's too late

BY VINOD K. BHUTANI, MD, LOIS H. JOHNSON, MD, AND RON KEREN, MD, MPH

Early signs of bilirubin-induced neurologic damage in healthy term and near-term newborns are often vague. A comprehensive approach to management helps prevent rapid progression and irreversible consequences.

A late-night telephone call from a parent of a recently discharged newborn reporting that the baby has, or may have, jaundice heralds a potential medical emergency—especially when jaundice is coupled with concerns about poor feeding, excessive sleepiness, irritability, or lethargy. This constellation of complaints requires detailed questioning about specific signs and symptoms, a review of the birthing and postnatal history and predischarge data, and, possibly, an emergency neurologic evaluation of muscle tone, alertness, and cry pattern for evidence of bilirubin-induced neurologic dysfunction (BIND).

Although the clinical signs described by the parent sound vague, and may simply reflect a new parent's anxiety or inexperience, they also could be early, nonspecific—but nevertheless sentinel—signs of acute bilirubin encephalopathy (ABE). ABE refers to the acute, and often progressive, manifestations of bilirubin toxicity that are seen in the first weeks after birth. When unmonitored or untreated, they may progress rapidly to advanced manifestations such as opisthotonus and seizures. If intervention to reduce the bilirubin load rapidly is neither timely nor efficient, chronic, permanent clinical sequelae of bilirubin toxicity—referred to as kernicterus—result and become increasingly apparent during infancy.

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TABLE 1

**Early signs of acute bilirubin encephalopathy**

<table>
<thead>
<tr>
<th>Feeding difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent arching</td>
</tr>
<tr>
<td>Irritability and fussiness, difficult consoling, high-pitched cry</td>
</tr>
<tr>
<td>Lethargy with altered awake-sleep pattern</td>
</tr>
</tbody>
</table>

Newborn jaundice generally has a reassuringly benign outcome. It is kernicterus following an acute, brief, preventable exposure to extreme hyperbilirubinemia that can have lifelong deleterious effects. This article discusses the clinical signs, symptoms, and known causes of kernicterus and presents a systems-based strategy for preventing it. The strategy is based on predischarge screening and a bilirubin measurement plotted on the hour-specific bilirubin nomogram to identify newborns at risk of severe hyperbilirubinemia and to target follow-up to prevent irreversible damage.

**The broad spectrum of BIND**

Bilirubin-induced neurologic dysfunction refers to a wide spectrum of disorders, including kernicterus, that are caused by increasingly severe hyperbilirubinemia. The common insult in all cases of BIND results from a total serum bilirubin (TSB) level that exceeds the infant's neuroprotective defenses and leads to neuronal injury, primarily to the basal ganglia, central and peripheral pathways, hippocampus, brain stem nuclei for oculomotor function, and cerebellum.

The damage ranges from minimal to severe with signs of ABE: kernicteric sequelae, isolated auditory neuropathy (a form of sensorineural hearing loss), extrapyramidal movement disorders, or a combination of neuromotor, sensorineural hearing disability, and visual disability. Some experts believe that BIND may have milder, subtler neurologic manifestations, but this theory is unproven.

The actual incidence of ABE is unknown for several reasons: No longitudinal surveillance studies of the condition have been performed; awareness and recognition of the diagnosis in healthy babies is limited; and the diagnosis usually is not coded on discharge summaries. Recent case reports and registries, however, suggest that kernicterus has reemerged as a public health problem after years of near extinction (see "Kernicterus makes a comeback," page 74).

**Clinical signs of ABE**

The classic signs of ABE in the severely hyperbilirubinemic term infant (Figure 1) include increasing hypotonia—especially of extensor muscles and accompanied by retrocollis (spasmodic torticollis in which the head is pulled straight backward) and opisthotonus—along with varying degrees of drowsiness, poor feeding, and hypotonia or hypertonia. Alternating hypertonia and hypotonia also may be evident, depending on the infant's state of arousal. These signs (Table 1) can be described in terms of the infant's mental status, muscle tone, and cry. Table 2 outlines a system for grading the

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**TABLE 2**

**Tracking the clinical progression of acute bilirubin encephalopathy**

<table>
<thead>
<tr>
<th>Clinical evaluation</th>
<th>Nonspecific, subtle</th>
<th>Progressive toxicity</th>
<th>Advanced toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score for clinical sign*</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ranges of score</td>
<td>1-3</td>
<td>4-6</td>
<td>7-9</td>
</tr>
<tr>
<td>Mental status</td>
<td>Sleepiness + poor feeding</td>
<td>Lethargy + irritability</td>
<td>Semi-coma or seizures</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Slight decrease</td>
<td>Hypotonia or hypotonia, depending on arousal state OR Mild nuchal or truncal arching, or both</td>
<td>Markedly increased (opisthotonus) or decreased tone OR Bicycling movements</td>
</tr>
<tr>
<td>Cry</td>
<td>High-pitched</td>
<td>Shriil</td>
<td>Inconsolable</td>
</tr>
</tbody>
</table>

*A 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 indicates worsening BIND.*

As adapted by Volpe.

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TABLE 3

When is the bilirubin level potentially neurotoxic?

<table>
<thead>
<tr>
<th>Postnatal age*</th>
<th>Total serum bilirubin (TSB) level†</th>
<th>Why can this level be dangerous?†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;72 hours</td>
<td>TSB &gt;99.9th percentile (≥25 mg/dL)</td>
<td>These TSB levels may exceed the binding ability of serum albumin; the neurotoxicity risk increases exponentially (see Table 4)</td>
</tr>
<tr>
<td></td>
<td>TSB &gt;95th percentile (17 mg/dL) but &lt;99.9th percentile (25 mg/dL) AND B:A ratio &gt;7.0 mg/g</td>
<td>Low levels of albumin (&lt;3.4 g/dL) can occur in term newborns and, more commonly, near-term or bruised infants (see Table 4)</td>
</tr>
<tr>
<td>&lt;72 hours</td>
<td>TSB &gt;95th percentile regardless of B:A ratio</td>
<td>During the first 72 hours, the binding ability of albumin is compromised and lower TSB levels may be neurotoxic</td>
</tr>
<tr>
<td></td>
<td>TSB &gt;75th percentile and a rate of increase &gt;0.20 mg/dL/hr</td>
<td>An increase in bilirubin load &gt;1 mg/5 hr or ~5 mg/day is likely to result in a TSB &gt;95th percentile and may reach neurotoxic levels</td>
</tr>
</tbody>
</table>

*A jaundiced baby of any age with neurologic signs suggestive of BIND must be assumed to have severe hyperbilirubinemia until proved otherwise.†TSB levels based on hour-specific values as described on the hour-specific bilirubin nomogram.

severity of ABE that has been used as a clinical tool to help accurately document the progression of ABE in a retrospective study. Increasing scores indicate worsening BIND and may have prognostic value.

Because the earliest signs of ABE are subtle and nonspecific, they may be missed. They need to be elicited by direct questioning of parents and close clinical observation. During the early phases of BIND, prompt, effective intervention can prevent chronic kernicteric sequelae. BIND that progresses to scores between 4 and 6 is often reversible.

Early signs of BIND include mild hypertonia and reticollis, which increase in severity and are usually accompanied by a shrill cry and unexplained irritability alternating with increasing lethargy.

Advanced signs include cessation of feeding, bicycling movements, insinuolable irritability and crying, fever, possibly seizures, and coma. They are ominous predictors of severe kernicteric sequelae, even with intensive treatment. Rapid reduction of the bilirubin load by intensive phototherapy and exchange transfusion can reduce brain damage.

The rate of progression of clinical signs depends on the rate of increase of bilirubin levels, duration of hyperbilirubinemia, adequacy of albumin binding reserves, level of unbound bilirubin, host susceptibility, and presence of comorbidities. Death from acute kernicterus is caused by respiratory failure and progressive coma, or intractable seizures.

Clinical sequelae of ABE

Chronic, irreversible bilirubin encephalopathy (kernicterus) in its various presentations may include: extrapyramidal movement disorders (dystonia and athetosis), gaze abnormalities (especially upward gaze) and other visual problems with focusing and recognition, auditory disturbances (especially sensorineural hearing loss with central processing disorders or auditory neuropathy), dysplasia of the enamel of the deciduous teeth.

Although earlier reports described cognitive deficits, these are actually rare. The reports probably reflected inability to accurately assess intelligence in children who have hearing, communication, and coordination problems.

The neuromotor manifestations of extrapyramidal damage, which are present to some degree in almost all cases, may occasionally be apparent only with repeated testing and attempts at skilled movements. Auditory disturbances—both central (brainstem) and peripheral (auditory nerve) in origin—also are almost always present and may be the only noticeable sequelae of ABE. They may be subtle, difficult to diagnose (as with auditory neuropathy), or delayed in clinical expression.

Total serum bilirubin and ABE

No specific total serum bilirubin threshold for neurotoxicity can be established. The threshold for reversible or irreversible acute-stage damage is influenced by postnatal age, maturity within the range of term gestational age, albumin level, affinity of albumin-bilirubin binding, duration of hyperbilirubinemia, and rate of increase of the TSB level (Table 3). Comorbidities predispose a newborn to BIND at lower TSB values. They include:
near-term gestation (35 to less than 38 weeks)
- hypoalbuminemia
- disruption of the blood-brain barrier (asphyxia or trauma)
- hemolysis (intravascular or extravascular)
- factors that interfere with the affinity albumin binding of bilirubin
- infection
- hypoglycemia.

A more appropriate predictor of neurotoxicity would be a measure of unbound, or “free,” bilirubin. Preliminary US and Japanese studies suggest that unbound bilirubin levels greater than 0.8 μg/dL increase the risk of BIND. No commercial assays for albumin binding reserve or unbound bilirubin are available in the US, however. These assays, available through Japanese manufacturers, are not yet approved by the US Food and Drug Administration but are used in US research laboratories.

The only prospective study that has shown an association between TSB levels and ABE is Mollison's and Cutbush's 1954 follow-up report of babies with hyperbilirubinemia and hypoalbuminemia caused by Rh hemolytic disease. These data are more than four decades old, however, and the sample is small (n=60) and comprises babies with severe Rh hemolytic disease. The study, as well as data from the 1959 Collaborative Perinatal Project database, simply demonstrate a direct relationship between kernicterus and neurologic abnormalities and increasing TSB levels.

Since these reports were published, no direct evidence linking specific TSB levels to a specific neurologic abnormality has appeared in the literature. It is now well recognized, however, that kernicterus can occur in well babies with severe hyperbilirubinemia. The historical data and subsequent studies demonstrate that a TSB level greater than 30 mg/dL carries a decidedly higher risk of kernicterus.

More recent data from the Pilot Kernicterus Registry shows that the median readmission TSB level for all babies studied was 35 mg/dL, but seven of the babies, who had a peak TSB level lower than 30 mg/dL at readmission, had classic signs of kernicterus by 7 days of age. All of the babies, including the seven with a TSB level below 30 mg/dL, had a readmission TSB level greater than the 99.9th percentile.

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- Hypoallergenic and fragrance-free

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- Non-greasy, intensive hydration

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for age in hours. A majority had a predischarge TSB level greater than the 75th percentile for age in hours (based either on actual predischarge TSB values or an estimated progression of TSB values). 5

Well babies with a predischarge TSB greater than the 75th percentile for age in hours have an increased bilirubin load often caused by undiagnosed hemolysis or impaired bilirubin clearance. 22-24 Subsequent increase in the bilirubin load (rate of rise of TSB greater than 0.20 mg/dl/hour) increases the likelihood of severe hyperbilirubinemia (greater than the 95th percentile). Predischarge identification of infants at risk therefore helps to target a much smaller group of well babies with TSB levels greater than the 75th percentile in whom strategies for kernicterus prevention can be effective. 23

Bilirubin, albumin, and risk of ABE

Albumin concentration is a powerful neuroprotective agent as well as a major determinant of both bilirubin toxicity and the level of unbound bilirubin in excessively jaundiced babies. The total integrity of binding (below the 1:1 bilirubin-to-albumin molar ratio) is compromised in newborns because their albumin has poor binding ability compared to adult albumin. Binding is further compromised by:

- prematurity, sickness, or acidosis
- protein-bound drugs that compete for albumin binding sites (sulfisoxazole, third-generation cephalosporins such as ceftriaxone, high doses of ibuprofen)
- postnatal age less than 72 hours
- relative hypoalbuminemia (serum albumin level lower than expected for gestational age).

In severely hyperbilirubinemic but otherwise healthy newborns (older than 72 hours with TSB levels greater than the 95th percentile), the bilirubin-to-albumin ratio (B:A) is a useful tool for determining the potential risk for BIND. 11

For practical purposes, B:A can be expressed in terms of milligrams of bilirubin to grams of albumin. A B:A of 7.0 mg/g corresponds to a B:A molar ratio of 0.80. Exposure to a B:A of 7.0 mg/g or higher carries a clear risk of irreversible neurotoxicity, especially if exposure is prolonged. Available clinical and experimental data suggest that B:A ratios higher than 5.3
### Table 4

**How the TSB level relates to the serum albumin value**

<table>
<thead>
<tr>
<th>Serum albumin (g/dl) (healthy term newborn &gt;72 hr of age)</th>
<th>TSB (mg/dl) associated with B:A ratio of 5.3 mg/g (0.63 molar ratio)</th>
<th>TSB (mg/dl) associated with B:A ratio of 6.9 mg/g (0.79 molar ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>3.6</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>4.3</td>
<td>23</td>
<td>30</td>
</tr>
</tbody>
</table>

* B:A ratio < 5.3 mg/g: low risk of neurotoxicity; B:A ratio 5.3 to 6.9 mg/g: indeterminate risk of neurotoxicity (ABE is generally reversible with prompt reduction of the bilirubin load); B:A ratio > 7.0 mg/g: high risk of neurotoxicity

Examples are based on serum albumin cord values in term babies: mean = 3.9 g/dl; range = 3.0 to 4.9 g/dl.\(^{11,12}\)

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mg/g and lower than 7.0 mg/g (molar ratios higher than 0.63 and lower than 0.80) are generally associated with reversible abnormalities of auditory brainstem response (ABR).\(^{11,16-18,25}\) Table 4 provides examples of TSB values at these B:A ratios with commonly observed serum albumin values in healthy term newborns.\(^{25}\) In a term newborn with subtle signs of BIND, these B:A ratios can be reassuring—as long as the bilirubin load is rapidly reduced and there are no signs of progression.

### Strategies to prevent and manage ABE

Prevention of ABE is the most effective strategy—for example, using a systems-based approach as an institutional practice. Such an approach should include individualized care to accommodate the clinician's concerns, informed participation of the family, and monitoring of the progression of hyperbilirubinemia in at-risk newborns.\(^{5,26}\)

**Clinical risk-based approach.** The practice parameters developed by the American Academy of Pediatrics (AAP) provide useful guidelines for managing term healthy newborns—provided they are followed diligently.\(^{27,28}\) The guidelines are based predominantly on visual recognition of jaundice and identification of clinical and epidemiologic risk factors for severe hyperbilirubinemia. This risk-based strategy has been the basis of clinical practice for several years and is popular among pediatricians. It is based on consensus but has limited evidence-based validation, leading to concerns about newborn safety.

Newman and colleagues have further studied the additional risk-based evaluation to provide an evidence-based ranking of individual risk factors for potential use as a predictive instrument. In their study, a risk index or score incorporates clinical predictors of hyperbilirubinemia obtained from the medical history and physical examination.\(^{29}\) Eight predictors were identified from a multivariate logistic regression model and weighted to approximately equal the odds ratio for each risk factor to predict the development of a total serum bilirubin 25 mg/dL or greater—a threshold at which to consider intensive phototherapy and possible exchange transfusion in an intensive care nursery.

More recently, Keren and associates have identified the most predictive and useful risk factors and compared the predictive performance of clinical risk factor assessment and predischarge bilirubin measurement to identify infants at risk of developing significant neonatal hyperbilirubinemia (postdischarge TSB greater than the 95th percentile). This study demonstrated that the predischarge bilirubin expressed as a risk zone on an hour-specific bilirubin nomogram is more accurate and generates wider risk stratification than a clinical risk factor score.\(^{30}\)

**A systems-based screening approach** should be used to identify infants at risk of developing severe hyperbilirubinemia. Such an approach enables the provider to cost-effectively target infants most likely to benefit from closer clinical and laboratory follow-up (or new prophylactic therapies) while avoiding the cost and potential harm of intervention for low-risk infants.

We explored a systems-based strategy to prevent ABE and kernicterus in view of the following circumstances:

- shortened hospital stays after normal birthing
- follow-up programs for newborns that are not seamless
- the fact that a follow-up visit within 48 hours of discharge is nonmandated and nonreimbursable
- a need to promote breastfeeding
- our concern about the visual assessment of jaundice.\(^{5,23,26,31}\)

The fundamental elements of this approach included:

- universal predischarge TSB screening
- risk-based targeted follow-up of newborns to monitor the trajectory and rate of rise of the bilirubin level
- safe and effective treatment to reduce the bilirubin load
systematic evaluation and documentation of signs indicating progressive ABE.

Our method of predicting risk of severe neonatal hyperbilirubinemia (TSB level greater than the 95th percentile, the threshold for considering phototherapy) relies simply on the infant's predischage, hour-specific bilirubin value: The TSB value plotted on the hour-specific bilirubin nomogram provides a percentile-based estimate of the bilirubin value and stratifies patients according to risk of developing severe neonatal hyperbilirubinemia (see “Lapses in managing jaundice in a newborn,” page 68, and “Effective management of early-onset jaundice,” page 70). Figures 2 and 3 present a graph and an algorithm that use hour-specific TSB values to guide management decisions. This strategy was implemented at Pennsylvania Hospital in the fall of 2000. It corrects the root causes of the morbidity and mortality associated with the reemergence of kernicterus.2,32

**Birthing hospital-based management**

A systems-based approach to managing hyperbilirubinemia at the birthing hospital addresses parental education, clinical recognition of jaundice, and predischage risk assessment. It uses multidisciplinary strategies to:

- recognize the clinical significance of jaundice within the first 24 hours after birth
- recognize the limitations of visual identification of jaundice
- recognize clinical jaundice and document its severity by measuring bilirubin before mother and baby are discharged from the hospital
- ensure postdischage follow-up based on the severity of predischage hyperbilirubinemia
- respond to parental concerns about lactational difficulties and jaundice, poor feeding, and changes in behavior and activity in the newborn
- provide ongoing lactational support to mothers who are breastfeeding their babies to ensure adequate intake
- recognize the impact of race, ethnicity, and family history on the severity of newborn jaundice
- diagnose the cause of severe hyperbilirubinemia
- intervene to prevent severe hyperbilirubinemia when bilirubin is rising more rapidly than expected
- consider the level of serum albumin in babies with a TSB level greater than the 95th percentile in order to
gauge susceptibility to neurotoxicity
- treat increasingly severe hyperbilirubinemia aggressively with intensive phototherapy or exchange transfusion
- educate parents and health-care providers about the risks of jaundice during the neonatal period.

**Postdichage management**

After the newborn is discharged from the birthing hospital, mother and child should receive a seamless continuation of care that provides the following services:

**Outpatient follow-up appointments.** All babies should have mandatory follow-up appointments with a physician or nurse with pediatric credentials within 48 hours after discharge (24 hours when the child is deemed at high risk). Follow-up should include careful observation for jaundice and confirmation with transcutaneous bilirubin (TcB) or TSB measurement. Follow-up staff and personnel should be alerted to babies at high risk of subsequent development of hyperbilirubinemia so that these children can be followed more closely and their families monitored for noncompliance.

**Outpatient phone assessment of a jaundiced newborn.** Ask the following questions of parents who report jaundice in their newborn:

- Has the baby's feeding decreased?
- Is the baby arousable?
- Is the baby excessively sleepy and irritable on waking?
- Has the baby's feeding pattern deteriorated?
- What are the color, frequency, and amount of bowel movements?
- What are the color, frequency, and amount of urine output?
- Does the baby lie with the head tilted back? Does the baby exhibit arching of the body?
- Has the baby's cry pattern changed? Has it become more shrill?

Continued on page 66
**Figure 2** A care map to prevent acute bilirubin encephalopathy

- **Intensive phototherapy** for total serum bilirubin (TSB) increase greater than 0.20 mg/dL/hr
- **"Crash cart" interventions** at different percentile levels:
  - 99th percentile
  - 95th percentile
  - 75th percentile
  - 40th percentile
- **Clinical follow-up** or transcutaneous bilirubin (TcB) within 48 hours of discharge at MD discretion
- Check for jaundice every 8 to 12 hours and confirm by TcB/TSB

**Figure 3** Systems-based management of neonatal jaundice

1. **Birth**
   - Check for jaundice q 8-12 hr until discharge
   - None

2. **Jaundice present at <36 hr of age**
   - One or more risk factors present; assess parental education and nutritional intake and ensure feasibility of and compliance with follow-up

3. **Measure TSB/TcB for age in hr as soon as feasible**
   - TSB/TcB >75th percentile
     - Review clinical findings for BIND and nutritional intake and evaluate for hemolysis
     - 76th-95th percentile
     - Initiate intensive phototherapy for TSB rate of increase >0.20 mg/dL/hr and >95th percentile for age in hr
     - Repeat TSB/TcB in 12-24 hr
   - TSB/TcB <75th percentile
     - Provide parental education and discharge instructions, arrange follow-up, and discharge
     - 76th-95th percentile
     - Repeat TSB/TcB in 48 hr
     - 40th-75th percentile

4. **Perform predischarge TSB/TcB screening at the same time as routine metabolic screening**
   - TSB/TcB <75th percentile
   - <40th percentile
   - Reevaluate clinically or measure TcB in 48 hr and continue routine care

5. **Check for jaundice q 8-12 hr until discharge**
   - None
   - None
Lapses in managing jaundice in a newborn

This case report describes the birthing experience of a term newborn discharged healthy from a US well-baby nursery and his postdischarge care and readmission. The numbers in parentheses correspond to the numbers in the table on page 69, which identify specific points in the evaluation and management of the infant at which errors were made or opportunities missed for more appropriate and timely interventions. The graph at left plots the magnitude of hyperbilirubinemia and the rate of increase of total serum bilirubin (TSB) against the background of the hour-specific bilirubin nomogram.

Baby boy Kareem was born on December 18 at 9:48 p.m. His birth weight was 3,451 g and he was 38 weeks gestational age. His mother was 26 years old, blood type O+, with no history suggesting perinatal sepsis. She had had an uneventful pregnancy and was eager to start breastfeeding. Kareem was the first child born to the family, which had emigrated recently from Nigeria (1).

The night nurse noted slight jaundice but, on a follow-up exam, considered the baby to be pink (2). During early morning rounds, a pediatrician ordered a serum bilirubin level for suspicious jaundice (3). The TSB reported a few hours later was 9.2 mg/dL (4). The infant's mother said she was not aware of any family history of jaundice. Later in the evening on December 19, the mother asked to be discharged (5). Follow-up was arranged for two days after discharge (6).

On December 20, the mother called the hospital to inquire about jaundice because she thought her son's eyes looked yellow and a visiting relative was concerned (7). She was reassured over the phone and instructed to place the baby in the sun (8). On the morning of December 21, she called again to state that her son was

Rapid emergency department or office intervention. Severely jaundiced babies and symptomatic babies often are seen first at the pediatrician's office or ED. The front office and triage staff should be familiar with an intensive, “crash-cart approach” to managing ABE, as described later. Phototherapy lights (Phillips F-20 T12/BB) in the 425- to 475-nm range should be easily and rapidly accessible and inspected and maintained regularly to ensure proper functioning. If such lights are not available, providers should periodically review mechanisms for rapid transfer of hyperbilirubinemic infants to a neonatal intensive care unit. Travel time should not exceed 30 minutes. If it does, arrangements for transport phototherapy should be considered. Transport plans should include direct communication with a responsible neonatologist so that care can be started before and during the trip.

Intensive preventive approach. The AAP practice parameters and a recent review article by Denny and colleagues describe strategies to reduce the bilirubin load rapidly. Attention to the following additional aggressive steps facilitates effective, safe, efficient management of the severely hyperbilirubinemic infant with early, nonspecific signs of possible ABE:

- Assess for clinical signs of acute bilirubin encephalopathy or an abnormal automated auditory brainstem (you can also use an automated ABR with a “pass” or “fail” response). If specific signs of ABE are present, exchange transfusion is recommended regardless of the TSB level.
Baby Kareem: Missed opportunities and management errors

<table>
<thead>
<tr>
<th>Action points</th>
<th>Age (hr)</th>
<th>Action, evaluation, or intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal</td>
<td>Birth</td>
<td>Certain ethnic groups are at risk of hemolytic disorders such as G6PD deficiency</td>
</tr>
<tr>
<td>2-4 Post-birth</td>
<td>~8-12</td>
<td>2 Suspicion of jaundice needs to be confirmed by an objective test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Jaundice at &lt;36 hr of age is a serious clinical issue; bilirubin test should have been done when jaundice was suspected at &lt;24 hr of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 Hour-specific TSB level (for postnatal age) is &gt;95th percentile: HIGH RISK</td>
</tr>
<tr>
<td>5-8 Predischarge</td>
<td>~20-36</td>
<td>5 Not a candidate for early discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 If discharged, earlier follow-up with detailed parental education is warranted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 Family concerns need to be objectively evaluated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 Sunlight is not an effective therapy</td>
</tr>
<tr>
<td>9-12 Home-based</td>
<td>~56-70</td>
<td>9, 10 Serious symptoms need urgent evaluation, direct admission to nursery, and immediate therapy and office care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11, 12 Needs &quot;crash cart&quot; approach; do not refer to emergency room. Minutes matter</td>
</tr>
<tr>
<td>13-15 Readmission</td>
<td>~72-74</td>
<td>13-15 Acute stage kernicterus or acute bilirubin encephalopathy, when progressive, is generally associated with irreversible damage</td>
</tr>
</tbody>
</table>

feeding poorly and that the yellow color of his skin was deeper. She was told to keep her afternoon appointment (9).

On the afternoon of December 21, the mother brought the infant to the hospital for his scheduled visit. The triage nurse performed an intake history and, after consultation with a physician, drew a heel-stick sample for bilirubin (10). The TSB measured at 4 p.m. was 32 mg/dL (11). Kareem was then referred to the hospital emergency room and transferred from there to the intensive care unit (12). On admission to the nursery, intensive phototherapy was ordered at 8 p.m., and arrangements were made for exchange transfusion. The admission TSB (measured at 8 p.m. and reported at 9:30 p.m.) was 38 mg/dL (13). Urgent calls were made to the blood bank (14). Kareem became apneic at 10:30 p.m. and was intubated at 10:45 p.m. He began to have seizures at about 11 p.m., and a bolus of phenobarbital was given (15). He died after an unsuccessful attempt at resuscitation for respiratory failure at 11:47 p.m. TSB measured just before death 9 mg/dL, a decline attributable to acute influx of bilirubin from the blood into the brain.

Other laboratory results showed signs of mild anemia and evidence of hemolysis. His blood type was O+ with a negative Coombs test, indicating hemolytic anemia with hyperbilirubinemia unrelated to blood group compatibility. Quantitative enzyme analysis subsequently showed that he had G6PD deficiency.

- Immediately obtain a TcB measurement (if available) and send a blood sample to the laboratory for total bilirubin, serum albumin, electrolytes, calcium, and type and cross match for 170 mL/kg of blood (for double-volume exchange transfusion).
- Admit the infant directly to the intensive care nursery and start intensive phototherapy. Perform all procedures while the infant is under intensive phototherapy. Irradiance and intensity of phototherapy units should be previously configured as a routine maintenance policy.
- Prepare for exchange transfusion by assessing for vascular access through cannulation of central (if umbilical vessels are accessible) or peripheral vessels (arterial and venous).
- Evaluate the baby for hydration and consider enteral feeds to decrease enterohepatic circulation and increase intestinal clearance of bilirubin.28,29

Other concurrent preventive and therapeutic options to reduce the bilirubin load (Table 5) may be initiated based on clinical needs.

The "crash-cart approach" for ABE
Once specific signs of ABE are recognized, the goal of therapy is prompt but safe reduction of the bilirubin load. The AAP practice parameters outline strategies to accomplish this goal.27 Our "crash-cart" approach is based on the following considerations:
- Only exchange transfusion can rapidly and effectively clear bilirubin to minimize brain damage in a symptomatic neonate.
Effective management of early-onset jaundice

Baby Boy Robinson was born on March 18 at 5:18 p.m. by spontaneous vaginal delivery to a 26-year-old primigravida mother who had an uncomplicated pregnancy. The Apgar score was 8 at one minute and 9 at five minutes; the baby was admitted to the well-baby nursery. Birth weight was 3,564 g, gestational age was assessed to be 38 weeks, and the physical examination was normal.

During a routine clinical evaluation at 4 a.m. (about 11 hours of age), the nurse noted that the baby was jaundiced. She obtained a Stat serum bilirubin level by heel-stick sample. The total serum bilirubin (TSB) level was 20 mg/dL. This was reported to the pediatrician, who ordered intensive phototherapy and requested blood typing and a Coombs test of the cord blood as well as further evaluation for hemolysis.

A newly available, noninvasive test to measure bilirubin production by evaluating exhaled carbon monoxide was conducted. It indicated increased bilirubin and confirmed hemolysis, which was caused by the baby's B+ blood type and a positive Coombs test. Follow-up TSB levels were measured (see graph). No clinical disturbances of mental state, muscle tone, or cry patterns were noted.

Because the TSB increased to 23.4 mg/dL despite intensive phototherapy and because hypalbuminemia (serum albumin 3.3 g/dL, B:A = 7.1 mg/g) was present at 25 hours of age, a double-volume exchange transfusion was performed. Intensive phototherapy was discontinued at 96 hours of age after the TSB level declined to less than the 40th percentile. A predischarge hearing screen (by automated auditory brainstem response test) was normal, and subsequent one-year follow-up showed no neurologic sequelae.

- The risk of performing exchange transfusion (in experienced hands) must be weighed against the potential risk of ABE itself.35,36
- Babies with ABE should be treated with intensive phototherapy (confirmed irradiance of greater than 30 μwatts/cm²/mm) to the entire body surface area with a goal of reducing the bilirubin load by more than 0.5 mg/dL/hr while preparations are made for an urgent exchange transfusion.
- Exchange transfusion is performed as an isovolumic procedure with concurrent withdrawal from an arterial line and infusion through a venous line. Double-volume exchange (170 mL/kg) is ideal but, in the event of technical difficulties, single-volume exchange transfusion may be adequate if supplemented with intensive phototherapy. The entire process should take three or four hours.

Also consider exchange transfusion when no specific signs of ABE are apparent but one of the following situations raises significant concerns about neurotoxicity:
- the TSB level is greater than 30 mg/dL.21
- intensive phototherapy fails to produce a dramatic drop in TSB levels—that is, TSB decreases by less than 0.5 mg/dL/hour or less than 2 mg/dL over four hours.31
- an infant who had a successful universal hearing screen now fails an automated ABR screen.

Before performing exchange transfusion, you may want to consider an albumin infusion (1 g/kg), especially if serum albumin is low (less than 3.4 g/dL), or administration of immune globulin (IVIG) when hyperbilirubinemia is attributed to ABO sensitization.37

Quality improvement and peer review

A surveillance program has been maintained at Pennsylvania Hospital to monitor term and near-term babies for occurrence of ABE, readmission for a TSB level greater than 25 mg/dL after 72 hours of age, re-admission for a TSB level greater than 20 mg/dL before
TABLE 5

Strategies to reduce the bilirubin load (>95th percentile) and manage ABE

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Mode of therapy</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Crash-cart approach&quot;</td>
<td>Organized team effort</td>
<td>See text. Goal: prompt and expeditious reduction of bilirubin load</td>
</tr>
<tr>
<td>Reduction by rapid systemic clearance</td>
<td>Intensive phototherapy</td>
<td>Blue lights (Phillips F20 T12/BB fluorescent bulbs) at an irradiance of &gt;30 μWatts/cm²/mín in the 425-475 nm range Goal: decrease bilirubin level at &gt;0.5 mg/dL/hr</td>
</tr>
<tr>
<td>(within 2-4 hr)</td>
<td>Exchange transfusion</td>
<td>Double-volume (170 mL/kg), isovolumetric exchange conducted over 60 to 90 min Goal: rapidly reduce bilirubin load</td>
</tr>
<tr>
<td>Reduction by enteral clearance</td>
<td>Continuation and encouragement of feeding (in babies with BIND score &lt;4)</td>
<td>Supplement with formula feeding and expressed breast milk to decrease enterohepatic circulation and increase intestinal clearance of bilirubin²³</td>
</tr>
<tr>
<td>Reduction of bilirubin production</td>
<td>Control of hemolysis</td>
<td>Consider immune globulin (IVIG) therapy in presence of blood group incompatibility³</td>
</tr>
<tr>
<td>Neuroprotection for BIND</td>
<td>Inhibition of production</td>
<td>Ongoing clinical trials of heme-oxgenase inhibitors</td>
</tr>
<tr>
<td>Systemic support for BIND</td>
<td>Enhancement of albumin binding of bilirubin</td>
<td>Consider albumin infusion at a dose of 1 g/kg before an exchange transfusion</td>
</tr>
<tr>
<td></td>
<td>Intravenous fluid and electrolyte support to supplement enteral nutrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory support as needed for apnea and respiratory failure</td>
<td></td>
</tr>
</tbody>
</table>

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48 hours of age, and use of exchange transfusion. Clinical management is also reviewed for any adverse events associated with severe hyperbilirubinemia or procedures used to reduce the bilirubin load.

Outcome of the systems-based approach

Since 1994, all well babies have been screened using a predischarge bilirubin measurement, and a targeted bilirubin follow-up program has been pursued. In the fall of 2000, we augmented this program with a systems-based approach that incorporated predischarge bilirubin screening into the well-baby clinical pathway.

From 1991 to December 2001, we followed 30,059 well babies. Only two developed a TSB level greater than 25 mg/dL (1:15,000), and none had a level greater than 30 mg/dL.³⁷ This compares to a 1 in 700 occurrence of TSB levels greater than 25.0 mg/dL reported in a recent study from Northern California.³⁸

Based on our experience, we believe a systems-based approach provides early, effective, targeted intervention for babies less than 72 hours of age with TSB levels greater than the 75th percentile and promises safer, more targeted, baby-friendly, and cost-effective follow-up.³¹ Further evaluation of the Pennsylvania Hospital program and alternate systems-based approaches is needed to determine practical, safe, cost-effective options.

Improving management, reducing risk

ABE is a continuing risk for infants discharged healthy from the hospital. To meet societal expectations of zero tolerance for kernicterus and our personal standards for ensuring the safety and well-being of healthy newborns, we must increase our awareness of adverse outcomes attributable to neonatal hyperbilirubinemia.

Management should be evidence-based, focused on patient safety, and family-centered. It should conform to national and hospital-based standards. A systems-based program to prevent ABE should include parent education, surveillance for clinical risk factors and comorbidities, universal predischarge TSB or icB measurement, and targeted follow-up based on the hourspecific bilirubin value.

Quality improvement efforts should monitor, evaluate, and respond to episodes of severe hyperbilirubinemia, review procedures that reduce bilirubin load, and investigate associated adverse events. Comprehensive management programs should be evaluated from their inception for their ability to improve treatment of jaun-
Kernicterus makes a comeback

In the early 1950s, kernicterus accounted for 6% of cases of cerebral palsy seen in large clinics. It was virtually eradicated after the introduction in the 1960s of Rh(D) immune globulin (Rhogam) to prevent Rh sensitization and erythroblastosis, and exchange transfusion and phototherapy to treat hyperbilirubinemia. In the two decades before 1991, not one report of kernicterus in healthy, full-term infants was published.

During the early and mid-1990s, case reports reappeared in the literature, coinciding with trends toward earlier postpartum discharge (before jaundice is clinically evident or peaks) and decreased concern about the toxic potential of bilirubin. The most troubling feature of the reports was that, contrary to popular belief, many of the affected infants were otherwise well term newborns without evidence of hemolytic disease. In response to the reappearance of kernicterus in the well-baby population, several national health-care quality promotion agencies met at Pennsylvania Hospital in Philadelphia in February 2001 in cooperation with Parents of Infants and Children with Kernicterus (PICK) and their medical advisory board. A Sentinel Alert by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) followed in April 2001; it required all hospitals to report new cases of kernicterus and develop plans to prevent future cases. In July 2002, the National Quality Forum added kernicterus and a serum bilirubin level greater than 30 mg/dL in term and near-term babies to its list of "never events" (serious adverse events that should never occur).

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