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Managing Newborn Hyperbilirubinemia and Preventing Kernicterus

Bilirubin is the yellow breakdown product created from the destruction of hemoglobin in circulating red blood cells; they have a shortened lifespan in the newborn. Approximately 35 mg of unconjugated bilirubin is formed from each gram of hemoglobin, and newborns produce up to 10 mg/dl/day. Bilirubin production is elevated in the first 24-48 hours of life. Unconjugated bilirubin is lipid-soluble and must be transported to the liver in plasma, reversibly bound to albumin. In the liver, bilirubin is transported across hepatic cell membranes where it is bound to ligandin for conjugation. A liver enzyme conjugates bilirubin, converting it to water-soluble bilirubin pigments that can be excreted into the bile and urine. It is eliminated from the body via the intestines and to a lesser degree through the renal system. Bilirubin pigments that are not eliminated can be reabsorbed into the circulation as unconjugated bilirubin, a process called enterohepatic recirculation. In term newborns, conjugation is delayed during the first hours after birth but increases by about 24 hours of age. Hemolysis or bruising at birth can increase the bilirubin load. Elimination of bilirubin is often delayed in preterm infants. Other factors can impair its elimination, such as poor feeding, bowel obstruction or immature liver conjugation. Breastfed babies typically have higher bilirubin levels than formula fed infants. Babies with reduced conjugation or elimination of bilirubin are at risk for hyperbilirubinemia.

Definitions

- *Total serum bilirubin (TSB)*: Bilirubin is the catabolic product of heme metabolism, which is formed by the breakdown of heme present in hemoglobin, myoglobin, cytochromes, catalase, peroxidase, and tryptophan pyrrolase. Several laboratory techniques have been developed for measuring the serum bilirubin concentration. The specific technique used has implications for the interpretation of serum values.

- *Direct or conjugated bilirubin*: concentration of bilirubin conjugated with glucuronic acid
- *Indirect or unconjugated bilirubin:* the lipid-soluble form of bilirubin that circulates in loose association with the plasma proteins
- *Transcutaneous bilirubin (TcB)*: noninvasive measure of the yellow color of blanched skin and subcutaneous tissue; used as screening tool to help determine whether the TSB should be measured; provides an estimate of the TSB value expressed in mg/dl; measurements can be plotted on the same nomogram as TSB measurements
- *Hyperbilirubinemia*: TSB level of <13 mg/dl or a TSB rise of <0.5 mg/dl/hour; results in physiologic jaundice
- *Physiologic jaundice*: yellow color in skin and sclera that appears as bilirubin levels increase; begins cephalically, usually seen in face first and progresses caudally to trunk and extremities
- *Severe hyperbilirubinemia*: TSB above the 95th percentile for age in hours; requires treatment with phototherapy
- *Phototherapy*: visible light delivered in measurable doses; causes photoisomerization whereby bilirubin present in superficial capillaries and interstitial spaces of the skin and subcutaneous tissues is converted to water-soluble isomers that are excretable without further metabolism by the liver
- *Intensive phototherapy*: implies irradiance in the blue-green spectrum (wavelength band of approximately 430-490 nm) of at least 30 μW/cm^2 per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible; the most efficient units positioned for maximum skin coverage can lower TSB by as much as 5 mg/dl/hour
- *"Bronze baby syndrome"*: complication of phototherapy where a grayish-brown discoloration of the skin occurs; seen exclusively in infants with an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice)
- *Acute bilirubin encephalopathy (ABE)*: acute and reversible clinical manifestations of bilirubin neurotoxicity caused by an accumulation of unconjugated bilirubin in the brain; seen in the first weeks after birth; presenting signs are subtle and nonspecific; early signs include lethargy, hypotonia and poor suck; intermediate phase is characterized by moderate stupor, irritability and hypertonia manifested by backward arching of the neck (retrocollis) and trunk (opisthotonos); infant may develop fever and high-pitched cry which alternates with drowsiness and hypotonia; advanced phase may be irreversible and is characterized by pronounced retrocollis-opisthotonos, shrill cry, no feeding, apnea, fever, deep stupor to coma, possible seizures and death
- *Kernicterus*: yellow staining of specific areas of brain tissue caused by an accumulation of unconjugated bilirubin in the brain; results in bilirubin neurotoxicity and chronic bilirubin encephalopathy
- *Chronic bilirubin encephalopathy*: chronic and irreversible clinical neurologic sequelae associated with bilirubin neurotoxicity, including severe choreoathetoid cerebral palsy, sensorineural hearing loss, dental- enamel dysplasia, paralysis of upward gaze and intellectual deficits

Scope of the Problem

More than 60% of healthy full term and late preterm infants will develop hyperbilirubinemia during the first week of life. Most are discharged from their birth hospital before the peak of TSB occurs, usually at 72-120 hours of age. Hyperbilirubinemia typically resolves by 7-10 days of life. Approximately 5-11% of infants will develop severe hyperbilirubinemia. Without intervention, TSB levels can progress to values greater than 25 or 30 mg/dl (above the 99th percentile for age in hours) which puts the infant at risk for acute bilirubin encephalopathy and kernicterus. It is estimated that about one in seven infants with TSB levels greater than 30 mg/dl will develop kernicterus, resulting in chronic bilirubin encephalopathy.[1,2] The relationship between extremely high TSB levels and bilirubin neurotoxicity is not known because routine surveillance is not available. Cases of extremely high levels of serum bilirubin in infants with no apparent sequelae have been reported. Conversely, infants without documented high serum bilirubin levels have been found to have kernicterus.[3] The critical level in otherwise healthy newborns is likely influenced by postnatal age, maturity, duration of hyperbilirubinemia and rate of TSB rise.

The current incidence of bilirubin encephalopathy in the US is unknown; however, kernicterus is still being reported. The majority of these affected infants are term and late-preterm infants who are discharged from the hospital as healthy newborns, yet subsequently develop extreme hyperbilirubinemia and the neurodevelopmental findings associated with kernicterus.

Current Guidelines for Management and Follow-Up

In July 2004, the American Academy of Pediatrics (AAP) released a clinical practice guideline, "Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation."[4] The focus of this guideline was to reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy while minimizing the risks of unintended harm, such as maternal anxiety, decreased breastfeeding and unnecessary costs and treatment through appropriate identification, follow-up and therapy.

The key elements of the AAP guideline are summarized in the following recommendations:

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to the infant's age in hours. (See Figure 2, AAP guideline[4])
6. Recognize that infants less than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.

7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia. (See Table 2, AAP guideline[4])
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion. (See Figures 3 & 4, AAP guideline[4])

In 2009, a panel of experts reviewed the relevant literature including the report on screening for neonatal hyperbilirubinemia by the Tufts-New England Medical Center Evidence-Based Practice Center[5] and the current report by the US Preventive Services Task Force.[3] New evidence suggests that combining a predischarge measurement of TSB or TcB with clinical risk factors including gestational age might improve the prediction of the risk of subsequent hyperbilirubinemia. In October 2009, Maisels et al published their commentary article, "Hyperbilirubinemia in the Newborn Infant ≥35 Weeks' Gestation: An Update With Clarifications."[6] In addition to clarifying several areas addressed in the 2004 AAP guideline, the authors introduced new recommendations for management and follow-up testing according to predischarge screening, gestation, and risk factors for subsequent hyperbilirubinemia. Their recommendations are summarized in Figure 3 of the guideline.[6] 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.

TcB Measurement

TcB or transcutaneous bilirubin measurement is being performed more frequently in hospitals and outpatient settings. This noninvasive screening tool provides a good estimate of the TSB expressed in mg/dl and helps to determine whether the TSB should be measured. As with any point-of-care testing, regular monitoring for quality assurance by comparing TcB measurements with the TSB is necessary. Studies in term and late preterm infants have indicated that the TcB tends to underestimate the TSB, particularly at higher TSB levels. In the 2009 updated guidelines, Maisels et al provide specific evidence-based strategies for determining when TSB measurement is indicated.[6]

Measurement of the TSB should be performed if:

- The TcB value is at 70% of the TSB level recommended for the use of phototherapy[7]
- The TcB value is above the 75th percentile on the Bhutani nomogram (Fig 1) or the 95th percentile on a TcB nomogram[8]
- At follow-up after discharge, the TcB value is >13mg/dl (222µmol/L)[9]

Treatment

In 2011, the AAP published a technical report, "Phototherapy to Prevent Severe Neonatal Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation."[10] Their intent was to standardize the use of phototherapy in the management of hyperbilirubinemia. The most important intervention for infants with severe hyperbilirubinemia is to initiate phototherapy without delay. The clinical response to phototherapy depends on the efficacy

of the phototherapy device, as well as the infant's rates of bilirubin production and elimination. The following characteristics contribute to the effectiveness of the phototherapy device: emission of light in the blue-to-green range that overlaps the in vivo plasma bilirubin absorption spectrum (~460-490 nm); irradiance of at least 30 μW/cm^2 per nm (confirmed with an appropriate irradiance meter calibrated over the appropriate wavelength range); illumination of maximal body surface; and demonstration of a decrease in total bilirubin concentrations during the first 4 to 6 hours of exposure. Serial measurements of bilirubin concentrations are recommended to monitor the effectiveness of phototherapy treatment.

The efficacy of commercial neonatal phototherapy devices varies widely. These devices can be categorized according to their light source as follows: gallium nitride light-emitting diodes (LED), halogen spot lights (metal halide bulbs), fiberoptic blankets and fluorescent tube devices. The performance characteristics of the most commonly used phototherapy devices are summarized in Table 1 of the 2011 technical report.[10] The AAP has recommended that the irradiance for intensive phototherapy be at least 30 μW/cm^2 per nm over the wavelength band interval of 460-490 nm.[4] Devices that emit lower irradiance may be supplemented with auxiliary devices. The AAP further recommends that ***"All nurseries and services treating infants should have the necessary equipment to provide intensive phototherapy."***[4]

The AAP recommendations for exchange transfusion are summarized in Figure 4 of the 2004 guidelines.[4] During the birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. The following guidelines are provided for infants readmitted to the hospital with severe hyperbilirubinemia: if the TSB concentration is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange transfusion if the TSB remains above the levels indicated after intensive phototherapy for 6 hours. Immediate exchange transfusion is recommended if the infant with hyperbilirubinemia shows signs of acute bilirubin encephalopathy: hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry.

In cases of isoimmune hemolytic disease, the AAP recommends administration of immunoglobulin (IgG, 0.5-1.0 g/kg over 2 hours) if the TSB is rising despite intensive phototherapy or the TSB level is within 2 to 3 mg/dl (34-51 μmol/L) of the exchange level (Fig 3). If necessary, this dose can be repeated in 12 hours.[4]

Several pharmaceutical agents have been investigated for their ability to prevent or treat neonatal hyperbilirubinemia. Tin mesoporphyrin, a potent inhibitor of heme oxygenase, has been shown to effectively reduce TSB levels in term and preterm infants. It is currently being investigated for use in infants with severe hyperbilirubinemia.[12]

Parent Education and Resources

Before the infant is discharged from the hospital, parents should be given both written and verbal information about newborn jaundice, including risk factors, identification and treatment. As part of their Safe and Healthy Beginnings program, the AAP offers a resource toolkit for hospitals and providers. *"Safe & Healthy Beginnings: A Resource*

Toolkit for Hospital and Physician's Offices" is based on the key aspects of the revised AAP hyperbilirubinemia guideline, including 1) the assessment of a newborn's risk for severe hyperbilirubinemia, 2) support for breastfeeding mother, and 3) coordination of care between newborn nursery and primary care practice. It is available for purchase at the AAP Bookstore. This on-line resource includes tools for clinicians and parent handouts. An on-line demo is available at, http://www.aap.org/pubserv/shb/index.html.

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