Series Editors: Angelo P. Giardino, MD, PhD
Patrick S. Pasquariello, Jr., MD

A 5-Day-Old Neonate with Jaundice

Brandy R. Robinson, MD
Shobha Rao, MD

CASE PRESENTATION

Initial Presentation

A 5-day-old Hispanic male neonate with no significant past medical history presented to the emergency department with jaundice that began on the second day of life. According to his mother, the neonate was breastfeeding every 2 to 3 hours, seemed satisfied after each feed, and produced about 3 to 4 yellow seedy stools per day. She denied vomiting, diarrhea, or fevers.

Birth History

The infant was born via spontaneous vaginal delivery to a primigravid mother. His Apgar score was 9/9 and his birth weight was 7 lb 15 oz (3.6 kg). The mother had an uncomplicated pregnancy and prenatal care with normal laboratory tests. Her blood type is A positive, and she was Rh-antibody negative and tested negative for hepatitis B virus surface antigen. The mother was also rubella-immune and had negative results on testing for syphilis, chlamydia, gonorrhea, and HIV. At the time blood testing was performed, hemoglobin was 14 g/dL with a hematocrit of 42%. There was no significant family medical history. The patient spent 2 days in the hospital after birth and was breastfeeding well at the time of discharge.

Physical Examination and Laboratory Studies

On examination, the neonate was alert and active. He was afebrile (temperature, 98.6°F) with a heart rate of 120 bpm and respiratory rate of 40 breaths/min, and he weighed 7 lb 14.6 oz (3.59 kg). He was jaundiced on the face, chest, and abdomen extending to his mid thighs. There were no overt signs of sepsis or dehydration. His eyes were icteric bilaterally with normal red reflex and tracking to light. The infant's mouth was moist and his suck was normal. On neurologic examination, he had normal tone and resistance in all muscle groups and positive Moro, rooting, and plantar reflexes. The limbs moved spontaneously and equally. The anterior fontanelle was soft and flat, and there was no sign of cephalohematoma. On cardiovascular examination, the infant's heart rate was regular with no murmurs, and he had brisk femoral pulses. His lungs were clear without any wheezes. The infant's abdomen was soft and nondistended with normoactive bowel sounds, and there was no hepatosplenomegaly.

Laboratory testing revealed a total bilirubin level of 21 mg/dL, a hemoglobin level of 16.6 g/dL, hematocrit of 47.5%, and a white blood cell count of 11,100 cells/μL with a normal differential. Direct Coombs' test was negative.

Hospital Course

The patient was diagnosed with physiologic jaundice with bilirubin levels in the high-risk category (> 95th percentile; **Figure 1**). He was admitted to the general neonatal ward, and conventional overhead phototherapy with adjunctive "bili blankets" was initiated to reduce the bilirubin level to prevent neurodevelopmental sequelae. After 3 hours of phototherapy, the patient's total serum bilirubin level decreased from 21 to 19 mg/dL. The patient's total serum bilirubin was subsequently monitored every 6 hours, and phototherapy was discontinued when the bilirubin level decreased to 14 mg/dL. The neonate was discharged the next day with a bilirubin level of 10 mg/dL with close follow-up with his primary pediatrician.

- **What are the risks associated with jaundice?**

JAUNDICE IN THE NEONATE

Jaundice is the most common condition requiring medical attention in newborns, occurring in

At the time this manuscript was submitted, Dr. Robinson was a resident, University of Texas Southwestern Medical Family Practice Residency Program, Dallas, TX; she is now in private practice, Methodist Family Health Center, Grand Prairie, TX. Dr. Rao is an associate professor, University of Texas Southwestern Medical Family Practice Residency Program.

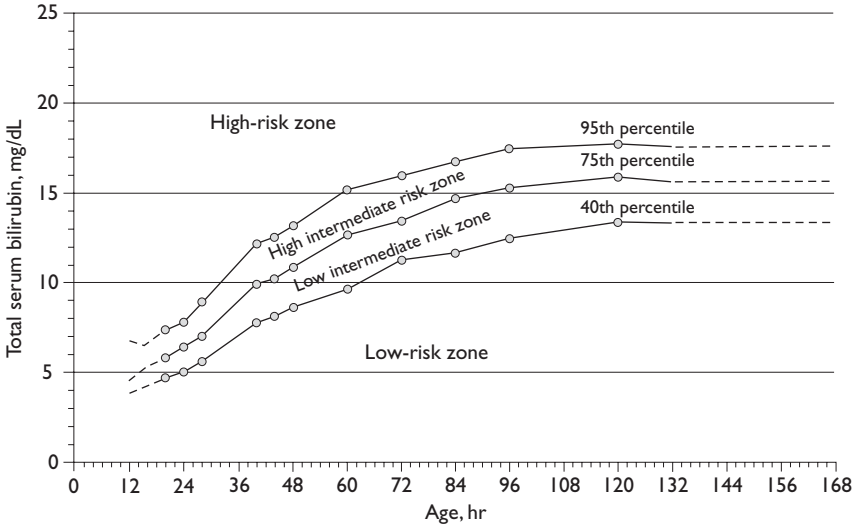


Figure 1. Risk for significant hyperbilirubinemia in healthy term and near-term well newborns. (Adapted with permission from Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999; 103:9.)

approximately 50% of term and 80% of premature infants,[1] and is a common cause of hospital readmission after early discharge.[2] Neonatal jaundice is a concern because of the potential for encephalopathy and the possibility that it may be a sign of serious underlying illness.

A physiologic elevation of serum unconjugated bilirubin develops during the second or third day of life in almost all newborns, particularly premature infants, and often resolves spontaneously. Factors that contribute to physiologic jaundice include increased bilirubin load on liver cells (eg, increased erythrocyte volume, decreased erythrocyte survival, increased early-labeled bilirubin), increased enterohepatic circulation of bilirubin, decreased hepatic uptake of bilirubin from plasma (eg, decreased binding protein ligandin), decreased bilirubin conjugation (eg, decreased uridine diphosphoglucuronosyl transferase activity), or defective bilirubin excretion.[3] However, jaundice can be a sign of a more serious or life-threatening condition. As a general rule, jaundice in the first 24 hours of life should be considered pathologic until proven otherwise. Common causes of pathologic jaundice include blood group incompatibility (eg, Rh or ABO incompatibility), sepsis, bruising, occult hemorrhage, metabolic disorders, and Gilbert or Crigler-Najjar syndromes.[1]

Key Point

It is important to establish whether jaundice is physiologic or associated with an underlying condition. Jaundice that occurs in the first 24 hours of life should be considered pathologic until proven otherwise.

If jaundice is left untreated, neurologic sequelae can result. The term *kernicterus* has been used interchangeably to describe both acute and chronic findings of bilirubin encephalopathy. However, the American Academy of Pediatrics (AAP)[4] recommends using the term *acute bilirubin encephalopathy* to describe acute manifestations of bilirubin toxicity seen in the first weeks after birth and reserving *kernicterus* to describe chronic and permanent clinical sequelae of bilirubin toxicity. Signs of acute bilirubin encephalopathy are often nonspecific and include hypertonia, arching, poor sucking, retrocollis, opisthotonos, fever, and a high-pitched cry. If the newborn survives the initial neurologic insult, kernicterus can occur, leading to developmental and motor delays, sensorineural deafness, and mild mental retardation.

- **What is the relationship between jaundice and breastfeeding?**

Jaundice and Breastfeeding

Several studies have found a strong association between breastfeeding and an increased incidence of neonatal hyperbilirubinemia.[5] In most cases, jaundice that occurs in the first 2 to 4 days of life, called breastfeeding jaundice or breastfeeding-associated jaundice,[3] can be attributed to decreased calorie intake by the neonate in the first few days of life (ie, as a result of failed breastfeeding) and the resulting increased enterohepatic circulation of bilirubin. Failure to establish breastfeeding in the first few days of the postpartum period may be due to maternal factors such as improper technique, breast engorgement, cracked nipples, and fatigue as well as neonatal factors such as an ineffective suck. Late-onset breastfeeding jaundice, also called breast milk jaundice, occurs after the first 5 days of life and peaks within 2 weeks.[6] The exact mechanism of breast milk jaundice

is not well understood. Substances in breast milk, such as β-glucuronidases and nonesterified fatty acids, may inhibit normal bilirubin metabolism.[7–9] The bilirubin level usually decreases continually after the newborn is 2 weeks old, but it may remain persistently elevated for 1 to 3 months.[6] Gilbert syndrome predisposes the neonate to breast milk jaundice as well as to more prolonged jaundice.[3] Discontinuation of breastfeeding to treat jaundice is not recommended. Both breastfeeding jaundice and breast milk jaundice are an exaggeration of physiologic jaundice. Interventions by lactation consultants and education of the parents may be helpful.

- **What does the diagnostic evaluation for jaundice include?**

DIAGNOSIS

Physical Examination

Jaundice becomes clinically apparent at serum bilirubin concentrations greater than 5 mg/dL and, in newborns, may be noticed on routine examination prior to hospital discharge or during routine posthospital follow-up. Yellow color of skin and sclera is one of the most reliable signs of jaundice. Jaundice appears first on the face and then moves caudally down to the feet as the bilirubin level increases. Cephalocaudal progression of jaundice roughly correlates with serum bilirubin level,[10] with bilirubin levels of approximately 5 mg/dL (86 μmol/L) generally indicated by jaundice on the face, levels of approximately 15 mg/dL (257 μmol/L) indicated by jaundice on the mid abdomen, and levels of approximately 20 mg/dL (342 μmol/L) indicated by jaundice that has reached the soles of the feet. Of note, visual estimation of bilirubin levels by clinical examination is not accurate and may lead to errors.[11] Therefore, it is important to measure bilirubin levels to assess the degree of jaundice. Examination of the infant's skin should include applying gentle pressure to determine the true color of the skin and checking for petechiae and signs of dehydration. Additionally, a complete neurologic examination, abdominal examination for hepatosplenomegaly, growth evaluation to assess for feeding difficulties, and cardiovascular examination to rule out murmurs and congenital abnormalities must be performed. The main diagnostic challenge for the clinician is differentiating between normal physiologic jaundice and pathologic jaundice. There is no single diagnostic test to distinguish between a physiologic and pathologic cause of jaundice, and instead physicians must rely on a combination of history, patient age, and results of physical examination to guide their suspicions. If the patient has jaundice accompanied by poor feeding, dehydration, decreased activity, lethargy, and weight loss, a pathologic cause is likely and appropriate laboratory tests should be performed to confirm the cause (**Table 1**).

Table 1. Laboratory Evaluation of the Jaundiced Infant (≥ 35 Weeks of Gestation)

Indications	Assessment
Jaundice in first 24 hr	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (ie, crossing percentiles [Figure 1]) and unexplained by history and physical examination	Blood type and Coombs' test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin Perform reticulocyte count, G6PD, and $ETCO_c$, if available (optional) Repeat TSB in 4–24 hr depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, and $ETCO_c$ (if available)
Elevated direct (or conjugated) bilirubin level	Urinalysis and urine culture Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin is elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen and evaluate infant for signs or symptoms of hypothyroidism

$ETCO_c$ = ambient carbon monoxide; G6PD = glucose-6-phosphate dehydrogenase; TcB = transcutaneous bilirubin; TSB = total serum bilirubin. (Adapted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published erratum appears in Pediatrics 2004;114:1138]. Pediatrics 2004;114:300.)

Key Point

Although the cephalocaudal progression of jaundice generally correlates with serum bilirubin levels, bilirubin should always be measured to determine the degree of jaundice.

Laboratory Testing

Total serum bilirubin and direct bilirubin levels should be obtained in all neonates with signs of jaundice on physical examination (Table 1). Transcutaneous bilirubinometry (TcB) offers a less invasive alternative to blood tests and is often used in place of serum bilirubin measurement. In an evidence-based review by the Agency for Healthcare Research and Quality, TcB measurements were found to have a linear correlation to total serum bilirubin and may be useful as screening devices to detect

Table 2. Risk Factors for Development of Severe Hyperbilirubinemia in Infants (Aged ≥ 35 Weeks of Gestation) in Approximate Order of Importance

Major risk factors
Predischarge TSB or TcB level in the high-risk zone*
Jaundice observed in the first 24 hr
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race†
Minor risk factors
Predischarge TSB or TcB level in the high intermediate risk zone
Gestational age 37–38 wk
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a diabetic mother
Maternal age ≥ 25 yr
Male gender
Decreased risk (in order of decreasing importance)
TSB or TcB level in the low-risk zone*
Gestational age ≥ 41 wk
Exclusive bottle feeding
Black race†
Discharge from hospital after 72 hr

$ETCO_c$ = ambient carbon monoxide; G6PD = glucose-6-phosphate dehydrogenase; TcB = transcutaneous bilirubin; TSB = total serum bilirubin. (Adapted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published erratum appears in Pediatrics 2004;114:1138]. Pediatrics 2004;114:297–301).

*See Figure 1.

†Race as defined by mother's description.

clinically significant jaundice and decrease the need of serum bilirubin determinations.[12] Hemoglobin, reticulocyte count, blood type, Coombs' test, and examination of peripheral blood smear for evidence of hemolysis and abnormal red cell morphology may be considered to rule out pathologic causes of newborn jaundice. Additional work-up of hyperbilirubinemia is recommended when a pathologic cause of jaundice is suspected.

- **How is hyperbilirubinemia risk classified?**
- **Can jaundice be prevented?**

RISK ASSESSMENT AND PREVENTION

Based on age-specific total serum bilirubin levels in hours, the potential risk for development of clinically significant hyperbilirubinemia can be classified as high (> 95th percentile), intermediate (40th–95th percentile), or low (< 40th percentile) (Figure 1).[13] Once risk is determined, appropriate follow-up and intervention can be undertaken. BiliTool (www.bilitool.org) is a useful Web site designed to help clinicians assess the risks of hyperbilirubinemia in newborns.

Although hyperbilirubinemia may not be completely prevented, the risk of clinically significant jaundice can often be reduced. Appropriate prenatal care is essential to recognize and manage high-risk conditions, such as ABO or Rh incompatibilities or maternal and intrauterine infections. Poor caloric intake and dehydration due to inadequate breastfeeding causes increased accumulation of bilirubin in the newborn. Increasing the number of feedings allows for more rapid elimination of bilirubin and can reduce the development of hyperbilirubinemia in breastfed infants. The AAP recommends at least 8 to 12 feeds per day for the first several days.[4] Supplementation with water or dextrose does not prevent hyperbilirubinemia and may disrupt the mother's breast milk production. Providing early assistance, education, and support to mothers increases the likelihood of successful breastfeeding.

An effective secondary prevention strategy includes routinely monitoring all newborns for the development of jaundice. Nursery protocols should be established for periodic assessments of jaundice, and the nursing staff should be able to obtain total serum bilirubin levels without a physician's order. The AAP recommends performing a systematic predischarge risk assessment for severe hyperbilirubinemia on all infants and providing follow-up based on the time of discharge and results of the risk assessment. **Table 2** outlines risk factors for development of hyperbilirubinemia. Any infant discharged at less than 72 hours of age should be seen within 2 days of discharge. Infants who have many risk factors might need to be seen earlier (ie, within 24 hr of discharge).

Key Point

The risks of hyperbilirubinemia can be reduced by recognizing high-risk conditions in the mother (ABO or Rh incompatibility) prior to delivery and monitoring the number of feedings in the breastfed infant (8–12 feedings/day is recommended). Periodic jaundice assessments should be established by nursery protocols, and appropriate follow-up should be scheduled based on results of risk assessment and time of discharge.

- **What are the recommended treatment options for hyperbilirubinemia?**

TREATMENT

An evidence-based review of 28 reports of term or late preterm infants affirmed the role of elevated bilirubin levels in kernicterus.[12] Although infrequent, kernicterus is associated with significant mortality and long-term morbidity in approximately 10% and 70% of affected neonates, respectively.[12] To avoid kernicterus, the emphasis is placed on prevention by identifying infants at high risk of hyperbilirubinemia, with therapeutic interventions initiated when clinically indicated. The therapeutic interventions available for managing hyperbilirubinemia are phototherapy and exchange transfusion. The decision to initiate phototherapy or exchange transfusion is based on the newborn's age, hour-specific total serum bilirubin levels, and the presence or absence of risk factors for neurotoxicity, including isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, or albumin level less than 3 g/dL.[4] These conditions increase the risk of brain damage because of their negative effects on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of brain cells to damage by bilirubin. A clinical pathway for management of the newborn readmitted for phototherapy or exchange transfusion is provided in **Table 3**. **Figure 2** and **Figure 3** outline AAP recommendations for phototherapy and exchange transfusion in neonates aged 35 weeks of gestation and older.[4]

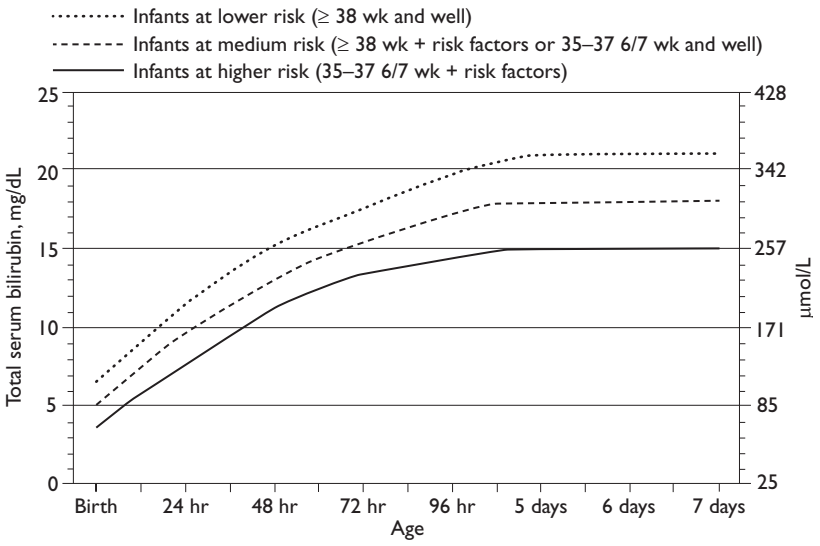
Phototherapy

Phototherapy has been the mainstay of management of unconjugated hyperbilirubinemia in newborns. Phototherapy converts bilirubin to less toxic, water-soluble photoisomers that are excreted in the bile and urine without the need for conjugation. Standard phototherapy units deliver a spectral irradiance of 8 to 10 μW/cm^2 per nm. Intensive phototherapy delivers high levels of irradiance in the 430 to 490-nm band (> 30 μW/cm^2 per nm) to as much of the infant's surface area as possible.[4] Special blue tubes provide light predominantly in the blue-green spectrum and are highly effective. At wavelengths in the blue-green spectrum, light penetrates the skin well and is absorbed maximally by bilirubin.[14] Adequate eye protection is essential to prevent retinal damage. Phototherapy should not be used to treat infants with conjugated hyperbilirubinemia because of the risk of cholestatic jaundice, which may result in bronze baby syndrome, a dark grayish-brown discoloration of the skin. Although exposure to sunlight lowers total serum bilirubin,[15] it is

Table 3. Clinical Pathway for Management of the Newborn Readmitted for Phototherapy or Exchange Transfusion

Treatment
Use intensive phototherapy and/or exchange transfusion as indicated (see Figure 2 and Figure 3)
Laboratory tests
TSB and direct bilirubin levels
Blood type (ABO, Rh)
Direct antibody test (Coombs' test)
Serum albumin
Complete blood cell count with differential and smear for red cell morphology
Reticulocyte count
$ETCO_c$ (if available)
G6PD if suggested by ethnic or geographic origin or if poor response to phototherapy
Urine for reducing substances
If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture
Interventions
If TSB ≥ 25 mg/dL (428 μmol/L) or ≥ 20 mg/dL (342 μmol/L) in a sick infant or infant < 38 wk of gestation, obtain a type and crossmatch and request blood in case an exchange transfusion is necessary
In infants with isoimmune hemolytic disease and TSB level rising despite intensive phototherapy or within 2–3 mg/dL (34–51 μmol/L) of exchange level (Figure 3), administer IV immunoglobulin 0.5–1 g/kg over 2 hr and repeat in 12 hr if necessary
If infant's weight loss from birth is > 12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give IV fluids
For infants receiving intensive phototherapy:
Breastfeed or bottle-feed (formula or expressed breast milk) every 2–3 hr
If TSB ≥ 25 mg/dL (428 μmol/L), repeat TSB within 2–3 hr
If TSB 20–25 mg/dL (342–428 μmol/L), repeat within 3–4 hr. If TSB < 20 mg/dL (342 μmol/L), repeat in 4–6 hr. If TSB continues to fall, repeat in 8–12 hr
If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds indicated levels, consider exchange transfusion (see Figure 3)
When TSB is < 13–14 mg/dL (239 μmol/L), discontinue phototherapy
Depending on the cause of hyperbilirubinemia, measuring TSB 24 hr after discharge to check for rebound is an option

$ETCO_c$ = ambient carbon monoxide; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; Rh = rhesus; TcB = transcutaneous bilirubin; TSB = total serum bilirubin. (Adapted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published erratum appears in Pediatrics 2004;114: 1138]. Pediatrics 2004;114:297–303.)



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors: isoimmune hemolytc disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured).
- For well infants 35–37 6/7 wk, can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wk and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 µmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

Figure 2. Guidelines for phototherapy in hospitalized infants aged 35 weeks of gestation and older. Note: These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when total serum bilirubin (TSB) exceeds the line indicated in each category. G6PD = glucose-6-phosphate dehydrogenase. (Adapted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published erratum appears in Pediatrics 2004;114:1138]. Pediatrics 2004;114:304.)

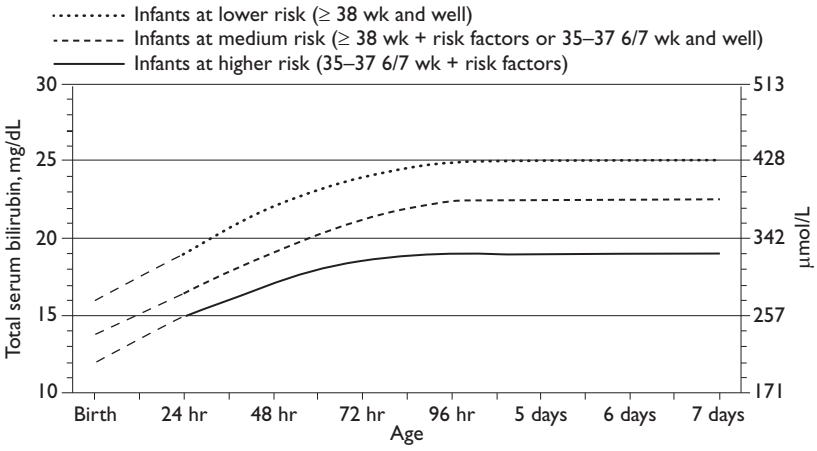
not routinely recommended for management of severe hyperbilirubinemia due to an increased risk for sunburn.

The rate of decline of total serum bilirubin during phototherapy depends on several factors. The rate is higher with increased irradiance, greater exposure of surface area to phototherapy, and higher initial total serum bilirubin levels.[4] A 6% to 20% reduction can be expected in the first 18 to 24 hours of conventional phototherapy.[16,17] Intensive phototherapy can result in a decline of at least 2 to 3 mg/dL (34–51 µmol/L) within 4 to 6 hours.[18] A decrease in total serum bilirubin can be noted as early as 2 hours after initiation of treatment.[19] In infants aged 35 weeks of gestation and older, 24 hours of intensive phototherapy can result in a 30% to 40% decrease in total serum bilirubin levels.

Fiberoptic technology. Fiberoptic technology delivers light to the skin of the infant via optical fibers in the form of "bili blankets." Bili blankets have several advantages: they result in less heat loss, offer parents and nurses greater accessibility, and enable the infant to be nursed fully clothed. To maximize its effectiveness, the bili blanket should be placed on the skin directly under the infant's clothes with the blue light of the bili blanket facing inward towards the infant's skin.[4] For the greatest benefit, the light setting should be high, which delivers up to 35 to 40 $\mu W/cm^2$ per nm of light intensity.

Studies have shown that both conventional and fiberoptic phototherapy are effective for reducing serum bilirubin levels in neonatal hyperbilirubinemia, although conventional phototherapy is superior to fiberoptic phototherapy.[20,21] Bili blankets can be used as an adjunct to overhead fluorescent lights or during feedings when overhead fluorescent lights are discontinued. They should not be used for treating pathologic jaundice or for infants with very high bilirubin levels who may require exchange transfusion. Both conventional and fiberoptic phototherapy are generally safe; however, the infant should be monitored for side effects, including burns, thermoregulatory instability, dehydration, skin rashes, and loose stools.

Discontinuing phototherapy. Discontinuation of phototherapy depends on the infant's age when phototherapy was initiated and the underlying cause of hyperbilirubinemia.[19] For infants who are readmitted after their birth hospitalization, phototherapy may be discontinued when the serum bilirubin level falls below 13 to 14 mg/dL.[4] In the infant with physiologic jaundice, significant rebound in total serum bilirubin after phototherapy is discontinued is rare. In general, it is unnecessary to delay discharge from the hospital to observe for rebound. A repeat total serum bilirubin measurement or clinical follow-up 24 hours after discharge may be considered.



- The dashed lines for the first 24 hr indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is ≥ 5 mg/dL (85 μmol/L) above these lines.
- Risk factors: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate bilirubin/albumin ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.
- If the TSB is at or approaching the exchange level, send blood for immediate type and cross-match. Blood for exchange transfusion is modified whole blood (red cells and plasma) crossmatched against the mother and compatible with the infant.

Figure 3. Guidelines for exchange transfusion in infants aged 35 weeks of gestation and older. Note: These guidelines are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. For readmitted infants, if TSB is above exchange level, repeat TSB every 2 to 3 hours, and consider exchange if TSB remains above levels indicated after intensive phototherapy for 6 hours. G6PD = glucose-6-phosphate dehydrogenase. (Adapted with permission from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published erratum appears in Pediatrics 2004;114:1138]. Pediatrics 2004;114:305.)

Key Point

The rate of decline of total serum bilirubin level during phototherapy depends on which type of phototherapy is used (ie, conventional, intensive, fiberoptic), irradiance level, surface area covered, and initial total serum bilirubin level. Decreasing bilirubin levels may be seen in as little as 2 hours after initiation of phototherapy. When serum bilirubin decreases to less than 14 mg/dL, phototherapy can be discontinued.

Exchange Transfusion

Exchange transfusion replaces the infant's blood with donor blood and is the most effective method to rapidly remove excess bilirubin. This procedure is rarely necessary in current practice because of increased awareness and risk assessment protocols. However, exchange transfusion is indicated in neonates who display signs of acute bilirubin encephalopathy (eg, hypertonia, arching, poor sucking, retrocollis, opisthotonos, fever, high-pitched cry) or in infants with a total serum bilirubin level greater than threshold values established by the AAP (Figure 3).[4] Bilirubin is tightly bound to albumin in plasma, and the portion that is unbound can more readily leave the intravascular space and cross the intact blood-brain barrier.[22] Low albumin levels can cause elevations of unbound bilirubin, and an increase in unbound bilirubin has been associated with kernicterus in sick preterm newborns.[23]

The AAP recommends measurement of serum albumin level and use of the bilirubin/albumin ratio (infants aged ≥ 38 0/7 wk, 8.0; well infants aged 35 0/7–36 6/7 wk or ≥ 38 wk if higher risk, isoimmune hemolytic disease, or G6PD deficiency, 7.2; infants aged 35 0/7–37 6/7 wk if higher risk, isoimmune hemolytic disease, or G6PD deficiency, 6.8) in conjunction with total serum bilirubin level to determine the need for exchange transfusion (Figure 3).[4] For infants readmitted after birth discharge with a total serum bilirubin level above the threshold for exchange level, the AAP recommends a repeat total serum bilirubin measurement every 2 to 3 hours, and exchange transfusion should be considered only if the levels remain above the threshold levels for transfusion after intensive phototherapy for 6 hours.[4] Exchange transfusions should be performed only by trained personnel in a neonatal intensive care unit.

The general consensus is that exchange transfusion is effective for reducing serum bilirubin levels and for preventing neurodevelopmental sequelae.[11] Exchange transfusion can be used successfully to reduce serum

bilirubin levels when other interventions such as phototherapy have failed to control the rise of serum bilirubin.[1] Exchange transfusion has an estimated mortality of 3 to 4 per 1000 infants, and among the survivors approximately 5% to 10% developed permanent sequelae such as aortic thrombosis, intraventricular hemorrhage, and pulmonary hemorrhage.[11]

Key Point

Exchange transfusion is used to rapidly remove excess bilirubin and is indicated in neonates displaying signs of acute bilirubin encephalopathy and in those with total serum bilirubin levels exceeding recommended thresholds despite phototherapy.

Monitoring

Timing of follow-up measurements of serum bilirubin after initiation of phototherapy and completion of exchange transfusion must be individualized based on the initial total serum bilirubin values:[4]

- Bilirubin level greater than 25 mg/dL, repeat within 2 to 3 hours
- Bilirubin level 20 to 25 mg/dL, repeat within 3 to 4 hours
- Bilirubin level less than 20 mg/dL, repeat within 4 to 6 hours
- If bilirubin level continues to decrease, repeat within 8 to 12 hours

Feeding

Feeding should be increased to every 2 to 3 hours. Increased feedings can augment peristalsis and stool frequency, decreasing bilirubin resorption into the enterohepatic circulation. Formula supplements or expressed breast milk should be considered if the infant's weight loss from birth is greater than 12% or if there is clinical or biochemical evidence of dehydration.[4] Although it is important to maintain adequate hydration, routine supplementation with intravenous fluids is not recommended. Intravenous fluids are rarely indicated in infants who are able to take oral nutrition.

CONCLUSION

Hyperbilirubinemia is a common problem encountered in newborns and is one of the most common causes of readmission after an infant is discharged home. In most infants, the jaundice is physiologic and there is no underlying cause. Phototherapy is effective for reducing hyperbilirubinemia in the newborn period and should be initiated when the bilirubin levels exceed AAP-recommended thresholds for treatment according to the infant's age in hours, gestational age, and presence/absence of neurotoxicity risk factors. Exchange transfusion should be considered in selected patients with hyperbilirubinemia and is the most effective method to rapidly reduce serum bilirubin levels. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 41.

Corresponding author: Brandy R. Robinson, MD, Methodist Family Health Centers, 5224 S. State Highway 360, Suite 230, Grand Prairie, TX 75052; brandianh@yahoo.com.

REFERENCES

1. Akobeng A. Neonatal jaundice. Clin Evid 2004;(12):501–7.
2. Lee KS, Perlman M, Ballantyne M, et al. Association between duration of neonatal hospital stay and readmission rate. J Pediatr 1995;127:758–66.
3. Maisels MJ. Neonatal jaundice. Pediatr Rev 2006;27:443–54.
4. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published erratum appears in Pediatrics 2004;114:1138]. Pediatrics 2004;114:297–316.
5. Gourley GR. Breastfeeding, diet, and neonatal hyperbilirubinemia. Pediatr Rev Neonatal Rev 2000;1:e25–e31.
6. Porter ML, Dennis BL. Hyperbilirubinemia in the term newborn. Am Fam Physician 2002;65:599–606.
7. Gartner LM, Herschel M. Jaundice and breastfeeding. Pediatr Clin North Am 2001;48:389–99.
8. Poland RL. Breast-milk jaundice. J Pediatr 1981;99:86–8.
9. Brodersen R, Herman LS. Intestinal reabsorption of unconjugated bilirubin. Lancet 1963;1:1242.
10. Kramer LI. Advancement of dermal icterus in the jaundiced newborn. Am J Dis Child 1969;118:454–8.
11. Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004;114:e130–53.
12. Ip S, Glicken S, Kulig J, et al. Management of neonatal hyperbilirubinemia. Evidence report/technology assessment No. 65 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019). AHRQ Publication No. 03-E011. Rockville (MD): U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality; 2003. Available at www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1a.chapter.22160. Accessed 28 Jul 2008.
13. 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.
14. Ennever JF. Blue light, green light, white light, more light: treatment of neonatal jaundice. Clin Perinatol 1990;17:467–81.
15. Salih FM. Can sunlight replace phototherapy units in the treatment of neonatal jaundice? An in vitro study. Photodermatol Photoimmunol Photomed 2001;17:272–7.
16. Garg AK, Prasad RS, Hifzi IA. A controlled trial of high-intensity double-surface phototherapy on a fluid bed versus conventional phototherapy in neonatal jaundice. Pediatrics 1995;95:914–6.
17. Tan KL. Comparison of the efficacy of fiberoptic and conventional phototherapy for neonatal hyperbilirubinemia. J Pediatr 1994;125:607–12.
18. Newman TB, Liljestrand P, Escobar GJ. Infants with bilirubin levels of 30 mg/dL or more in a large managed care organization. Pediatrics 2003;111 (6 Pt 1):1303–11.
19. Maisels MJ, Kring E. Bilirubin rebound following intensive phototherapy. Arch Pediatr Adolesc Med 2002;156:669–72.
20. Scheidt PC, Bryia DA, Nelson KB, et al. Phototherapy for neonatal hyperbilirubinemia: six-year follow-up of the National Institute of Child Health and Human Development clinical trial. Pediatrics 1990;85:455–63.
21. Mills JF, Tudehope D. Fibreoptic phototherapy for neonatal jaundice. Cochrane Database Syst Rev 2001;(1):CD002060.
22. Bratlid D. How bilirubin gets into the brain. Clin Perinatol 1990;17:449–65.
23. Cashore WJ, Oh W. Unbound bilirubin and kernicterus in low-birth-weight infants. Pediatrics 1982;69:481–5.

Copyright 2008 by Turner White Communications Inc., Wayne, PA. All rights reserved.