A 5-Day-Old Neonate with Jaundice

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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 cephalo-hematoma. 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
approximately 50% of term and 80% of premature infants, and is a common cause of hospital readmission after early discharge. 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. 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.

**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) 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. In most cases, jaundice that occurs in the first 2 to 4 days of life, called breastfeeding jaundice or breastfeeding-associated jaundice, 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. 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. The bilirubin level usually decreases continually after the newborn is 2 weeks old, but it may remain persistently elevated for 1 to 3 months. Gilbert syndrome predisposes the neonate to breast milk jaundice as well as to more prolonged jaundice. 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, 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. 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).

**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...
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). 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. 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).

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

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Minor risk factors</th>
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<tbody>
<tr>
<td>Predischarge TSB or TcB level in the high-risk zone*</td>
<td>Predischarge TSB or TcB level in the high intermediate risk zone</td>
</tr>
<tr>
<td>Jaundice observed in the first 24 hr</td>
<td>Gestational age 37–38 wk</td>
</tr>
<tr>
<td>Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCO₂</td>
<td>Jaundice observed before discharge</td>
</tr>
<tr>
<td>Gestational age 35–36 wk</td>
<td>Previous sibling with jaundice</td>
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<tr>
<td>Previous sibling received phototherapy</td>
<td>Macroscopic infant of a diabetic mother</td>
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<tr>
<td>Cephalohematoma or significant bruising</td>
<td>Maternal age ≥ 25 yr</td>
</tr>
<tr>
<td>Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive</td>
<td>Male gender</td>
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</tbody>
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**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

ETCO₂ = ambient carbon monoxide; G6PD = glucose-6-phosphate dehydrogenase; TcB = transcutaneous bilirubin; TSB = total serum bilirubin.


*See Figure 1.

†Race as defined by mother’s description.

clinically significant jaundice and decrease the need of serum bilirubin determinations. 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 workup of hyperbilirubinemia is recommended when a pathologic cause of jaundice is suspected.

- How is hyperbilirubinemia risk classified?
- Can jaundice be prevented?
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. Although infrequent, kernicterus is associated with significant mortality and long-term morbidity in approximately 10% and 70% of affected neonates, respectively. 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. These increases 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.

Phototherapy

Phototherapy has been the mainstay of management of unconjugated hyperbilirubinemia in newborns. Phototherapy converts bilirubin to less toxic, water-soluble photosomers 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/cm² per nm. Intensive phototherapy delivers high levels of irradiance in the 430 to 490-nm band (> 30 µW/cm² per nm) to as much of the infant’s surface area as possible. 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. 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, it is absorbed maximally by bilirubin.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Use intensive phototherapy and/or exchange transfusion as indicated (see Figure 2 and Figure 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory tests</td>
<td>TSB and direct bilirubin levels</td>
</tr>
<tr>
<td>Blood type (ABO, Rh)</td>
<td>Direct antibody test (Coombs’ test)</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Complete blood cell count with differential and smear for red cell morphology</td>
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<tr>
<td>Reticulocyte count</td>
<td>ETCO₂ (if available)</td>
</tr>
<tr>
<td>G6PD if suggested by ethnic or geographic origin or if poor response to phototherapy</td>
<td>Urine for reducing substances</td>
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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. If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture.

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.
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. A 6% to 20% reduction can be expected in the first 18 to 24 hours of conventional phototherapy. Intensive phototherapy can result in a decline of at least 2 to 3 mg/dL (34–51 µmol/L) within 4 to 6 hours. A decrease in total serum bilirubin can be noted as early as 2 hours after initiation of treatment. 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. For the greatest benefit, the light setting should be high, which delivers up to 35 to 40 µW/cm² 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. Bili blankets can be used as an adjunct to overhead fluorescent lights 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. 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. 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.

**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 suckling, 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). 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. Low albumin levels can cause elevations of unbound bilirubin, and an increase in unbound bilirubin has been associated with kernicterus in sick preterm newborns.

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). 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. 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. Exchange transfusion can be used successfully to reduce serum levels established by the AAP (Figure 3).
bilirubin levels when other interventions such as phototherapy have failed to control the rise of serum bilirubin. 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.\footnote{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:\footnote{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.\footnote{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. \footnote{HP}

**REFERENCES**