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Objectives

After completing this article, readers should be able to:

1. List the risk factors for severe hyperbilirubinemia.
2. Distinguish between physiologic jaundice and pathologic jaundice of the newborn.
3. Recognize the clinical manifestations of acute bilirubin encephalopathy and the permanent clinical sequelae of kernicterus.
4. Describe the evaluation of hyperbilirubinemia from birth through 3 months of age.
5. Manage neonatal hyperbilirubinemia, including referral to the neonatal intensive care unit for exchange transfusion.

Introduction

For centuries, neonatal jaundice (icterus neonatorum) has been observed in newborns. As early as 1724, Juncker, in the *Conspectus Medicinae Theoreticopraticae*, began distinguishing between "true jaundice" and "the icteric tinge which may be observed in infants, immediately after birth." In 1875, Orth noticed during autopsies the presence of bilirubin in the basal ganglia of infants who had severe jaundice, which was labeled kernicterus by Schmorl in 1903. (1) In 1958, however, a nurse in the nursery of the General Hospital in Rothford, Essex, Great Britain, reported "an apparent fading away of the yellow pigmentation in the skin of the jaundiced babies when they had been a short time in sunlight." (2)

Icterus neonatorum occurs in approximately two thirds of all newborns in the first postnatal week. Jaundice results from bilirubin deposition in the skin and mucous membranes. For most newborns, such deposition is of little consequence, but the potential remains for kernicterus from high bilirubin concentrations or lower bilirubin concentrations in preterm infants. (3) Although rare, kernicterus is a preventable cause of cerebral palsy.

Hyperbilirubinemia was treated aggressively in the 1950s to 1970s because of a high rate of Rh hemolytic disease and kernicterus. However, data from the 1980s and 1990s showed that pediatricians may have been too aggressive in their approach, almost making kernicterus a disease of the past. Pediatricians subsequently became less aggressive, discharging newborns earlier from nurseries before bilirubin concentrations peaked. These factors helped lead to an increase in kernicterus in the 1990s. (4) Because of these events, an American Academy of Pediatrics (AAP) Subcommittee on Hyperbilirubinemia established guidelines for the approach to neonatal jaundice. (5)

Bilirubin Metabolism

When red blood cells undergo hemolysis, hemoglobin is released. Within the reticuloendothelial system, heme oxygenase degrades heme into biliverdin and carbon monoxide. Biliverdin reductase reduces biliverdin to unconjugated (indirect) bilirubin. Unconjugated bilirubin binds to albumin and is transported to the liver. Unconjugated bilirubin can become unbound if albumin is saturated or if bilirubin is displaced from albumin by medications (eg, sulfisoxazole, streptomycin, chloramphenicol, ceftriaxone, ibuprofen). The unbound unconjugated bilirubin can cross the blood-brain barrier and is toxic to the central nervous system. (5)(6)

Once unconjugated bilirubin reaches the liver, it is conjugated by uridine diphosphate glucuronosyl transferase (UGT1A1). Hepatic UGT1A1 increases dramatically in the first few weeks after birth. At 30 to 40 weeks' gestation, UGT1A1 values are approximately 1%

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of adult values, rising to adult concentrations by 14 weeks of age. (7) Conjugated (direct) bilirubin is excreted into the intestine via the gallbladder and bile duct. Bacteria in the intestine can deconjugate bilirubin, allowing it to be reabsorbed into the blood. The rest of the bilirubin is excreted with the stool. (5)(6)

Causes of Neonatal Hyperbilirubinemia

Nonpathologic

PHYSIOLOGIC JAUNDICE Physiologic jaundice is an unconjugated hyperbilirubinemia that occurs after the first postnatal day and can last up to 1 week. Total serum bilirubin (TSB) concentrations peak in the first 3 to 5 postnatal days and decline to adult values over the next several weeks. The TSB concentrations vary greatly in infants, depending on race, type of feeding, and genetic factors. (8) Initially, the cord TSB concentration in term newborns is approximately 1.5 mg/dL (25.7 μmol/L). The TSB concentration peaks at approximately 5.5 mg/dL (94.1 μmol/L) by the third postnatal day in white and African American infants. The mean TSB concentration peaks are higher in Asian infants at approximately 10 mg/dL (171.0 μmol/L). (9) By 96 hours of age, 95% of infants have TSB concentrations of less than 17 mg/dL (290.8 μmol/L). Therefore, bilirubinemia above this value is no longer considered physiologic jaundice.

Physiologic jaundice occurs in infants for a number of reasons. They have a high rate of bilirubin production and an impaired ability to extract bilirubin from the body. Bilirubin production also is increased as a result of elevated hematocrit and red blood cell volume per body weight and a shorter life span of the red blood cells (70 to 90 days). (10) Finally, infants have immature hepatic glucuronosyl transferase, a key enzyme involved in the conjugation of bilirubin that facilitates excretion from the body. (5)(10)

BREASTFEEDING/HUMAN MILK JAUNDICE. Early-onset breastfeeding jaundice is the most common cause of unconjugated hyperbilirubinemia. (6)(8) Breastfeeding exaggerates physiologic jaundice in the first postnatal week because of caloric deprivation, leading to an increase in enterohepatic circulation. Mild dehydration and delayed passage of meconium also play roles. Successful breastfeeding decreases the risk of hyperbilirubinemia. Infants need to be fed at least 8 to 12 times in the first few days after birth to help improve the mother's milk supply. The best way to judge successful breastfeeding is to monitor infant urine output, stool output, and weight. Newborns should have four to six wet diapers and three to four yellow, seedy stools per day by the fourth day after birth. Breastfed infants should lose no more than 10% of their body weight by the third or fourth postnatal day. Formula supplementation may be necessary if the infant has significant weight loss, poor urine output, poor caloric intake, or delayed stooling. (4)(7) Water and dextrose solutions should not be used to supplement breastfeeding because they do not prevent hyperbilirubinemia and may lead to hyponatremia.

Late-onset human milk jaundice usually occurs from the sixth through the fourteenth day after birth and may persist for 1 to 3 months. A few theories hypothesize the cause of human milk jaundice, but the exact mechanism is not entirely clear. It is believed that human milk contains beta-glucuronidases and nonesterified fatty acids that inhibit enzymes that conjugate bilirubin in the liver. Human milk jaundice is the most likely cause of unconjugated hyperbilirubinemia in this age group, but rarely, conjugation defects can occur. If the diagnosis is in question, breastfeeding can be discontinued for 48 hours to observe whether a decrease in TSB concentration occurs. During this time, the mother should continue to express milk to maintain her supply and supplement the infant with formula. TSB concentrations usually peak between 12 and 20 mg/dL (205.2 and 342.1 μmol/L) and should decrease 3 mg/dL (51.3 μmol/L) per day. If this decrease occurs, breastfeeding should be restarted. (6)

PREMATURITY. Although preterm infants develop hyperbilirubinemia by the same mechanisms as term infants, it is more common and more severe in preterm infants and lasts longer. This outcome is related to the relative immaturity of the red blood cells, hepatic cells, and gastrointestinal tract. Sick preterm newborns are more likely to have a delay in initiating enteral nutrition, resulting in an increase in enterohepatic circulation. Despite the prevalence of hyperbilirubinemia in preterm newborns, kernicterus is extremely uncommon. However, kernicterus does occur at lower TSB concentrations, even without acute neurologic signs. (11) It is unclear, however, at what value of bilirubin central nervous system injury occurs. TSB values as low as 10 to 14 mg/dL (171.0 to 239.5 μmol/L) have resulted in milder forms of bilirubin-induced neurologic dysfunction (BIND) in preterm infants. (11)(12)

Pathologic

UNCONJUGATED HYPERBILIRUBINEMIA. Pathologic hyperbilirubinemia in a newborn can be separated into four categories: increased bilirubin production, defi-

Table. Risk Factors for Hyperbilirubinemia

Increased Bilirubin Production
• Hemolytic disease
–Isoantibodies
ABO
Rh
Minor antibodies
–Enzyme defects
Glucose-6-phosphate deficiency
Pyruvate kinase deficiency
–Structural defects
Spherocytosis
Elliptocytosis
• Birth trauma
–Cephalohematoma
–Excessive bruising
• Polycythemia
Impaired Bilirubin Conjugation
• Gilbert syndrome
• Crigler-Najjar syndrome I and II
• Human milk jaundice
Decreased Bilirubin Excretion
• Biliary obstruction
–Biliary atresia
–Choledochal cyst
–Dubin-Johnson syndrome
–Rotor syndrome
Other/Combination
• Asian ethnicity
• Prematurity
• Metabolic disorder
–Hypothyroidism
–Galactosemia
• Maternal diabetes mellitus
• Infection
–Urinary tract infection
–Sepsis
• Breastfeeding
• Drugs
–Sulfisoxazole
–Streptomycin
–Benzyl alcohol
–Chloramphenicol

ciency of hepatic uptake, impaired conjugation of bilirubin, and increased enterohepatic circulation (Table 1). (5) Increased production occurs in infants who have erythrocyte-enzyme deficiencies, blood group incompatibility, or structural defects in erythrocytes. ABO incompatibility may cause anemia in the first-born child, but Rh incompatibility rarely does. Pediatricians also should consider glucose-6-phosphate dehydrogenase (G6PD) deficiency, especially in African American infants. G6PD deficiency is a sex-linked disorder occurring in 11% to 13% of African American newborns in the United States and is a significant risk factor for kernicterus. (8)

Multiple conditions can cause hyperbilirubinemia through impaired bilirubin conjugation. Gilbert syndrome is an autosomal recessive condition in which UGT1A1 activity decreases mildly in hepatocytes, typically resulting in a benign unconjugated hyperbilirubinemia. The likelihood of severe hyperbilirubinemia is increased if the infant also has G6PD deficiency. In Crigler-Najjar syndrome type I, severe deficiency of UGT1A1 results in bilirubin encephalopathy in the first few days or month after birth. In Crigler-Najjar syndrome type II, the incidence of bilirubin encephalopathy is low. (5)

CONJUGATED HYPERBILIRUBINEMIA. Conjugated hyperbilirubinemia is defined by a conjugated bilirubin concentration greater than 1 mg/dL (17.1 μmol/L) when the TSB concentration is 5 mg/dL (85.6 μmol/L) or less. If the TSB concentration is greater than 5 mg/dL (85.6 μmol/L), conjugated hyperbilirubinemia is defined when the value is 20% or greater of the TSB concentration. Elevated conjugated hyperbilirubinemia may be related to a urinary tract infection or sepsis. In an infant older than 3 weeks of age, total and conjugated bilirubin should be measured to rule out cholestasis and biliary atresia, which are associated with elevated conjugated bilirubin concentrations. The newborn screen also should be reviewed because thyroid abnormalities and galactosemia are additional causes of conjugated hyperbilirubinemia.

Kernicterus

The term kernicterus was used originally for staining of the brainstem nuclei and cerebellum. Acute bilirubin encephalopathy describes the neurologic changes that occur in the first postnatal weeks from bilirubin toxicity. Kernicterus is the chronic or permanent neurologic sequela of bilirubin toxicity. (13) The level at which bilirubin toxicity occurs is not completely known, and multiple factors influence whether bilirubin toxicity does occur. Bilirubin can cross the blood-brain barrier and enter the brain tissue if it is unconjugated and unbound to albumin or if there is damage to the blood-brain barrier. Asphyxia, acidosis, hypoxia, hypoperfusion, hyperosmolarity, and sepsis can damage the blood-brain barrier, allowing bilirubin bound to albumin to enter the brain tissue. Pedi-

atricians should consider acute bilirubin toxicity in a term infant if there are no signs of hemolysis and the TSB concentration is greater than 25 mg/dL (427.6 μmol/L). If the TSB concentration is above 20 mg/dL (342.1 μmol/L) in a term infant who has hemolysis, the physician should be concerned. (6)

Acute bilirubin toxicity occurs in three phases during the first few weeks after birth. Phase 1 occurs during the first 1 to 2 days and results in poor suck, high-pitched cry, stupor, hypotonia, and seizures. Phase 2 occurs during the middle of the first postnatal week and results in hypertonia of extensor muscles, opisthotonus, retrocollis, and fever. Phase 3 occurs after the first postnatal week and presents with hypertonia. If bilirubin concentrations are not reduced, long-term morbidity can result in BIND. Neuronal injury occurs primarily in the basal ganglia and brainstem nuclei, but the hippocampus and cerebellum also may be affected. (12) BIND or kernicterus occurs in two phases. The first phase is seen during the first postnatal year and is characterized by hypotonia, active deep-tendon reflexes, obligatory tonic neck reflexes, and delayed motor skills. The second phase, which occurs after the first postnatal year, results in choreoathetotic cerebral palsy, ballismus, tremor, upward gaze, dental dysplasia, sensorineural hearing loss, and cognitive impairment. (6)

Evaluation

The following recommendations are based on information from the AAP Subcommittee on Hyperbilirubinemia. Evaluation for hyperbilirubinemia should occur before birth and extend through the first few postnatal weeks. Hemolytic anemia caused by isoantibodies in the infant is a major risk factor for severe hyperbilirubinemia and bilirubin neurotoxicity. (13) ABO incompatibility may occur if the mother's blood type is O and the infant's blood type is A or B. (13) Mother-infant ABO incompatibility occurs in approximately 15% of all pregnancies, but symptomatic hemolytic disease occurs in only 5% of these infants. Hyperbilirubinemia in infants who have symptomatic ABO hemolytic disease usually is detected within the first 12 to 24 hours after birth. (14) Hence, ABO and Rh (D) blood types and a screen for unusual isoimmune antibodies should be evaluated for all pregnant women. If such testing is not performed or if the mother is Rh-negative, the infant's cord blood should be evaluated for a direct antibody (Coombs) test, blood type, and Rh determination. If the newborn is assessed adequately and the mother's blood type is not O and is Rh positive, cord blood does not need to be tested. (13)

After birth, the infant should be assessed for jaundice at a minimum of every 8 to 12 hours. Jaundice can be detected on a physical examination, but darker skin makes for a harder assessment. Jaundice has a cephalocaudal progression, but visual assessment has been shown to predict the TSB concentration unreliably. Jaundice in an infant is best assessed by a window in daylight; otherwise, a well-lit room is adequate. The sclera and mucous membranes are assessed for icterus, and the color of the skin and subcutaneous tissues can be revealed by blanching the skin with digital pressure.

For any infants who develop jaundice in the first 24 hours after birth, the clinician should assess whether it seems excessive for gestational age. If there is any doubt in the visual evaluation, transcutaneous bilirubin (TcB) or TSB should be assessed. Newer devices used to detect TcB have been shown to correlate well with TSB. (15) Once a TcB or TSB has been measured, the result should be interpreted based on the nomogram in Figure 1. Reassessment should be based on the zone in which the bilirubin falls on the nomogram. It is important to realize that the nomogram is based on infants of greater than 35 weeks' gestation who had no evidence of hemolytic disease. Preterm infants or infants who have risk factors for bilirubin toxicity are at higher risk of bilirubin toxicity at lower TSB concentrations. Therefore, the nomogram may not accurately predict the infant's risk based solely on the degree of hyperbilirubinemia in these high-risk infants. (13)

Sometimes further laboratory evaluation is required to determine the cause of hyperbilirubinemia. If the cause is not evident after a thorough history assessing current risk factors or significant hyperbilirubinemia occurred in siblings, evaluation is appropriate for any infant who is receiving phototherapy or when the TSB crosses percentiles on the nomogram. A complete blood count with smear and direct bilirubin concentration should be checked in these instances. A reticulocyte count, G6PD measurement, and end-tidal carbon monoxide (ETCO) determination (if available) can be considered. (12) ETCO is a good indicator of ongoing bilirubin production. As noted previously, biliverdin and carbon monoxide are the byproducts of bilirubin breakdown. Measuring the ETCO allows identification of infants experiencing increased bilirubin production and possibly infants who have hemolytic disease. (5) The TSB concentration should be rechecked in 4 to 24 hours, depending on the infant's age, TSB value, and risk factors. If the TSB is increasing despite phototherapy or if the infant is being considered for exchange transfusion, a reticulocyte count, bilirubin/albumin ratio, G6PD concentration, and ETCO should be checked. Urinalysis and urine

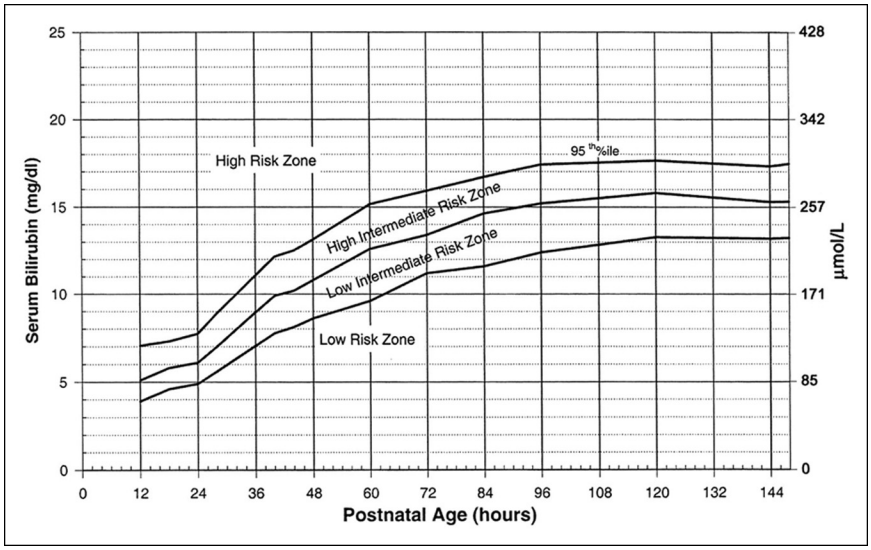

Figure 1. Nomogram for designation of risk for hyperbilirubinemia in 2,840 well newborns at 36 or more weeks' gestational age whose birthweights were 2,000 g or more or 35 or more weeks' gestational age whose birthweights were 2,500 g or more, based on the hour-specific serum bilirubin values. The serum bilirubin was measured before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin value exceeding the 95th percentile (high-risk zone). Reproduced with permission from Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics.* 1999;103: 6–14. © 1999 by the American Academy of Pediatrics.

culture are appropriate if the infant has an elevated direct bilirubin value. If indicated by the history and physical examination, a sepsis evaluation should be completed. (13)

Although human milk jaundice is a common cause of prolonged jaundice in breastfed infants, more concerning conditions should be ruled out first. Total and direct bilirubin should be measured for the infant who develops jaundice or when jaundice persists after 3 weeks of age. In addition, the newborn screen should be reviewed specifically to rule out galactosemia and congenital hypothyroidism. An elevated direct bilirubin value should prompt an evaluation for cholestasis. (13)

Because TSB concentrations peak at 3 to 5 days of age, after many infants have left the nursery, it is important to perform a risk assessment on all infants before they leave the hospital, and appropriate follow-up evaluations should be stressed. Although some controversy surrounds screening and risk assessment, based on insufficient evidence, the AAP Subcommittee has recommended assessing TSB or TcB on all newborns before discharge. (16) The value should be plotted on the nomogram to assess the risk level. (13) Some authors suggest checking a TSB on all newborns when the newborn screen is obtained. Other authors argue that data are insufficient to justify screening all infants at discharge. (16)

Exclusive breastfeeding, phototherapy in a sibling, gestational age less than 37 weeks, jaundice in the first 24 hours, hemolytic disease, East Asian race, cephalohematoma or significant bruising, and a TSB or TcB in the high risk zone before discharge are the most common clinically relevant risk factors for severe hyperbilirubinemia. Each risk factor individually has little predictive value, but the greater the number of risk factors, the greater the likelihood of the baby developing severe hyperbilirubinemia. In general, a term infant who is fed predominately formula has a very low likelihood of developing severe hyperbilirubinemia. (13)

The timeframe for following up with a pediatrician once infants are discharged from the hospital depends on the baby's age at the time of discharge. A newborn discharged at 48 to 72 hours of age should be evaluated for jaundice, weight gain or loss, stool patterns, voiding patterns, and adequacy of oral intake by 120 hours of age. The child should be evaluated at 96 hours of age if discharged between 24 to 48 hours and at 72 hours if discharged before 24 hours of age. Infants discharged before 48 hours of age may need a second visit to ensure evaluation during the time when the TSB peaks. Infants who have more risk factors may need more frequent follow-up evaluations. Also, if follow-up cannot be ensured, delaying discharge is appropriate until follow-up is determined or until the infant is older than 72 to 96 hours of age. One of the most important measures is educating all parents on the risks and assessment of hyperbilirubinemia as well as necessary follow-up evaluations. (13)

Treatment

Helping mothers breastfeed appropriately can decrease the likelihood of severe hyperbilirubinemia. Mothers should breastfeed at least 8 to 12 times in the first few days after birth to aid in bringing in the milk supply. Mother should be asked about any difficulties and lactation consultants involved when needed. The stool pat-

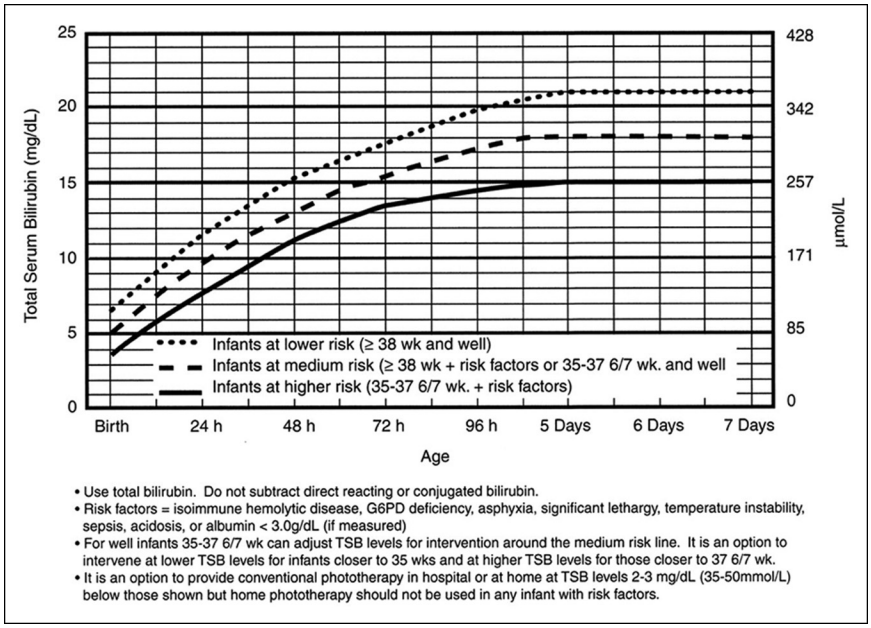

Figure 2. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation. Reproduced with permission from Subcommittee on Hyperbilirubinemia. *Pediatrics.* 2004;114:297–316. © 2004 by the American Academy of Pediatrics.

terns, voiding patterns, and weight of newborns are good indicators of whether the baby is receiving adequate milk. (6)(8)

Phototherapy

Since the discovery of the effects of sunlight on lowering bilirubin concentrations in 1958 (2), the need for exchange transfusions because of severe hyperbilirubinemia has decreased significantly. (17) Phototherapy works by converting bilirubin into a water-soluble compound called lumirubin, which is excreted in the urine or bile without requiring conjugation in the liver. The two biggest factors in the conversion of bilirubin to lumirubin are the spectrum of light and the total dose of light delivered. Bilirubin is a yellow pigment, so it most strongly absorbs blue light in the 460-nm wavelength. (5) Also, a phototherapeutic effect is seen only when the wavelength can penetrate tissue and absorb bilirubin. Lamps with output in the 460- to 490-nm range are the most effective in treating hyperbilirubinemia. Multiple types of phototherapy units are used today that contain daylight, cool white, blue, or "special blue" fluorescent tubes or tungsten-halogen lamps. Fiberoptic blankets are also available that provide light in the blue-green region. The special blue fluorescent lights are the most effective and should be used when intensive phototherapy is required. (5)(17) Ultraviolet light is not used for phototherapy. (17) Although sunlight has been shown to decrease bilirubin concentrations, it is not recommended because it is difficult to determine a timeframe that is safe to expose a naked infant to sunlight without getting sunburned. (13)

The total dose delivered, or spectral irradiance, is affected significantly by the distance the infant is from the light and the surface area to which he or she is exposed. Therefore, infants should be placed as close as possible to the light. Placing an infant in a bassinet rather than an incubator allows the light to be closer to the infant. When using fluorescent tubes, it is possible to bring the light source to within 10 cm of the infant without overheating him or her. Halogen lights can burn the infant, so the manufacturer's instructions should be followed to determine the correct distance between the light source and the baby. (13)(17) Exposing the infant as much as possible while covering his or her eyes results in a faster decline in bilirubin concentrations. It is probably unnecessary to remove the diaper unless the bilirubin concentrations are approaching the level requiring an exchange transfusion. The bassinet should be lined with aluminum foil or white cloth when nearing the point of an exchange transfusion. In most instances, it is acceptable to interrupt phototherapy to feed the infant or for brief parental visits. Continuous phototherapy should be used if exchange transfusion is likely. (13)

While an infant is receiving phototherapy, his or her temperature and hydration status should be monitored. Because bilirubin is excreted in the urine and the stool, it is important to assure good urine output. If the infant is dehydrated, intravenous fluids should be started, Oral nutrition is sufficient for the infant who is not dehydrated. Supplementing breastfeeding with formula is an option to reduce enterohepatic circulation and decrease the TSB faster. (13)

Initiation of phototherapy should be based on the TSB concentration, age in hours, and risk factors, as recommended in guidelines from the AAP (Fig. 2). The TSB value should be used, and the direct bilirubin value should not be subtracted from the total when determining when to initiate therapy. There are no guidelines

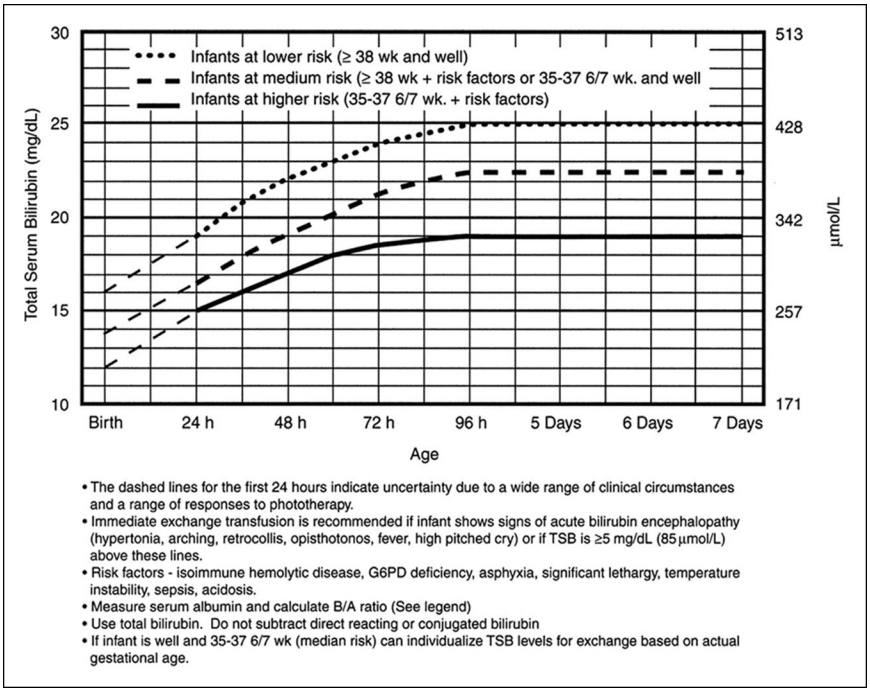

Figure 3. Guidelines for exchange transfusion in infants 35 or more weeks' gestation. Reproduced with permission from Subcommittee on Hyperbilirubinemia. *Pediatrics.* 2004;114:297–316. © 2004 by the American Academy of Pediatrics.

published for infants born earlier than 35 weeks' gestation. When using intensive phototherapy, a decrease of 0.5 mg/dL (8.6 µmol/L) per hour can be expected in the first 4 to 8 hours. When the TSB does not decline or rises during phototherapy, ongoing hemolysis is likely.

Discontinuation of phototherapy is not standardized. Therefore, clinical judgment is recommended. (5) Some authors suggest stopping once the bilirubin decreases 4 to 5 mg/dL (68.4 to 85.5 µmol/L). (5) Others state that the value should decrease to 13 to 14 mg/dL (222.4 to 239.5 µmol/L) if the child is readmitted for hyperbilirubinemia. A common misconception is that discontinuation of phototherapy results in a rebound hyperbilirubinemia. Rebound is a rare event in an infant who weighs more than 1,800 g and has no evidence of hemolysis. (5) Whether this observation holds true for smaller infants or those who have evidence of hemolysis is uncertain. A rebound bilirubin determination is not recommended, but if an infant is readmitted, a repeat TSB measurement or clinical follow-up in 24 hours is optional. (13)

Phototherapy is performed safely for millions of infants, but rare adverse effects do occur. The infant who has cholestatic jaundice with elevated conjugated hyperbilirubinemia has the potential for developing bronze infant syndrome. Affected infants develop a dark, grayish-brown color of the skin, serum, and urine. Generally, the syndrome is of little clinical significance. The only true contraindication to phototherapy is congenital porphyria or a family history of porphyria. Phototherapy in these patients could result in severe blistering and photosensitivity. (17)

Exchange Transfusion

Exchange transfusion was the first successful treatment for severe hyperbilirubinemia. These procedures should be performed only in a neonatal intensive care unit by a trained physician. An exchange transfusion for an infant is a medical emergency, and the patient should be admitted directly to the neonatal intensive care unit, bypassing the emergency department. (9) Basically, the physician rapidly removes from the circulation bilirubin and any antibodies that may be contributing to ongoing hemolysis. The procedure involves taking small aliquots of the infant's blood and replacing them with the same quantity of donor red cells via one to two central catheters until the infant's blood volume has been replaced twice. (5) An infusion of albumin 1 to 4 hours before the procedure can increase the amount of bilirubin that is removed. Intravenous gamma globulin is recommended for infants who have isoimmune hemolytic disease if the TSB is rising despite phototherapy or the TSB is within 2 to 3 mg/dL (34.2 to 51.3 µmol/L) of the level for an exchange transfusion in hopes of avoiding an exchange transfusion. Another dose can be administered in 12 hours, if needed. (13)

Figure 3 shows guidelines for initiating an exchange transfusion. Exchange transfusion should be started immediately in a jaundiced infant demonstrating signs of acute bilirubin encephalopathy, even if the TSB value is falling. Risk factors for severe hyperbilirubinemia and the albumin/bilirubin ratio should be taken into account when considering when to start an exchange transfusion. (13)

Although exchange transfusions are successful in infants who have severe hyperbilirubinemia, there are many complications, including infection, portal venous throm-

Summary

- Based on strong research evidence, breastfeeding, prematurity, significant jaundice in a previous sibling, and jaundice noted before discharge from the nursery are the most common risk factors associated with severe hyperbilirubinemia. (13)
- Based on research evaluating benefit versus harm, jaundice in the first 24 hours after birth is not physiologic jaundice and needs further evaluation.
- All newborns should undergo a risk assessment for hyperbilirubinemia before discharge from the newborn nursery and have appropriate follow-up evaluation after discharge.
- Visual assessment of jaundice does not assess the TSB reliably; clinicians should check either a TSB or TcB when in doubt.
- The infant's age in hours is used when evaluating and managing bilirubin concentrations.

bosis, thrombocytopenia, necrotizing enterocolitis, electrolyte imbalances, graft versus host disease, and even death. The complication rate is reported to be approximately 12%. (5) Because of these risk factors, phototherapy should be maximized to reduce the need for an exchange transfusion. (13)

Conclusion

Kernicterus, although a rare event, is a preventable cause of cerebral palsy. Now that infants are being discharged at earlier ages, it is important to consider screening with a TcB or TSB before discharge because visual assessment is not always reliable. It is equally important to arrange for follow-up evaluation after discharge, ideally within 48 hours, for additional screening. Mothers should be educated about feeding to ensure that the infants are receiving adequate caloric intake and monitoring stool and urine output. Weight can be checked at the follow-up visit. When evaluating bilirubin concentrations, nomograms can be used to guide initiation of phototherapy and exchange transfusions. Guidelines and published nomograms can support clinical judgment and individualize the approach to the infant who has hyperbilirubinemia.

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HealthyChildren.org Parent Resources From the AAP

The reader is likely to find material to share with parents that is relevant to this article by visiting this link: http://www.healthychildren.org/English/ages-stages/baby/Pages/Jaundice.aspx.

PIR Quiz

Quiz also available online at: http://pedsinreview.aappublications.org.

15. You are evaluating a 3-day-old term infant who has jaundice. His neonatal course was unremarkable and he is breastfed exclusively. He has approximately seven wet diapers and three stools per day. Findings on his physical examination are normal except for jaundice. His bilirubin measures 12 mg/dL (205.2 μmol/L) and is all unconjugated. Of the following, the *most* appropriate management is to

    A. Admit the baby for phototherapy.
    B. Continue breastfeeding.
    C. Discontinue breastfeeding for 3 days, then resume.
    D. Supplement the human milk with water.
    E. Supplement the human milk with cow milk-based formula.

16. A 4-day-old girl is brought to your office for evaluation of jaundice. She was born at 39 weeks' gestation and had no complications. Her and her mother's blood types both are A+. She is breastfeeding well and has normal stools and urine output. She has significant jaundice on examination but is vigorous and well hydrated. At what total serum bilirubin value should phototherapy be initiated for this infant?

    A. 10 mg/dL (171.0 μmol/L).
    B. 12 mg/dL (205.2 μmol/L).
    C. 15 mg/dL (256.5 μmol/L).
    D. 17 mg/dL (290.8 μmol/L).
    E. 20 mg/dL (342.1 μmol/L).

17. Which of the following is *most* likely to be present during the initial phase of acute bilirubin toxicity?

    A. Cerebral palsy.
    B. Chorea.
    C. Opisthotonus.
    D. Retrocollis.
    E. Seizures.

18. Which of the following statements regarding the optimal use of phototherapy is true?

    A. Infants receiving phototherapy should be placed in an incubator.
    B. Infants should wear full clothing during phototherapy to prevent burns.
    C. Intravenous fluids are required for all infants receiving phototherapy.
    D. The light source should be 30 cm from the infant's skin.
    E. Stopping phototherapy to allow for breastfeeding is acceptable in most cases.

Hyperbilirubinemia in the Newborn

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